Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document

METRELEPTIN (BLA STN125390)

Indication: Lipodystrophy

Meeting Date: 11 December 2013

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

BRISTOL-MYERS SQUIBB COMPANY
Research and Development
PO Box 4000
Princeton NJ 08543-4000

ASTRAZENECA AB
151 85 Södertälje
Sweden

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 EXECUTIVE SUMMARY

1.1 Disease Background and Proposed Indication

Lipodystrophy (LD) is characterized by loss of adipose tissue (with resultant leptin deficiency) and ectopic triglyceride (TG) deposition in tissues like liver and muscle. Lipodystrophy syndromes have been generally classified by etiology, either genetic or acquired, and by adipose tissue distribution as either generalized or partial. The loss of subcutaneous (SC) adipose tissue is variable, and may be either diffuse (generalized) or restricted to regional anatomical adipose depots (partial). The degree of the leptin deficiency is generally correlated with the extent of SC adipose tissue loss.

Lipodystrophy syndromes are often associated with severe metabolic abnormalities, primarily hypertriglyceridemia (with serum TG often elevated in the range of several 100s to 1,000s mg/dL), and severe insulin resistance with resultant hyperglycemia and type 2 diabetes mellitus. Ectopic lipid deposition in the liver can result in severe hepatic steatosis, which can lead to steatohepatitis characterized by fat accumulation, cellular injury, and inflammation that can eventually cause cirrhosis in LD patients.

Generalized LD differs from partial LD in the clinical presentation, and degree of metabolic abnormalities. Generalized LD is a condition associated with substantial morbidity and mortality due to complications from metabolic abnormalities and/or the serious co-morbidities typically associated with these syndromes. Partial LD is more heterogeneous in presentation due to the varying degree of SC adipose tissue loss. These patients can experience similarly severe metabolic abnormalities and co-morbidities as in generalized LD patients, although there may be greater variability in the severity of metabolic abnormalities at presentation between partial LD patients.

Uncontrolled hypertriglyceridemia, diabetes, and hepatic steatosis can lead to life threatening complications such as acute pancreatitis, accelerated cardiovascular disease, and steatohepatitis/cirrhosis. Thus, there is a significant unmet medical need for a therapy that effectively improves the metabolic disorders found in LD patients.

There are no approved therapies that specifically target the mechanism underlying metabolic abnormalities in LD patients. These metabolic abnormalities are often difficult to control even with high doses of currently available diabetes and lipid-lowering therapies. Not only are these treatments rendered less effective by the profound insulin resistance, they also do not correct the underlying pathophysiology resulting from leptin deficiency.

Leptin is a naturally occurring hormone and an important regulator of energy homeostasis and other diverse physiological functions. Circulating levels of leptin closely correlate with the amount of adipose tissue present. Metreleptin is a recombinant analogue of human leptin. Metreleptin has the same physiological effects as leptin, including regulation of energy homeostasis and metabolic function.

Metreleptin has also been shown to correct the metabolic abnormalities resulting from leptin deficiency in these patients. It decreases TG and other lipid intermediates and reduces their

accumulation in tissues such as liver and muscle, resulting in increased insulin sensitivity, thereby improving hypertriglyceridemia and hyperglycemia. It also improves insulin suppression of glucose production in the liver and increase insulin-stimulated peripheral glucose uptake in muscle. Metreleptin also corrects hyperphagia with concomitant reduction in caloric intake.

The initial draft indication for metreleptin proposed in the Biologics License Application (BLA) was for the treatment of metabolic disorders associated with LD, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired LD. Based on further analysis of the efficacy and safety in subpopulations of LD patients in the clinical studies, the Sponsor has refined the proposed indication statement to better identify patients with LD who will gain the most benefit from metreleptin treatment. The Sponsor anticipates dialogue with the Food and Drug Administration (FDA) during the BLA review to finalize an indication allowing appropriate access to generalized and partial LD patients who may benefit from treatment. The current proposed indication for metreleptin is:

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.

1.2 Clinical Development Program

The metreleptin clinical development program for LD supporting the BLA consists of 1 completed study at the National Institutes of Health (NIH Study 991265) and 2 ongoing studies (NIH 20010769 and FHA101) in LD patients. Data from the NIH studies contain the largest cohort of patients (N 72) and provide the pivotal efficacy and safety data for this BLA. Study FHA101 (N 28) provides additional supporting data. The BLA is based on efficacy and safety data in 100 patients with this very rare disease which is estimated to affect only a few thousand patients worldwide.

Metreleptin has also been evaluated in two clinical development programs in obese subjects, one for metreleptin monotherapy, in over 1,100 obese subjects, and a second for metreleptin in combination with pramlintide, in over 600 subjects. These programs, (halted due to lack of clinically meaningful benefit in obesity) provide valuable supportive placebo controlled safety data from a larger number of subjects, albeit from a different patient population than LD.

The NIH studies, the first of which dates back to the year 2000, were not originally intended to support a marketing application. However, given the clinical findings from the studies in LD patients with few therapeutic options and high unmet medical needs, the Sponsor proposed and the FDA agreed, to a registration pathway based on these studies that could form the basis of this marketing application. The data from the investigator-sponsored NIH studies were

retrospectively captured by the Sponsor into an industry-standard database using standardized conventions.

The first clinical study of metreleptin (NIH Study 991265) was an open-label, investigator-sponsored study to determine the safety and efficacy of metreleptin administration. Based on the efficacy observed in this initial pilot study of metreleptin in LD patients, a long term study of metreleptin (NIH Study 20010769) was initiated. A placebo control was not ethically justifiable in this patient population given the severity of their metabolic complications and the marked improvements demonstrated with metreleptin treatment in the initial pilot study (NIH Study 991265).

NIH Study 20010769 is an ongoing, open-label, investigator-sponsored study to determine the long term safety and efficacy of metreleptin administration in the treatment of LD. This study has broader inclusion criteria than NIH Study 991265. It allows enrollment of younger patients and patients with less severe leptin deficiency than in NIH Study 991265.

Between these 2 NIH studies, a total of 72 patients (7 who participated in both studies; 2 who participated only in NIH Study 991265, and 63 who participated only in NIH Study 2001769) have been exposed to metreleptin as of the 11 July 2011 data cutoff for the BLA.

In order to expand access to metreleptin, a third study (Study FHA101) was initiated by the Sponsor. Study FHA101 is an ongoing study enrolling patients with LD and associated diabetes mellitus and/or hypertriglyceridemia. This study has a less restrictive inclusion criterion in terms of age, leptin threshold, and fasting insulin levels than the NIH studies. As of the March 2012 data cutoff for the BLA, 28 patients have enrolled in this study. Given that the primary objective of the protocol was to expand access to metreleptin to this patient population, this study also has no placebo control or comparator group.

The recommended dosage for the marketed product is based on the experience from the LD clinical studies. For patients weighing ≤ 40 kg body weight, the proposed starting dose is 0.06 mg/kg daily. For patients weighing > 40 kg, a starting dose of 5 mg and 2.5 mg (female and male, respectively) is recommended daily. However, based on clinical response (e.g., inadequate metabolic control or excessive weight loss or tolerability issues), the starting dose in all patients can be adjusted in increments or decrements of 0.02 mg/kg for patients weighing ≤ 40 kg and 1.25 to 2.5 mg for patients weighing > 40 kg.

1.3 Summary of Efficacy

The pivotal efficacy data for the LD program are based on 72 patients treated with metreleptin in 2 open-label, investigator-sponsored NIH studies. Data from 28 patients enrolled in Study FHA101 provide important supplemental efficacy data in this patient population. Because of differences in study conduct, data collection, and overall exposure, data from the FHA101 study were not integrated with the NIH data.

The objectives of the NIH studies were to evaluate the efficacy of metreleptin for improving metabolic abnormalities in LD patients. The key endpoints included change over time in hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), TG, and liver function.

Substantial and clinically meaningful improvements in HbA1c, FPG, TG, and liver endpoints were observed in the NIH studies with metreleptin treatment. Reductions in these endpoints were more pronounced in patients with elevated baseline values. Larger mean reductions were observed in patients with generalized LD as compared to patients with partial LD, which appeared to correlate with greater abnormalities in mean metabolic parameters at baseline.

For the overall population, the (mean ± SE) change from baseline in HbA1c was -1.4 ± 0.2%, (mean ± SE 95% CI: -0.9, -1.8) at Month 12. The corresponding mean reduction in FPG at Month Month 12 was -42 ± 12 mg/dL (95% CI: -18, -65). For fasting TG concentrations, which were markedly elevated in many patients at baseline, the mean (± SE) reduction in fasting TG concentration was 673 ± 223 mg/dL at Month 12, and mean ± SE percent reduction of TG concentration was 32 ± 8% (95% CI: -17, -47) at Month 12.

Efficacy was demonstrated in patients with both generalized LD and partial LD, the most important determinant of overall response to metreleptin relating to the proportion of the studied population affected and the severity of the metabolic abnormalities at baseline. Thus, larger decreases in HbA1c were observed in patients with generalized LD because a higher proportion of generalized LD patients had elevated baseline HbA1c values, and individual baseline HbA1c values were also higher in magnitude. Similar proportions of patients in each group had baseline TG values ≥ 1000 mg/dL. Large decreases in TGs were observed in both generalized and partial LD patients with elevated baseline TGs.

The improvements in HbA1c, FPG, and TG are particularly notable given that they occurred in patients who were often uncontrolled on other anti-diabetes therapies (in some cases, extremely high doses of insulin). In some patients, substantial reductions of concomitants medications or discontinuation in the use of anti-diabetes medications (insulin and/or oral agents) occurred. In the NIH Studies, half of the LD patients were receiving at least 1 lipid-lowering medication at baseline. The doses of lipid-lowering medications in most (72%) patients were unchanged at Month 12, with 17% stopping or decreasing their medication. The majority (88%) of LD patients in the NIH studies were receiving at least 1 anti-diabetes medication at baseline. By Month 12, 43% of patients discontinued or decreased anti-diabetes medications. In 26 patients who took insulin at baseline and had Month 12 data, there was a reduction in median insulin doses by ~75% at Month 12. Eight of these patients were able to discontinue insulin at Month 12, from a median baseline of 550 U/day, reflecting substantial improvements in insulin sensitivity and/or increased insulin secretion.

Acknowledging that there was no placebo control employed in the NIH studies, these findings show the improvements in HbA1c, FPG, and TG were not simply due to increasing the dose or adding additional anti-diabetes therapies for the majority of the patients.

In addition to clinically meaningful reductions in TG, decreases in mean non-HDL cholesterol (a surrogate of cardiovascular risk reduction) were observed after metreleptin (mean change from baseline to Month 12 of 65 mg/dL) with minimal changes in HDL cholesterol.

In the NIH studies, a substantial percentage of patients had liver disease (85%) at baseline including hepatic steatosis, steatohepatitis and/or hepatomegaly. Hepatic steatosis is commonly

associated with elevated liver function tests, therefore measurements of alanine (ALT), aspartate aminotransferase (AST), and liver volume are a useful surrogate for hepatic steatosis. Most patients had elevated liver function tests at baseline (ALT and AST 2 to 3 times the upper limit of normal). Substantial reductions in ALT, AST, and liver volume occurred with metreleptin treatment, through to Month 12.

Improvements in mean ALT and AST were apparent at Month 4 (-37.5 U/L ALT and - 24.4 U/L AST), and were sustained to Month 12 (-31.4 U/L ALT and -23.7 U/L AST). There were greater mean reductions in generalized LD patients compared to patients with partial LD. In a subgroup of patients, a large mean reduction in liver volume was evident at Month 4 (-592 mL) with further reductions observed at Month 12 (-1,001 mL). These data highlight the importance of liver disease as part of the spectrum of metabolic abnormalities associated with LD, as hepatic steatosis and/or steatohepatitis may be the primary metabolic manifestation of LD in certain patients.

Clinically meaningful improvements in HbA1c, fasting TG, and liver endpoints were also observed in the pediatric population. Overall, pediatric patients had slightly larger improvements in HbA1c compared to adult patients.

The majority of patients studied in the NIH studies had baseline leptin levels below the 10^{th} percentile of the population as reported by National Health and Nutrition Examination Survey (NHANES) data. Since Study FHA101 did not have a leptin exclusion limit, leptin levels at study entry covered a broader range. The severity of baseline abnormalities and the change in HbA1c and TG in patients with baseline leptin levels > 12 ng/mL (exclusion limit for the NIH studies) were more heterogeneous. Leptin levels at baseline serve as a surrogate for the amount of adipose tissue, which is the tissue that secretes this hormone. Although, leptin measurements can provide qualitative information on the likelihood of improvements in HbA1c or TG, but a reliable quantitative threshold cannot be defined given limited clinical data in LD patients at higher leptin levels. Overall, improvements with metreleptin treatment in LD patients were related to the severity of baseline metabolic abnormalities, and not necessarily dependent upon the severity of leptin deficiency or the type of LD.

1.4 Summary of Safety

The total duration of exposure to metreleptin for the 72 NIH patients ranged from 2 months to approximately 11 years, with over 80% of patients having over 1 year of exposure. For Study FHA101, the total duration of exposure to metreleptin for 28 patients ranged from 0.1 years to approximately 3 years. The majority of patients (52 of 72 patients in the NIH studies and 20 of 28 patients in Study FHA101) were still continuing treatment as of the data cutoff for the BLA.

Metreleptin has an acceptable safety and tolerability profile in the LD patient population. In the NIH and FHA101 studies, the most common AEs considered related to metreleptin treatment included hypoglycemia, fatigue, nausea, decreased body weight, abdominal pain, injection site hematoma, and injection site urticaria. None of the events considered related to treatment led to discontinuation. One event of hypoglycemia and one event of abdominal pain were reported as serious adverse events (SAEs). Three patients (2 in the NIH studies and 1 in Study FHA101)

discontinued metreleptin due to a treatment-emergent adverse event (TEAE). The events that lead to discontinuation were: T-cell lymphoma and worsening proteinuria in the NIH studies and muscle spasm in Study FHA101, these events were assessed by the investigator as not related to metreleptin treatment.

Two cases of peripheral T-cell lymphoma and 1 case of a localized anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (a type of T-cell lymphoma) have been reported in the NIH studies. All 3 events occurred in patients with Acquired generalized lipodystrophy (AGL) known to be associated with autoimmune disease. There was evidence of pre-existing lymphoma and/or bone marrow abnormalities in the 2 patients with peripheral T-cell lymphoma before metreleptin treatment. The third case of anaplastic large cell lymphoma occurred in the context of a specific chromosomal translocation. Based on these observations, it is unlikely that metreleptin contributed to de novo development of the 3 lymphomas. It is also unlikely that metreleptin contributed to any progression of pre-existing lymphoma, although the latter cannot be excluded with certainty. In addition, 2 cases of peripheral T-cell lymphoma have been reported in the literature in patients with a clinical picture of acquired LD, who have not been treated with metreleptin. To help ensure appropriate patients receive treatment, the Sponsor proposes education of prescribers about the potential risk of lymphoma through physician certification as a goal of the Risk Evaluation and Mitigation Strategy (REMS) with further assessment via a metreleptin Safety Registry (refer to Section 8, Risk management and post marketing safety assessments).

Most patients in the NIH and FHA101 studies developed drug binding antibodies, which is not an unusual finding with biologic therapeutics. Assessment of binding (non-neutralizing) antibodies as well as neutralizing activity to metreleptin (based on an in vitro cell-based assay) has been performed in the NIH and FHA101 studies, as well the obesity program. Development of these binding antibodies had no apparent impact on overall efficacy or safety. In a small number of subjects, development of high-titer drug antibodies was coincident with detection of neutralizing activity.

From the available data, there is no clear evidence of adverse clinical consequences of in vitro neutralizing activity in patients with LD. As loss of efficacy represents the main potential concern of neutralizing activity, testing for neutralizing activity should be considered in patients in whom loss of efficacy is suspected and no other causes can be identified, such as noncompliance with treatment. To further evaluate the presence of metreleptin neutralizing activity and clinical consequences in the post marketing setting, the Sponsor has implemented an immunogenicity testing and safety follow-up program for patients who received treatment with metreleptin and develop metreleptin neutralizing activity (refer to Section 8).

A thorough review of AEs reported in the LD studies (supplemented by the placebo-controlled studies of metreleptin in obesity) suggests that the majority of serious AEs (e.g., chronic renal or liver disease, cardiovascular events, acute pancreatitis, etc) were related to the underlying disease state and do not result from metreleptin therapy. There were no major differences in the safety profile of patients with partial LD compared to patients with generalized LD independent of the baseline co-morbidities and underlying metabolic abnormalities. Similarly, the safety profile of

metreleptin was similar among the adult and pediatric LD population. Adverse events of decreased weight and abdominal pain occurred at a higher incidence in pediatric patients compared to adult patients. There was no evidence of an adverse effect of metreleptin on growth or pubertal maturation in pediatric patients.

In the LD studies, TEAEs of acute pancreatitis were reported in 5 patients. All of these patients who had a new event of pancreatitis while receiving metreleptin had a previous history of pancreatitis and hypertriglyceridemia. The events were considered to be related to severe hypertriglyceridemia, consistent with the underlying LD disease state. The risk of recurrent pancreatitis is increased in patients who discontinue metreleptin treatment or are noncompliant with treatment, particularly in patients with a previous history of pancreatitis. Dose tapering is recommended if metreleptin treatment is discontinued in patients with risk factors for pancreatitis.

Pharmacological effects of metreleptin (such as potential weight loss or hypoglycemia, particularly in combination with insulin as down titration becomes necessary) were manageable. Although hypoglycemia is not evident with metreleptin treatment alone, hypoglycemia may occur in the setting of rapid improvement in insulin sensitivity with metreleptin treatment in patients on high doses of insulin, and possibly in patients on insulin secretagogues. The risk for hypoglycemia can be managed by appropriate monitoring of blood glucose in patients on concomitant insulin secretagogues or insulin therapy and dose adjustment of concomitant diabetes therapies as needed.

No events of generalized hypersensitivity were assessed by the investigator as related to metreleptin treatment in the LD clinical studies. Events of generalized hypersensitivity were reported in obese subjects (without LD) treated with metreleptin but were infrequent, and no events with respiratory or circulatory compromise have been reported.

Leptin has a known role in regulating immune function that is complex. This has relevance given the potentially dysregulated immune systems of LD patients (especially those with acquired LD and/or autoimmunity). However, based on the available data from clinical studies of metreleptin, as well as other published data (in vitro, nonclinical, etc), there is no evidence that metreleptin has an adverse effect on immune function as it relates to promotion of malignancies, susceptibility to infections, or enhancement of autoimmunity.

Overall, metreleptin has a favorable safety profile with the majority of patients studied as part of this BLA remaining on treatment, some for over 11 years. This long-term data provides important safety information for a therapy intended for chronic administration.

1.5 Summary and Discussion of Risk-Benefit

Lipodystrophy is a heterogeneous disease that is associated with significant morbidity and mortality, and metreleptin is a unique therapy that treats the associated metabolic abnormalities and relative leptin deficiency due to the loss of SC adipose tissue. In the metreleptin clinical studies, LD patients with metabolic abnormalities (including diabetes, hypertriglyceridemia, and/or liver dysfunction) treated with metreleptin experienced clinically meaningful, and often substantial, improvements in these abnormalities. Metreleptin was efficacious in the majority of

patients with metabolic abnormalities (including diabetes, hypertriglyceridemia, and/or liver dysfunction) with an acceptable safety and tolerability profile, established over a period of 11 years.

At a fundamental level, there are three primary interrelated types of metabolic abnormalities in LD patients that arise as a consequence of ectopic lipid accumulation: diabetes, hypertriglyceridemia, and liver dysfunction. These disease elements all contribute to current co-morbidities in LD patients, and predispose patients to risks for future morbidities and mortality, and help define the need for metreleptin treatment in individual LD patients. The clinically meaningful improvements in metabolic abnormalities seen with metreleptin treatment in the LD clinical program may lead to reduced risks of serious complications such as acute pancreatitis, end stage liver disease, and accelerated cardiovascular disease. Responses in hepatic disease are not limited to reductions in serum transaminases, and include improvements in hepatic steatosis and/or hepatosteatosis. In pediatric patients with predominant fatty liver disease who otherwise have few alternatives for treatment and face a grave prognosis for progressive liver disease without intervention, metreleptin represents a potential treatment option.

Metreleptin treatment in LD patients over several years indicates an overall favorable safety profile. The main known or identified potential risks are lymphoma and the potential risk for loss of efficacy if neutralizing activity to metreleptin develops. In order to help ensure that the appropriate patients receive treatment, the Sponsor proposes education of prescribers about the potential risk of lymphoma and clinical consequences of neutralizing activity through physician certification as a goal of the REMS with further assessment via a metreleptin Safety Registry and immunogenicity follow-up program (refer to Section 8).

The benefits of metreleptin treatment apply to LD syndromes considered as a whole, but there are important distinctions to note for the individual LD subtypes. Overall, the treatment decision regarding use of metreleptin for patients with generalized LD can be more straightforward. Generalized LD, whether congenital or acquired, is a condition associated with substantial morbidity and mortality due to complications from severe metabolic abnormalities (which are often not responsive or suboptimally controlled on standard, currently available therapies). Both subtypes of generalized LD patients are typically diagnosed early in life, adding to their risk of developing severe morbidity and pre-mature mortality. As a consequence of marked SC adipose tissue deficiency, patients with generalized LD have leptin levels below the 10th percentile of measured concentrations observed in the normal population, and are indeed both adipose tissue and leptin deficient. Treatment of generalized LD patients with metreleptin has been demonstrated to improve the patient's metabolic abnormalities and the magnitude of improvement correlates with the severity of the specific baseline metabolic abnormalities present.

The treatment decision in patients with AGL must also consider two potential concerns, i.e. the potential risk of T-cell lymphoma and the concern of worsening autoimmune disease through pro-inflammatory effects. Available evidence from nonclinical studies supports the conclusion that metreleptin is unlikely to cause T-cell lymphoma de novo. The clinical assessment of the

potential role of metreleptin in contributing to progression of lymphoma is limited by the lack of placebo control. Thus, a potential role cannot be fully excluded. The potential for metreleptin to worsen autoimmune disease in patients with AGL is also of hypothetical concern but within the available dataset, autoimmune progression in AGL patients on metreleptin treatment is consistent with that reported in the literature. Balanced with this, by the nature of their extensive loss of SC adipose tissue, AGL patients tend to have very significant metabolic abnormalities which present in childhood or adolescence. This combination puts them at especially high risk of and morbidity and mortality associated with these complications. Therefore, the potential for these patients to achieve benefits which are particularly important needs to be taken into consideration for this population.

Patients with partial LD are more heterogeneous in presentation due to the varying degree of SC adipose tissue loss demonstrated at presentation. These patients can experience similar severe metabolic abnormalities and serious co-morbidities as generalized LD patients, although there is greater variability in the severity of metabolic abnormalities at presentation. Clinical diagnosis of significant loss of SC adipose tissue in regional distribution patterns based on thorough physical examination, combined with the presence of more severe metabolic abnormalities (including hypertriglyceridemia, diabetes mellitus with marked insulin resistance, and/or hepatic steatosis or hepatomegaly) are important considerations guiding a treatment decision in partial LD patients. Evidence of refractoriness to conventional treatment (for example anti-diabetic and lipid-lowering therapies) is another consideration. Overall, improvements with metreleptin treatment in partial LD patients are related most reliably to the severity of baseline metabolic abnormalities. Leptin measurements can provide qualitative information on the likelihood of improvements in HbA1c or TG, but a reliable quantitative threshold cannot be defined given limited clinical data in LD patients at higher leptin levels. In such patients who have no other effective means to effectively control their metabolic abnormalities, metreleptin fulfills an important unmet need.

2 BACKGROUND

2.1 Proposed Indications and Use

Metreleptin, a recombinant analogue of human leptin, is a 147-amino acid polypeptide that differs from the human leptin sequence by 1 additional amino acid, methionine, located at the amino-terminal end. This briefing document presents and evaluates the benefits and risks of metreleptin and its intended use in LD, based on all relevant clinical as well as nonclinical data. The initial draft indication for metreleptin proposed in the Biologics License Application (BLA) was for the treatment of metabolic disorders associated with LD, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired LD. Based on further analysis of the efficacy and safety in subpopulations of LD patients in the clinical studies, the Sponsor has refined the proposed indication statement to better identify patients with LD who will gain the most benefit from metreleptin treatment. The Sponsor anticipates dialogue with the Food and Drug Administration (FDA) during the BLA review to finalize an indication allowing appropriate access to generalized and partial LD patients who may benefit from treatment. The currently proposed indication for metreleptin is:

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.

HIV-related LD is not discussed in this document as the Sponsor is not seeking an indication in this population and, as such, it is not part of the BLA submission.

2.2 Lipodystrophy Syndromes

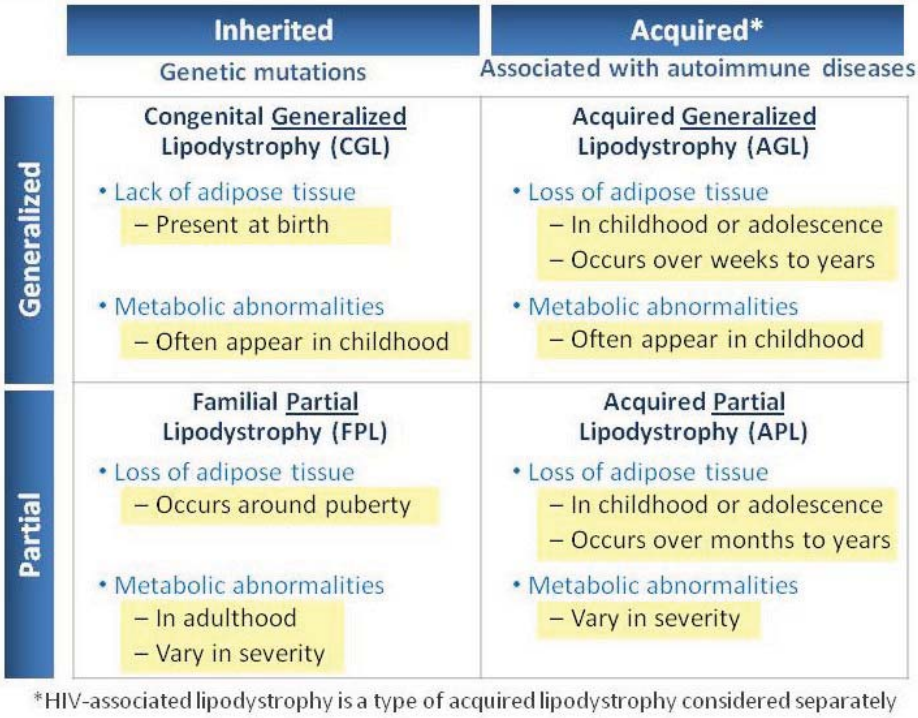
Lipodystrophy syndromes are clinically heterogeneous inherited or acquired disorders characterized by a common clinical phenotype of selective, variable and often progressive loss of adipose tissue, primarily SC adipose tissue [1,2] combined with a range of metabolic abnormalities associated with a profound or relative deficiency of leptin, a hormone which is normally secreted by adipose tissue. Lipodystrophy syndromes have been generally classified by etiology as either genetic or acquired, and by adipose tissue distribution as either generalized or partial. The loss of SC adipose tissue is variable, and may be either generalized or partial, i.e., restricted to limited anatomical areas with sparing or even accumulation of excess adipose tissue in certain regions (for example, around the face and neck in Dunnigan's syndrome).

While considerable progress has been made in elucidating the genetic basis of inherited lipodystrophies over the last decade, with 11 genetic loci discovered to date,[3] not all of the causative genes for inherited forms of LD have been identified, and it is likely that additional genetic defects will be identified in the future.

The exact etiology of acquired forms of LD is not well understood, although it has been hypothesized that destruction of adipocytes by either cell-mediated and/or antibody-mediated autoimmune processes may occur, especially given the association of autoimmune diseases with acquired forms of LD.[2,4,5] The putative autoantibody to adipocytes has not been well characterized, although an autoantibody against the adipocyte membrane has been described in a patient with aquired generalized LD (AGL).[6] In acquired partial LD (APL), activation of the alternate complement pathway accompanied by an auto-antibody called C3 nephritic factor has been hypothesized to play a role in adipocyte loss.[2] Finally, in some cases, infections that precede the onset of LD,[4,5] have been described, suggesting the possibility of environmental factors triggering an autoimmune phenomenon.

A framework for classification of LD syndromes has been described based on the underlying etiology (inherited or acquired) as well as the extent of subcutaneous adipose tissue [1,2] and is shown in Figure 2.2-1.

Figure 2.2-1: Classification of Lipodystrophy



Garg A. *N Engl J Med*. 2004;350:1220-1234; Chan JL, et al. Endocr Pract . 2010;16:310-323; Garg A. *Am J Med*. 2000;108:143-52

Clinical diagnosis of LD is largely based on patient medical history and physical examination, and is informed by genetic markers and blood tests, including adiponectin and leptin levels. Because LD is extremely rare these patients are often diagnosed and managed by specialists in a few centers in the United States. A multidisciplinary approach is required for ongoing care, which can include hepatologists, cardiologists, nephrologists, and rheumatologists.

Since LD syndromes are so rare, accurate epidemiology estimates are not available. According to a recent review, approximately 1350 (approximately 1000 patients with inherited forms of LD and 350 patients with acquired forms excluding HIV-related LD) cases have been reported in the literature.[3] The prevalence of genetic forms of LD in the general population was estimated at less than one in a million based on an assumption that only one fourth of patients are reported.[3] However, the actual rate of diagnosis (vs. reporting) is unknown, and it is possible that the disease may be under-diagnosed, particularly partial forms of LD which affect subcutaneous adipose tissue in distinct anatomical regions of the body.

Even though there is considerable heterogeneity in LD syndromes with variable presentations and different mechanisms by which fat loss can occur, all share the unifying feature of loss of SC adipose tissue. The loss of adipose tissue results in metabolic abnormalities that are typically more severe than those associated with obesity.[1]

The leptin deficiency due to the loss of adipose tissue in this disease state also contributes to hyperphagia, which further exacerbates the metabolic abnormalities as patients are driven to

ingest more calories than they are able to use or store. As a result, LD is often associated with a range of severe and progressive metabolic abnormalities (e.g. hypertriglyceridemia, insulin resistance, diabetes and/or liver dysfunction)[4,7,8] that can result in a high prevalence of end-organ complications and co-morbidities.

2.3 Morbidity and Mortality Associated with LD Syndromes

The metabolic and hepatic complications of LD are serious, and often contribute prematurely to substantial morbidity and mortality.

Severe insulin resistance and diabetes is a common feature of LD syndromes. Ectopic TG deposition in the liver and skeletal muscle leads to a syndrome of severe insulin resistance. Eventual β-cell failure in the setting of this severe insulin resistance leads to diabetes mellitus,[2]which in some patients may not be adequately controlled despite treatment with very high doses of insulin (several hundreds to even thousands of units per day).[8] The frequent occurrence of diabetes in LD patients is highlighted in one of the inherited forms of LD, in which a much higher incidence of diabetes was noted in patients with familial partial lipodystrophy (FPL) compared to unaffected family members, e.g., ~ 50% in 1 report of 23 patients compared to no diabetes in unaffected family controls.[9]

Diabetes often occurs at an early age, as reported in a case series and literature review of 79 patients with AGL, 78% of whom had diabetes with age of onset ranging from a mean of 16 to 19 years old.[4] This experience highlights the frequent occurrence of diabetes as well as the early age of onset of diabetes in LD patients.

Hypertriglyceridemia is the characteristic lipid abnormality in LD patients. In reviews of patients with generalized LD, 82% of 79 AGL patients,[5] and 100% of 70 CGL patients[10] had hypertriglyceridemia. In studies of patients with FPL, 78% had dyslipidemia compared to 12% of family controls,[9] and mean fasting TG levels were approximately 3 to 4 times higher than family controls.[9,11] The degree of hypertriglyceridemia in LD can be severe, as highlighted in 1 case report of a patient who developed LD between the ages of 10 and 12 years with hypertriglyceridemia at 13 years that became refractory to lipid-lowering agents and required weekly plasma exchange therapy.[12] This patient eventually became the first LD patient treated with metreleptin at the National Institutes of Health (NIH).

One of the primary organ complications of hypertriglyceridemia, especially when TG levels exceed 500 mg/dL, is acute and recurrent pancreatitis,[13]which can be life threatening with a mortality rate over 40% when accompanied by complications like infection or organ failure.[14] In 1 study of 39 patients with FPL, 15% (all female) had a history of acute pancreatitis compared to none of the family control subjects.[11] Thus, there is clear evidence for morbidity and mortality at a young age due to pancreatitis in LD patients, further reinforced by case reports of a 23-year-old patient with APL who had episodes of pancreatitis starting at age 8 with 14 episodes requiring hospitalization over 15 years,[15] a 13-year-old patient with APL who presented with acute

pancreatitis and died from infection,[16] and 2 patients with FPL who died at the age of 29 from acute pancreatitis.[11,17]

Ectopic lipid deposition in the liver can result in severe hepatic steatosis which can lead to steatohepatitis, which is characterized by fat accumulation, cellular injury, and inflammation in the liver and is one of the most common causes of cirrhosis in LD patients.[18,19,20] In a review of 79 patients with AGL, 84% had hepatomegaly, and 60% had elevated ALT levels, mostly due to hepatic steatosis or steatohepatitis, and a few patients had evidence of autoimmune hepatitis.[4] Some patients developed cirrhosis with portal hypertension and esophageal varices. Similarly, 60% of 255 patients with APL were reported to have hepatomegaly,[5] and hepatic steatosis was found on imaging in 15 out of 18 patients with FPL.[21] In a cohort of 10 LD patients (4 with CGL, 4 with AGL, 2 with FPL, ranging in age from 17-67 years) who had evidence of hepatic steatosis on imaging, liver biopsy demonstrated steatohepatitis in 8 (80%) of the patients.[22] The consequences of hepatic steatohepatitis can be significant, especially when occurring at an early age, as demonstrated in a 19-year-old patient with AGL who died while awaiting liver transplant.[23]

Chronic renal disease in LD patients may occur due to long-standing, suboptimally controlled diabetes or due to other renal diseases associated with LD. A high incidence of proteinuric nephropathies has been reported in a cohort study of 25 patients with generalized LD (18 with CGL, 7 with AGL, with median age 18 years), with 60% having macroalbuminuria (>300 mg/24 hours), and 20% having nephrotic range proteinuria (>3.5 g/24 hours).[24] In this cohort, 1 patient had typical diabetic nodular glomerulosclerosis at autopsy (age 30 at death), and 6 patients (ages 13 to 35 years) underwent renal biopsy due to excessive proteinuria (2.2 to 15.8 g/24 hours), 4 of whom were diagnosed with focal segmental glomerulosclerosis (FSGS) and 2 with membranoproliferative glomerulonephritis (MPGN).[24] APL has also been associated with MPGN, with an estimated prevalence of ~22% based on a review of over 250 patients with APL.[5] These nephropathies can rapidly progress to end stage renal disease (~40% of patients with MPGN within 10 years).[25] Evidence for rapid renal deterioration is provided by case reports in the literature, including a 35-year-old patient with FPL who died of cerebral hemorrhage 9 months after starting dialysis,[26] and a 12-year-old boy with APL who developed renal failure requiring dialysis within several weeks of presenting with proteinuria.[27] Several cases have been reported in the literature of LD patients undergoing renal transplantation, with the relatively young age at transplant being notable. Transplant was successful in a 45-year-old patient with CGL,[28] but a 26-year-old patient with CGL developed massive lipid deposits in the renal tubules with necrosis and hemorrhage 1 month after transplant and died 2 months later.[29] Three patients with APL (ages 21-31 years) underwent renal transplant for MPGN,[30,31,32] 2 of whom required a second transplant due to rejection[32] or recurrent disease.[31] Thus, the morbidity and mortality associated with renal disease in LD patients is substantial.

Given that the metabolic abnormalities associated with LD can be difficult to control and often occur at a young age, macrovascular complications are commonly observed and can occur at a relatively young age. In a review of 79 patients with AGL, premature coronary heart disease was noted in 4 female patients (age range: 31 to 55 years) with 2 requiring coronary artery bypass graft surgery at the ages of 42 and 55.[4] Cardiovascular complications have also been reported with increased prevalence and earlier onset in patients with FPL, with atherosclerotic vascular disease occurring in 45-53% of affected females compared with 0 to 15% of unaffected family controls in 2 separate studies.[9,11] The rate of hospitalization for coronary artery bypass graft in patients with FPL was approximately 3 orders of magnitude higher than that in the general population for the same age range and gender (1 in 3.75 vs. 1 in 7350).[9]

Cardiomyopathy (primarily hypertrophic) has been reported to occur with high frequency in patients with generalized LD (CGL or AGL), with one study noting that 55% of 44 patients (31 CGL, 13 AGL, mean age 23 years) had left ventricular hypertrophy.[33] Three of these patients died, including 1 patient who underwent heart transplantation at age 19 and died 1 year later from non-compliance with the transplant regimen, and another patient who died unexpectedly at age 30 (presumably from a cardiac arrhythmia) in the setting of pneumonia.[33] In a study of 70 patients with CGL from a variety of ethnicities and geographies, 24 to 33% of patients had hypertrophic cardiomyopathy.[10] While the exact cause of this cardiomyopathy is not known, it has been speculated that "lipotoxicity" secondary to persistent hypertriglyceridemia and ectopic fat deposition and/or a potential relationship to extreme insulin resistance may play a role.[33] Patients with FPL related to LMNA mutation (Dunnigan type) can also have cardiomyopathy, which can present as premature onset of congestive heart failure, dilated cardiomyopathy, and conduction system disturbances.[34]

Given that acquired forms of LD have been linked to an underlying autoimmune process, APL and AGL have been associated with a number of auto-immune diseases. These include juvenile dermatomyositis,[35] systemic lupus erythematosus,[5] and autoimmune hepatitis[23] as some of the more frequently reported ones, as well as Hashimoto thyroiditis, rheumatoid arthritis, vasculitis, undifferentiated connective tissue disease, Sjögren syndrome, scleroderma, celiac disease, idiopathic thrombocytopenic purpura, hemolytic anemia, dermatitis herpetiformis, and vitiligo, with some patients having multiple autoimmune disorders.[4,5] Chronic urticaria and angioedema have also been described.[5]

In the main published reviews of LD syndromes, non-lymphoid malignancies are not described as a common co-morbidity associated with LD syndromes which is to be anticipated given both the rarity of LD and the rarity of these types of malignancy. The few cases of malignancy described in the literature are all hematologic malignancies in patients with acquired forms of LD and/or other autoimmune diseases: 2 case reports of peripheral T-cell lymphoma in patients with lipoatrophy (in a generalized fashion)[36] or AGL,[37] a case report of an acute lymphoblastic leukemia in a patient with APL and acanthosis nigricans,[38] and a case report of a Hodgkin's lymphoma in a patient with generalized LD and scleroderma.[39]

Although robust epidemiological and natural history data are not available for this extremely rare condition, the case reports referenced above provide insights into the overall morbidity and mortality associated with LD. Based on the severe and chronic diseases that patients with LD develop, often at a young age, it is not surprising that premature mortality has been observed. A case series of 70 patients with CGL provides additional evidence for this; 8 (11%) of whom died prematurely (age: 19 months to 35 years) due to cardiac failure (N 4), renal failure (N 2), hepatic failure (N 1), and unknown (N 1). In addition, 2 patients with CGL were reported to have died while awaiting metreleptin at the NIH, 1 patient who had diabetes since age 10 years, developed nephrotic range proteinuria, and died at age 30 of sudden cardiac death, and another patient age 31 years who died of idiopathic pulmonary fibrosis.[22]

Not all LD patients will present with the same metabolic and/or hepatic abnormalities e.g., some patients may primarily have insulin resistance and diabetes mellitus with relatively little change in circulating triglyceride levels while others may present primarily with hypertriglyceridemia with normal glucose levels, or present with hepatic steatosis and/or steatohepatitis before overt diabetes or hypertriglyceridemia has developed.

Current anti-diabetic and lipid-lowering medications such as metformin, sulfonylureas, insulin, fibrates, and statins are usually ineffective due in part to the severity of metabolic abnormalities in LD patients. This treatment refractoriness is probably also a consequence of the underlying absence or partial deficiency of adipose tissue depots to store TGs and glucose, coupled with the lack of sufficient leptin and potentially other adipose mediators like adiponectin to direct appropriate storage and partitioning of ingested calories in the remaining non-adipose, insulin sensitive organs. In many LD patients, the use of insulin, even at high doses, is ineffective due to severe insulin resistance. Finally, there are no effective therapies approved to treat hepatic steatosis or steatohepatitis. Thus, there is a clear unmet need for effective treatments for LD.

2.4 Leptin Physiology

Leptin is a naturally occurring, adipocyte-derived hormone and an important regulator of energy homeostasis, including metabolism of key ingested fuels such as glucose, fatty acids and TGs, and other diverse physiological functions.[40,41] Circulating levels of leptin closely correlate with the amount of SC adipose mass present.[42] Although leptin was originally thought to be an "anti-obesity" hormone given its discovery as the missing gene product in the leptin-deficient ob/ob mouse model of obesity, the administration of recombinant human leptin (metreleptin) caused only minimal, if any, weight loss in individuals with general obesity and high circulating endogenous leptin levels.[43] Subsequent research clarified that the main physiological role of leptin is rather as a mediator of the adaptation to energy deficit or starvation.[44,45]

Although general obesity is associated with leptin resistance, and thus metreleptin treatment in obese subjects did not result in clinically meaningful weight loss, metreleptin treatment in patients with morbid obesity due to leptin gene mutations results in dramatic weight loss. These extremely rare individuals with congenital leptin deficiency due to homozygous mutations in the leptin gene (ob/ob genotype) have a phenotype of insatiable appetite and severe obesity in early childhood, along with neuroendocrine and immunological defects. Administration of metreleptin

to these individuals results in substantial reductions in body weight and correction of other neuroendocrine and immune defects.[46,47]

The loss of specific subcutaneous adipose depots in patients with LD is associated with reduced ability to produce leptin, and therefore leptin deficiency. Adipose mass is the primary determinant of leptin levels, but there is significant variability in individual leptin levels even when accounting for SC adipose mass[42]. In addition to fat mass, gender is an important determinant of leptin levels. Women have higher leptin levels than men, even after accounting for differences in body fat.[48] A number of other factors regulate circulating leptin levels, including nutritional status (fasting or overfeeding), glucose, insulin glucocorticoids, estrogen, cytokines, catecholamines, thyroid hormones, and androgens.[49] Patients with generalized LD typically have very low leptin levels, consistent with a very low fat mass. Patients with partial LD, where SC adipose tissue loss is less extensive, have more variable, although still relatively low, leptin levels.[7]

2.4.1 Mechanism of Action of Leptin and Rationale for Development of Metreleptin for Lipodystrophy

Lipodystrophy is characterized by leptin deficiency, secondary to loss of adipose tissue, rather than due to a primary defect in producing leptin as occurs in congenital leptin deficiency due to a leptin gene mutation. Studies in mouse models of LD provide strong evidence that leptin deficiency plays a key role in the pathophysiology of the metabolic abnormalities associated with LD. Thus, the rationale for metreleptin treatment of LD patients is analogous to other hormone deficiency conditions that can be corrected with replacement or supplementation of the deficient hormone.

The loss of adipose tissue results in metabolic abnormalities that are typically more severe than those associated with obesity.[1] The lack of normal depots for storage of ingested fats results in hypertriglyceridemia, which is often severe (with serum TG often elevated in the range of 1000's) and not readily amenable to treatment with conventional lipid-lowering agents such as fibrates. In addition, due to reduced or absent storage capacity, deposition of TG occurs in ectopic locations such as liver and muscle. Triglyceride deposition in these insulin-sensitive tissues, which are not intended to be organs of fuel storage other than for glycogen leads to extreme insulin resistance and ultimately to hyperglycemia that is difficult to control, even with high doses of insulin. The accumulation of TG in the liver can cause marked hepatomegaly and steatohepatitis. With the loss of adipose tissue, levels of the adipocyte-secreted hormone leptin are low.[7] The relative leptin deficiency observed in this disease state also contributes to hyperphagia (another feature of this disorder), which further exacerbates the metabolic abnormalities as patients are driven to ingest more.

Mouse models of LD have provided valuable insights into the pathophysiology of this condition. Two such models include the transgenic A-ZIP/F-1 mouse that inactivates a transcription factor important in adipocyte growth and differentiation, and the nSREBP-1c mouse that constitutively

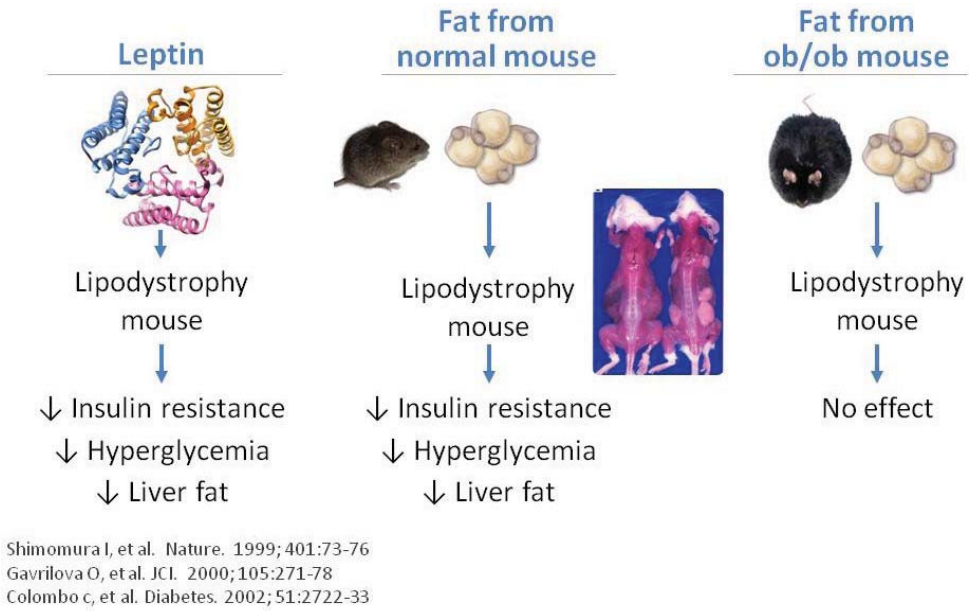
activates a gene that regulates fatty acid biosynthesis. Both the A-ZIP/F-1 and nSREBP-1c lack white adipose tissue and recapitulate the metabolic abnormalities observed in humans with LD.

Leptin deficiency leads to hyperglycemia, hyperinsulinemia, and insulin resistance in lipodystrophic mice.[50] The exact mechanism by which this occurs is unknown but may relate to suppression of insulin secretion by leptin, insulin over secretion resulting from hyperphagia, or insulin resistance in adipose tissue. Once initiated, hyperinsulinemia leads to down-regulation of IRS-2 (resulting in increased gluconeognesis) but also increases nSREBP-1c (resulting in increased fatty acid synthesis). The increased glucose production drives further insulin secretion, contributing to a vicious cycle of continued hyperglycemia and hypertriglyceridemia. Correcting leptin deficiency in this setting can help to break this vicious cycle and ameliorate the metabolic abnormalities.

Ectopic lipid deposition in tissues such as liver and skeletal muscle leads to insulin resistance, via the accumulation of fatty acid metabolites like long-chain acyl-CoA, diacylglycerol, and ceramides that impair insulin signaling.[51] In addition to a potential effect of leptin to decrease fatty acid synthesis as described above by reducing nSREBP-1c, leptin may also increase fatty acid oxidation in the liver, thus decreasing hepatic steatosis and improving insulin resistance. The mechanism by which leptin increases fatty acid oxidation has recently been elucidated in the A-ZIP/F-1 LD mouse model, in which administration of leptin was shown to activate hepatic AMPK (which potently stimulates fatty acid oxidation) through the central and sympathetic nervous systems.[52]

Administration of leptin in the nSREBP-1c LD mouse model reverses insulin resistance and diabetes,[53]demonstrating that leptin deficiency due to absent or deficient SC adipose tissue is a key component in the pathophysiology of the metabolic abnormalities of LD. This effect is not mimicked by chronic food restriction, indicating that leptin modulates insulin sensitivity, helping to direct fuel metabolism and appropriately partition TG and glucose disposal independently of its effect on food intake. Surgical transplantation of adipose tissue from wild-type mouse into A-ZIP/F-1 mice reverses diabetes,[54] but surgical transplantation of adipose tissue from ob/ob mice lacking the ability to produce leptin does not improve glucose homeostasis,[55] providing further support that leptin deficiency plays a major role in causing the metabolic complications of LD (Figure 2.4.1-1).

Figure 2.4.1-1: Use of Recombinant Leptin Therapy in a Lipodystrophic Mouse Model



The observation that LD is a state of leptin deficiency as well as the nonclinical findings discussed above formed the scientific basis for testing the hypothesis that metreleptin (a recombinant analogue of human leptin) may improve the insulin resistance, diabetes hypertriglyceridemia, and/or aberrant hepatic TG deposition (hepatic steatosis) in patients with LD.

2.5 Regulatory History and Background

A brief chronological summary of key scientific regulatory and clinical development milestones for metreleptin is provided below:

- 1994: Leptin discovered by Rockefeller University through positional cloning in the ob/ob mouse, and Amgen Inc. licensed the rights to develop leptin
- 1995 to 2000: NIH pilot study (NIH Study 991265) in LD patients initiated.
- 2001: Based on the results of the NIH pilot study in LD, Amgen was granted fast track designation of metreleptin for the treatment of metabolic disorders associated with LD.
- 2002: NIH initiates long term study (NIH Study 20010769) in LD patients.
- 2006: Amylin Pharmaceuticals Inc. licenses metreleptin from Amgen and initiates an obesity program of metreleptin and pramlintide combination therapy (3 clinical studies and an extension study). This program was terminated due to lack of clinically meaningful benefit in obesity.
- 2007: Data presented to FDA for 29 patients treated with metreleptin for up to 5 years (as of a cutoff date of July 2005). The FDA confirmed the sufficiency of the nonclinical and clinical data package for a filing.
- 2008: Treatment IND filed for Study FHA101 as a means to expand access to metreleptin for patients with metabolic disorders associated with LD until regulatory submission.

- July 2010: Agency accepts Sponsor's proposal to submit the BLA as a rolling submission in order to expedite availability of orphan drug for a patient population with high unmet medical need.
- December 2010: Updated efficacy and safety data based on a data cut in July 2009 (N 55 in NIH studies) and (N 10 in Study FHA101) submitted, which began the rolling BLA submission.
- May 2012: FDA requested updated safety and efficacy data from the NIH (N 72 based on a data cut of July 2011) and FHA101 (N 28 based on a data cut of March 2012)
- March 2013: Sponsor completes filing of metreleptin BLA.

3 NONCLINICAL DEVELOPMENT

The nonclinical safety profile of metreleptin has been assessed in a comprehensive toxicology program that included a battery of safety pharmacology, single- and repeated-dose toxicity, genotoxicity, developmental and reproductive toxicity, local tolerance, and special toxicology studies in rodents and non-rodents.

Repeated-dose toxicology studies have been conducted with metreleptin in mice, rats, dogs, and monkeys, including chronic 6-month Good Laboratory Practice (GLP)-compliant studies in mice and dogs using daily SC injection, the intended clinical route of administration. Mice and Beagle dogs were selected as the respective rodent and non-rodent species for the metreleptin pivotal toxicology program because both species are widely accepted models for use in toxicology studies, and the metreleptin pharmacological data indicate that both mice and dogs are biologically responsive to the effects of metreleptin. In addition, the sequence homology of leptin (82% to 91%) and the leptin receptor (81% to 97%) in different animal species (mice, rats, rabbits, Beagle dogs, Rhesus monkeys) is fairly well conserved compared to humans.

Overall, metreleptin was well tolerated across species (mice, rats, rabbits, dogs, and monkeys). The toxicity profile was primarily characterized by reversible exaggerated pharmacodynamic effects including significant reductions in food consumption and body weight leading to secondary effects such as fat and thymic atrophy, and clinical pathology changes (decreases in cholesterol, triglycerides, phospholipids, free fatty acids, glucose, serum amylase, β-hydroxybutyrate [mice], total protein, albumin and globulin) all of which were considered to be related to the expected pharmacological effect of metreleptin. Mortalities observed in both the mouse and dog chronic studies were generally associated with high doses leading to severe food consumption suppression and weight loss and mostly occurred following specific study procedures (overnight fasting, blood collections) in mice. Based on the study results, the no-observed-adverse-effect-level (NOAEL) was established at 1 mg/kg/day in mice and 1.5 mg/kg/day in dogs when metreleptin was administered by daily SC injection for 6 consecutive months.

In both mice and dogs, local subcutaneous injection site reactions were also observed, as would be expected following repeated subcutaneous dosing of a human recombinant protein to animals. The metreleptin-related effects observed were reversible following at least 28 days of recovery (treatment-free period). Dedicated local tolerance studies in rats and rabbits confirmed

granulomatous responses at high metreleptin concentrations (≥ 20 mg/mL), whereas only minimal to mild injection reactions were observed at lower clinically relevant concentrations (≤ 5 mg/mL). Safety pharmacology results, using doses of metreleptin up to 30 mg/kg in mice and rats and 25 mg/kg in dogs, did not indicate any significant risks for the central nervous, cardiovascular, respiratory, renal, and gastrointestinal systems in animals.

Pharmacokinetic (PK) and toxicokinetic (TK) data derived from short-term (≤ 28 days) treatment in animals using doses up to 30 mg/kg/day in mice and 5 mg/kg/day in dogs showed that exposure was generally dose-proportional with no apparent sex-related differences in all species tested. The metreleptin clearance was similar to the glomerular filtration rate in mice and dogs, suggesting that the renal clearance by filtration may be the main pathway of elimination. In addition, exposure generally tended to increase following repeated daily dosing possibly due to anti-metreleptin antibodies (ADAs) that could have decreased the renal elimination of metreleptin by binding to the protein and decreasing clearance. However, limited PK and TK assessments were conducted in the pivotal toxicology studies due to bioanalytical assay interference from ADAs in all animal species tested. Radioimmunoassay analysis of serum samples from mice, rats, and dogs indicated the presence of ADAs in most animals following subcutaneous administration of metreleptin for period greater than approximately 14 days. While the development of ADAs may have correlated with increased exposure to metreleptin over time, there was no apparent impact on metreleptin pharmacodynamic activity in any species tested. There was also no evidence of any adverse effects of ADA formation in mice, rats, or dogs as study results did not show any increased injection site reactions, hypersensitivity, autoimmune (dermal reactions, arthritis, anemia or aplasias, mucocutaneous reactions) or antibody/antigen complex-related pathology (arthritis, nephropathies).

The carcinogenic potential of metreleptin was assessed by conducting a full battery of genotoxicity assays and extensive examination (including proliferating cell nuclear antigen [PCNA] immunohistochemistry, a marker of cell proliferation) of tissues collected from repeated dose toxicity studies in mice (doses up to 30 mg/kg/day; representing 7- to 14-fold the maximum clinical dose) and dogs (doses up to 5 mg/kg/day; representing 8- to 17-fold the maximum clinical dose). In accordance with ICH S6 guidance document (preclinical safety assessment for biotechnology-derived products), rodent 2-year bioassays were not deemed warranted for the intended indication. Metreleptin was not genotoxic in in vitro or in vivo studies and no drug-related proliferative (preneoplastic or neoplastic) lesions, including in any lymphoid organs/tissues, were noted at any dose of metreleptin in the 6-month toxicology studies in mice and dogs. These results, in conjunction with the absence of any effect on cellular proliferation (measured by specific staining for PCNA in adrenal, brain, colon, duodenum, kidney, liver, lungs, mammary gland, pancreas, pituitary, spleen, stomach, testes and thyroid) support the absence of a carcinogenic signal for metreleptin in animals. These data served as the basis for discussions and agreement with the FDA on the adequacy of the existing nonclinical safety program to support the BLA.

A complete developmental and reproductive toxicity program was conducted to assess the effects of metreleptin on reproductive performance and fertility in mice, embryofetal development in

mice and rabbits, and peri- and post-natal development in mice using doses up to 30 mg/kg/day. The studies consistently demonstrated exaggerated pharmacodynamic effects (e.g., reduced maternal body weights and food consumption), and the results did not identify any direct metreleptin effects on fertility, embryo-fetal, and pre- and post-natal development. In pre- and post-natal studies in mice, decreased birth weight, survival, and delayed maturation were observed in neonates but were considered likely secondary to maternal effects including severe food consumption suppression leading to decreased body weight gain during pregnancy (approximately -20% to -32% compared to controls) and dystocia at delivery. Increased metreleptin exposure was noted in pregnant mice (2 to 3 times at 10 mg/kg) compared to non-pregnant animals likely related to an increased volume of distribution during pregnancy. Fetal serum and amniotic fluid drug concentrations assessments showed that fetal exposure to metreleptin was minimal (≤ 0.4% [serum] and ≤ 1.3% [amniotic fluid] the maternal exposure).

Overall, the safety profile of metreleptin determined in this comprehensive nonclinical safety program adequately supports the clinical use of metreleptin for the proposed indication and patient population.

4 CLINICAL PHARMACOLOGY AND DOSING EVALUATIONS

4.1 Clinical Pharmacokinetics

The PK of metreleptin (representing the total of metreleptin + endogenous leptin) has been quantified with data from 2 clinical trials in healthy subjects. This assessment was part of the prior clinical development program of metreleptin monotherapy in obesity and provides general knowledge on the PK of metreleptin. The PK of metreleptin in LD patients, albeit with limited data, suggests that the PK properties of metreleptin are consistent between LD patients and healthy subjects after correcting for differences in renal function (with higher estimated glomerular filtration rate in LD patients compared to healthy subjects). It should also be noted that leptin levels are affected by development of binding antibodies to metreleptin, with a relationship observed between higher metreleptin exposure and higher antibody titer. The higher total metreleptin levels observed during metreleptin treatment with development of binding antibodies presumably represents reduced clearance of antibody-bound metreleptin. There are limited data on the PK of metreleptin in LD patients, and therefore no formal exposure-response modeling has been performed.

Absorption

The absolute bioavailability of metreleptin in studies of healthy adult subjects evaluating intravenous (IV) and SC dosing was approximately 94% using doses of 0.3 to 3.0 mg/kg/day. Peak serum metreleptin concentration (C_{max}) occurred approximately 4.0 hours after administration of single SC doses ranging from 0.1 to 0.3 mg/kg. Area under the concentration-time curves (AUCs) in this same population and across the same dose range were dose-proportional, ranging from 1,180 ± 267 to 3,657 ± 781 ng•h/mL (mean ± SD).

In the NIH studies in LD patients, increases in mean ±SE fasting serum metreleptin concentrations (from baseline leptin concentrations of 2.8 ± 0.39 ng/mL) to metreleptin concentrations of 18.6 ± 2.7 ng/mL were observed at the first milestone visit (Month 4)

following metreleptin treatment and maintained throughout the entire treatment period. Mean fasting serum metreleptin concentrations in the 20-ng/mL to 30-ng/mL range were generally achieved over the entire treatment period.

Distribution

In studies of healthy adult subjects, the apparent volume of distribution of metreleptin was approximately 4 to 5 times plasma volume; the volumes ([Vz [mL/kg] [mean ± SD]) were 370 ± 184, 398 ± 92, and 463 ± 116 for 0.3, 1.0 and 3.0 mg/kg/day doses, respectively.

Metabolism and Elimination

Leptin is cleared intact via a renal mechanism. Nonclinical data suggest renal clearance is the major route of metreleptin elimination, with no apparent contribution of systemic metabolism or degradation.

Following multiple IV injections of metreleptin in healthy adults, terminal half-life values among the different dosing regimens (0.3-3.0 mg/kg/day) appeared to be similar. Serum metreleptin concentrations declined mono-exponentially, with a half-life of approximately 3.3 to 3.4 hours and a total body clearance (CL) of 80.0 to 96.0 mL/kg/h.

Drug Interactions

No formal drug-drug interaction (DDI) studies have been conducted in LD patients. The small sample size of patients included in the LD program prevented a useful assessment of drug interaction potential, and the potential for development of anti-leptin antibodies in healthy volunteers precluded the conduct of dedicated DDI studies. A dose adjustment of concomitant insulin secretagogue or insulin may be necessary in some patients to minimize the risk of hypoglycemia. Caution should be taken when adding metreleptin therapy to patients already on insulin or insulin secretagogues.

Special Populations

No formal studies have been conducted to evaluate the PK of metreleptin in special populations with LD. Because metreleptin is primarily cleared by the kidney, the PK of metreleptin may be altered in subjects with renal impairment, but hepatic dysfunction is not expected to affect the PK of metreleptin. Since the dose of metreleptin is titrated on the basis of clinical response, any potential subpopulation PK differences have been managed through individualized dose adjustment.

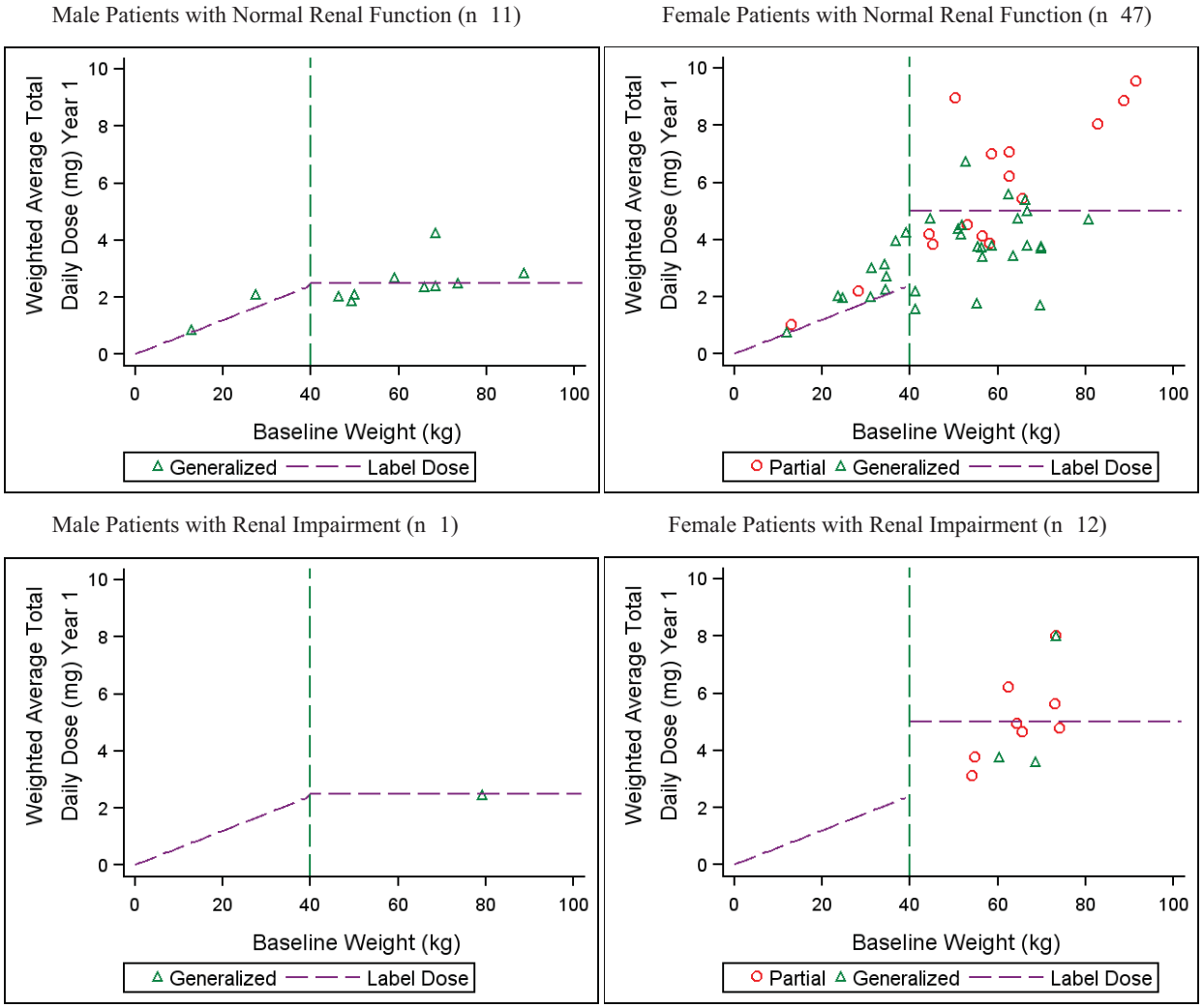
Renal Impairment

Since LD is a very rare disorder it was not feasible to assess the impact of renal impairment on the PK of metreleptin in patients with LD in a controlled fashion with adequate representation across varying degrees of renal impairment. In addition, the usefulness of a typical single-dose renal impairment study in subjects without LD would be limited. The clinical significance of renal impairment on the PK of metreleptin at steady state is confounded by the high frequency of development of binding (non-neutralizing) antibodies to metreleptin, which interferes with renal elimination of metreleptin. Since over 90% of patients receiving metreleptin develop antibodies

to metreleptin, it would be necessary to conduct a clinical trial with daily SC injections in non-LD subjects with varying degrees of renal impairment for at least two months (the approximate time needed to reach peak antibody titers) in order to assess the clinical relevance of renal impairment in conjunction with antibody formation for metreleptin.

Evaluation of the weighted average daily dose during the first year of treatment in LD patients in the NIH clinical studies indicated that similar doses were used in LD patients with renal impairment as for patients with normal renal function (Figure 4.1-1). Even though limited data are available, there were no observable trends for adverse events (AEs) for patients with renal impairment versus patients with normal renal function. This supports the recommendation that the starting dose of metreleptin does not require adjustment in the presence of impaired renal function. In addition, the starting dose of metreleptin can be subsequently adjusted up or down based on the patient's clinical response to metreleptin therapy (refer to Section 4.2, Dosing).

Figure 4.1-1: Average Weighted Daily Dose for Year 1 vs. Body Weight for NIH Patients with Normal Renal Function and Renal Impairment



4.2 Dosing

The dosing strategy for metreleptin evolved from targeting therapeutic leptin levels to focusing on clinical response. When the NIH study started in 2000, dosing was weight-based (0.06 to 0.08 mg/kg/day) with females receiving approximately twice the dose than males with the strategy of achieving concentrations similar to those observed in healthy subjects. The total daily dose was divided equally and administered twice daily with step-wise dose titration occurring over the first 2 months of the study.

Subsequent dose adjustments were made based on clinical response (e.g., insufficient efficacy requiring an increase in dose or excessive weight loss requiring a dose reduction). Although dosing has remained weight-based for the NIH study, the dosing has evolved over the course of the protocol to minimal initial dose titration, as it became apparent that there were no major safety considerations with the initial low starting dose and with once (QD) or twice daily (BID) dosing since once daily dosing facilitated compliance with therapy and appeared to be generally

as effective as twice-daily dosing. A comparison of TG and HbA1c response for NIH patients receiving either BID, QD, transitioning from BID to QD or transitioning from QD to BID dosing suggests no differences in HbA1c and TG response.

Although the 2 NIH pivotal studies used weight-based dosing, the Sponsor proposes a fixed starting dose for patients over 40 kg based on detailed analyses of the actual doses used in these clinical studies. This recommendation simplifies dosing and minimizes the potential for dosing errors. A weight-based dose is proposed for patients weighing ≤ 40 kg, which is intended to capture the majority of pediatric patients, especially younger pediatric patients for whom weight-based dosing is more appropriate.

The recommended metreleptin starting dose as shown in Table 4.2-1 is based on the actual doses used in the NIH studies during the first year of treatment. In patients weighing ≤ 40 kg body weight, the starting dose is calculated based on body weight and gender. In patients weighing > 40 kg a starting dose of 5 mg and 2.5 mg (for female and male LD patients, respectively) is recommended. However, based on clinical response (e.g., inadequate metabolic control or excessive weight loss or tolerability issues), the starting dose in all patients can be adjusted in increments or decrements of:

0.02 mg/kg for patients weighing ≤ 40 kg

1.25 to 2.5 mg for patients weighing > 40 kg

Table 4.2-1: Daily Dosing Recommendations for Metreleptin Therapy for Patients With LD

Body Weight	Gender	Daily Recommended Metreleptin Dose
≤ 40 kg	Male Female	0.06 mg/kg (0.012 mL/kg)
> 40 kg	Male	2.5 mg (0.5 mL)
	Female	5.0 mg (1.0 mL)

The clinical data from the NIH studies to support the proposed dosing recommendation are as follows:

1) Metreleptin appears to have a broad therapeutic window with a dose-response relationship supporting a fixed starting dose with dose adjustments based on clinical response.
2) Although the NIH pivotal studies utilized a weight-based dosing approach with calculation of doses based on the patient's body weight, additional analysis of metreleptin dosing in relation to key efficacy parameters (HbA1c and TG concentrations) provides support for fixed dosing.
3) Female patients received higher doses than male patients, as is consistent with gender dimorphism for normal adipose tissue distribution. Thus, a different fixed dose is proposed for patients > 40 kg based on gender (2.5 mg QD for men and 5 mg QD for women), irrespective of LD type. In the event of inadequate metabolic control, dose adjustments of 1.25 (males) to 2.5 mg (females) are proposed. Recommended magnitude of dose

adjustments is based on experience from dose titration in the NIH study. For consistency, the same increments are proposed for decreasing the dose for tolerability issues or excessive weight loss.

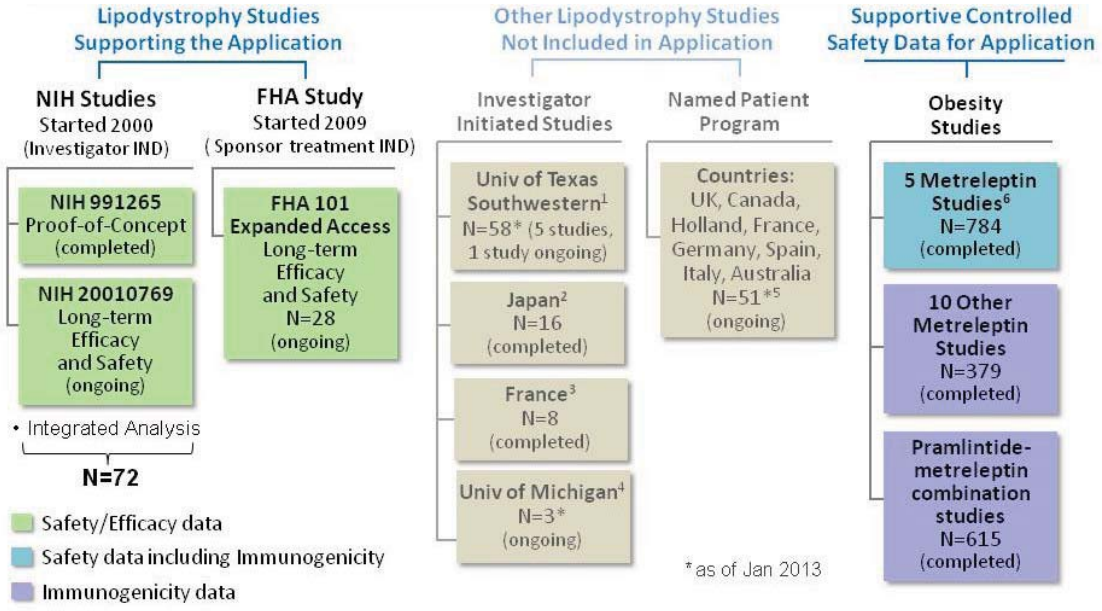
4) A weight-based (mg/kg of body weight) dosing regimen (0.06 mg/kg) is proposed for patients weighing ≤ 40 kg, which is consistent with common clinical practice for pediatric patients. The proposed dose of 0.06 mg/kg was chosen as this was the target dose specified in the protocol for patients ≥ 5 years to 10 years of age. In the event of inadequate metabolic control or tolerability issues, a change in dose increment of 0.02 mg/kg is proposed, which is consistent with the NIH protocol. The basis for proposing a ≤ 40 kg cut-off is the objective to capture the majority of pediatric patients, especially younger pediatric patients for whom weight-based dosing may be more appropriate. In addition, there is a precedent for a differential dosing approach for adult and pediatric patients (fixed vs. weight-based) and using a cut-off of 40 kg.[56]
5) Dosing of metreleptin in the NIH studies has evolved over time from a BID to a QD dosing regimen that does not compromise efficacy.
6) In clinical studies, a limited number of patients received doses greater than 0.13 mg/kg for patients weighing ≤ 40 kg and 10 mg per day for patients weighing > 40 kg, and therefore, there are insufficient data to recommend doses beyond these ranges, thus these represent the maximum recommended doses by weight stratum.

5 CLINICAL DEVELOPMENT PROGRAM

5.1 Overview

Figure 5.1-1 shows all studies conducted worldwide using metreleptin. The pivotal studies supporting the efficacy and safety of metreleptin in LD patients are the NIH studies conducted at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Clinical center under an Investigator IND. In addition, data from Study FHA101, a Sponsor-initiated open-label expanded access study, provide important supportive safety and efficacy data in LD patients.

Figure 5.1-1: Metreleptin Clinical Program



[1] A. Garg – Enrolled across 5 separate studies including 2 open-label extension studies
[2] K. Nakao; [3] C. Levy-Marchal; [4] E. Oral, Non-alcoholic steatohepatitis (NASH) in lipodystrophy patients is primary endpoint
[5] Does not include lipodystrophy patients who initiated metreleptin in NIH Studies
[6] Integrated Safety Summary (ISS): Placebo-controlled, subcutaneous administration, at least 12 weeks in duration

Metreleptin has also been studied in LD patients under other investigator-initiated studies that are not included in the BLA. The FDA agreed with the Sponsor that data from the NIH studies with the largest cohort of patients treated at a single center was sufficient for a BLA, with supporting efficacy and safety data from Study FHA101. Metreleptin monotherapy and a combination of metreleptin and pramlintide have also been studied as a potential treatment for obesity. Although from a different patient population, these completed programs in obese patients provide valuable supportive placebo controlled safety data from a larger number of subjects.

Only studies that support the BLA application for metreleptin use in LD patients (i.e., NIH studies, Study FHA101, and supportive safety data from placebo controlled metreleptin obesity studies) will be discussed in this briefing document. In total, the BLA is based on efficacy and safety data in 100 patients with this very rare condition, which is estimated to affect only a few thousand patients worldwide. In addition, clinical data from a larger number of subjects in the metreleptin obesity studies provide relevant placebo-controlled safety data.

The metreleptin clinical development program for LD consists of a single completed study (NIH 991265) and 2 ongoing studies (NIH 20010769 and FHA101) in LD patients. These studies were conducted in order to evaluate the safety and efficacy of metreleptin in treating the metabolic disorders associated with LD as well as to expand access to metreleptin to patients in need.

These studies were not originally designed to support a marketing application. However, given the clinical findings from the NIH studies in these patients with few therapeutic options and high unmet clinical need, the FDA agreed to a registration pathway that could form the basis of a marketing application. Data for the BLA (focused on metabolic endpoints) were captured

retrospectively by the Sponsor from the NIH studies and recorded into an industry-standard database using standardized conventions.

Details of each study are presented below:

- **NIH Study 991265** was the first clinical study of metreleptin in patients with LD. This was an open-label investigator-sponsored study to determine the safety and efficacy of metreleptin administration (initially 4 months, extended to 8 months, and then extended beyond 8 months in a few patients) in LD patients over the age of 14. Nine patients were enrolled in this study.

Based on the efficacy observed in this initial pilot study of metreleptin in LD patients, Study 20010769, a long-term study of metreleptin treatment was initiated. The NIH IRB deemed that a placebo control was not ethically justifiable given the patient population at risk for serious life threatening metabolic complications and the marked improvements with metreleptin demonstrated in the initial pilot study (NIH Study 991265).

- **NIH Study 20010769** is an ongoing open-label, investigator-sponsored study to determine the long term safety and efficacy of metreleptin administration in the treatment of LD with broader inclusion criteria.

  This study allowed enrollment of younger patients (initially >5 years of age, amended in 2009 to ≥ 6 months of age) and patients with less severe leptin deficiency than in NIH Study 991265.

Between these 2 NIH studies, a total of 72 patients (7 who participated in both studies; 2 who participated only in Study 991265, and 63 who participated only in NIH Study 2001769) have been exposed to metreleptin as of the 11 July 2011 data cutoff.

Study FHA101: The Sponsor submitted a treatment IND in May 2008 in order to expand access to metreleptin for patients in need (Study FHA101). Data based on a data cut of Mar 2012 from 28 patients enrolled at 3 sites (the majority at the University of Michigan) provide important supplemental safety and efficacy data in this patient population.

- **Study FHA101** This is an ongoing study enrolling patients ≥ 5 years of age with LD and associated diabetes mellitus and/or hypertriglyceridemia. Given that the primary objective of the protocol was to expand access to metreleptin for this patient population, this study has no placebo control or comparator group.

NIH studies 991265/20010769 were conducted at NIH under an Investigational New Drug Application (IND) filed by Dr. Philip Gorden and cross-referenced to Amylin Pharmaceuticals LLC (a wholly-owned subsidiary of Bristol-Myers Squibb) IND 50,259. The sponsorship of the IND, originally submitted by Amgen, was transferred to Amylin Pharmaceuticals in 2006. At the time of transfer of sponsorship, Study 991265 was completed and Study 20010769 was ongoing.

The key inclusion/exclusion criteria for the NIH studies and Study FHA101 are shown in Table 5.1-1

Table 5.1-1: Key Inclusion/Exclusion Criteria for NIH studies and Study FHA101 (Analysis Population)

	NIH	FHA
Inclusion Criteria		
Clinical diagnosis of lipodystrophy	■	■
Males and females	■	■
Age	≥6 months	≥5 years
Leptin levels (ng/mL)*	<6, <8, and <12	Not Applicable
At least 1 of the metabolic abnormalities:		
Diabetes mellitus	■	■
Hypertriglyceridemia >200 mg/dL	■	■
Fasting insulin level >30 µU/mL	■	Not Applicable
Exclusion Criteria		
HIV-infection	■	■
Infectious liver disease	■	■
Acquired LD with hematologic abnormalities	■	■

* Leptin levels are age and gender dependent. In the year 2008, the 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.
Acquired LD with hematological abnormalities was added as an exclusion criterion after 2 cases of peripheral T-cell lymphoma were reported in the NIH study. These 2 patients had significant hematologic abnormalities and are discussed in detail in Section 7.3.1.

The disposition of LD patients for the NIH studies and Study FHA101 based on data cuts supporting the BLA is shown in Table 5.1-2.

Table 5.1-2: Patient Disposition for the NIH Studies and Study FHA101 (Analysis Population)

	NIH	FHA
Initiated Metreleptin	**N=72**	**N=28**
Active	**52**	**20**
Discontinued	**20**	**8**
Transferred to Named Patient Program	6	–
Non-compliance	4	–
Death	3	2
Adverse Events	2	1
Withdrew Consent	–	3
Lost to Follow Up	–	1
Ineligibility Determined	2	–
Investigator Decision	–	1
Other*	3	–

*Includes 1 patient who completed NIH 991265 but did not enroll in NIH 20010769

5.2 Lipodystrophy Analysis Populations

5.2.1 Populations Supporting Efficacy

The pivotal efficacy data for the LD program are based on 72 patients treated with metreleptin in 2 open-label, investigator-sponsored NIH studies (completed Study 991265 and ongoing Study 20010769, integrated into a single analysis). Data from 28 patients enrolled in study FHA101 provide important supplemental efficacy data in this patient population.

Given that the primary objective of the FHA101 study was to expand access to metreleptin to LD patients with diabetes mellitus and/or hypertriglyceridemia, the data collected are more limited than for the NIH pivotal studies (focusing on key efficacy parameters collected as part of routine clinical assessments). In addition, this study has a smaller number of patients enrolled compared to the NIH studies (N 28 vs. N 72) with a shorter duration of exposure. FHA101 had study visits every 3 months during the initial year of treatment with metreleptin, whereas data are summarized at 4 month intervals for the NIH study. There were also differences in study conduct that had an impact on efficacy analyses, e.g. more proactive down-titration of concomitant insulin use in the FHA study (to avoid hypoglycemia) vs. concomitant medications were generally kept stable during the first year of treatment in the NIH study, excepting for adjustments needed for risk of hypoglycemia. For these reasons, data from Study FHA101 were not integrated with NIH studies.

Analysis Population: The Analysis population, consisting of all enrolled patients who received at least 1 dose of metreleptin during these LD clinical studies, was used for analyses of efficacy data. All 72 patients enrolled in the NIH studies and all 28 patients enrolled in Study FHA101 qualified.

Observed Case Data: All efficacy endpoints are presented for the Analysis population without imputation of missing data (i.e., Analysis Population but without imputation also referred to as the Observed Case analysis).

Unless otherwise specified, tables and figures in this briefing document present observed case data. Thus, the number of patients at each time point for each variable (e.g., HbA1c and TG) may vary based on the availability of data at specific time points for each patient. There were data collection limitations to the NIH data in that not all patients contribute data to each time point. The main reasons are: 1) the patient was not in the study long enough to have that visit as of the BLA data cut, 2) the patient had an early discontinuation (including death), 3) the patient missed the visit, or 4) the visit fell outside of the pre-specified visit window.

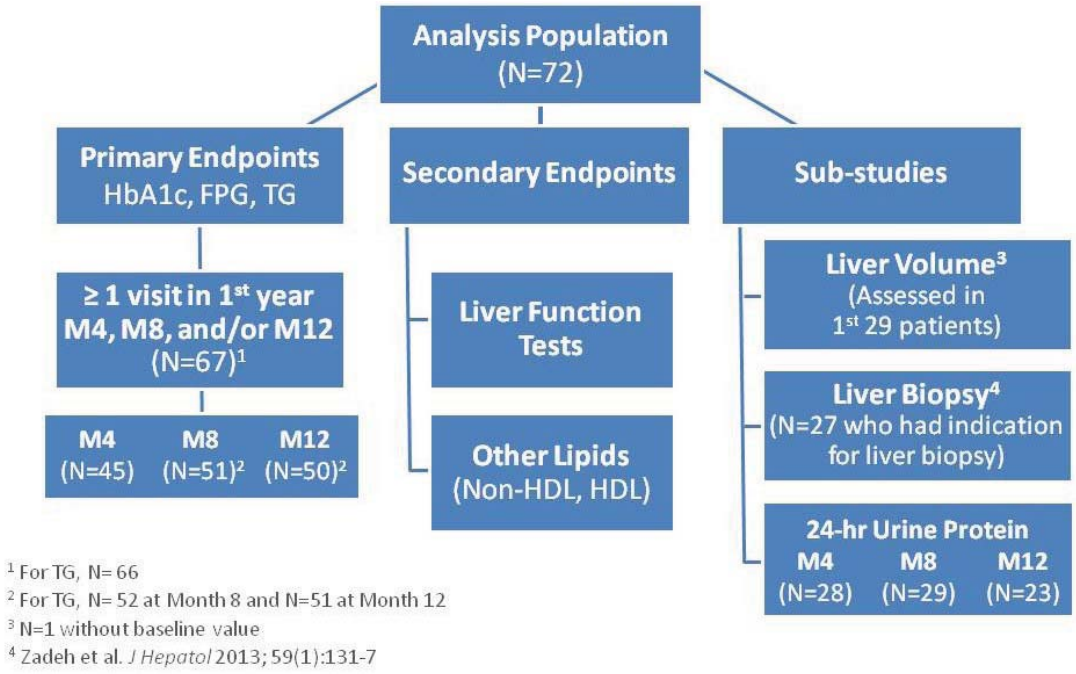
The number of patients supporting the primary efficacy assessments at Months 4, 8 and 12 as well as secondary endpoints and sub-studies are shown in Figure 5.2.1-1.

As with the NIH studies, key efficacy endpoints (HbA1c, TG, ALT, and AST) are presented for the Analysis Population without imputation of missing data (i.e., Observed Case).

Complete Set Population: HbA1c and TG data are also summarized for patients with complete data through a certain time period (e.g., patients who completed at least 3 years of metreleptin treatment and who had measurements at Baseline, Month 4, Month 8, Year 1, Year 2, and

Year 3). Specifically, this analysis addresses the major deficiency of the observed case summaries in that the same cohort of patients is summarized over time.

Figure 5.2.1-1: Endpoints and Available Data for NIH Studies



Sub-Study Populations:

A number of assessments, including data demonstrating meaningful improvements in hepatomegaly and hepatic steatosis/steatohepatitis, were performed on patients from sub studies of the Analysis Population (Figure 5.2.1-1).

- **Liver Volume:** In the NIH studies, the first 29 patients enrolled had liver volume assessments. Further details regarding these sub studies are provided in Section 6.3.5 (Liver Endpoints).
- **Liver Biopsy:** Twenty-seven patients had paired liver biopsies (at baseline prior to metreleptin and after metreleptin treatment) (published data, not in database). Further details regarding these sub studies are provided in Section 6.3.5 (Liver Endpoints).
- **Food intake:** Data on food intake from a subset of 8 patients from the NIH studies is presented (published data, not captured in database). Further details regarding this sub study are provided in Section 6.3.9 (Food Intake).
- **24-hour Urine Data:** Initially, 24-hour urine data was collected for all patients in the NIH studies; over time, it was collected only in patients with abnormal 24-hr urine data at baseline (e.g., proteinuria).

5.2.2 Lipodystrophy Populations Supporting Safety and Immunogenicity

The safety data are based on the Analysis population of 72 LD patients treated with metreleptin in the NIH studies, integrated into a single analysis and 28 LD patients from Study FHA101 as a separate analysis (Table 5.2.2-1).

For the NIH studies, safety was assessed by evaluation of data for adverse events (AEs), deaths, serious adverse events (SAEs), AEs leading to withdrawal, hematology, chemistry, urinalysis, and 24-hour urine creatinine, protein, and albumin measurements; and measurement of vital signs (blood pressure and heart rate), body weight, and antibodies to metreleptin. In Study FHA101, all deaths, SAEs as well as AEs that were judged by the investigator to be clinically significant and/or related to metreleptin were assessed. In addition standard laboratory tests, vital signs, body weight and antibodies to metreleptin were collected.

Deaths for the LD program are based on data submitted in the 4-Month Safety Update (4-MSU). The 4-MSU (using a data cut of Jan 2013 for both the NIH studies and Study FHA101) includes an additional 25 patients (18 in NIH and 7 in FHA101) compared to the BLA data cuts.

In the NIH studies, 39 of 72 patients were pediatric patients, therefore AEs for the pediatric vs. adult population; as well growth and pubertal development in pediatric patients were assessed. There were too few pediatric patients (3 of 28) in Study FHA101 for meaningful safety comparisons.

In order to provide an overall assessment of potential risks of metreleptin treatment to certain AEs (e.g., cases of malignancies and neutralizing antibody activity to metreleptin), the Sponsor has made efforts to solicit key safety data from other compassionate use and investigator-initiated LD studies that are not a part of the BLA.

Assessment of the impact of neutralizing activity to metreleptin and of antibodies to metreleptin on safety and efficacy were assessed in the NIH studies as well as Study FHA101. In the NIH studies, 55 patients had antibody status assessed.

Table 5.2.2-1: Overview of Study Population Supporting Analysis of Safety and Immunogenicity (Analysis Population)

	NIH Studies (N = 72)	Study FHA101 (N = 28)
General Safety Assessments[a]: Analysis Population	72	28
Immunogenicity Population	55[b]	22[c]
General Safety Assessments, including Growth and Pubertal Development : Pediatric Population	39	3

[a] Deaths are based on the 4-Month Safety Update data cut (N=90, NIH and N=35, FHA101)

[b] Samples were assayed retrospectively for antibody assessment by the Sponsor. Antibody status was not assessed in the remaining 17 of the 72 patients due to lack of availability of archived samples.

[c] The 6 patients for whom antibody data were not available include: 3 patients who discontinued from the study before Month 3, the first time point for antibody sample collection and 3 patients enrolled at 2 sites that operated under a clinical practice setting without any research assessments.

5.2.3 Other Populations Providing Supporting Safety Data

5.2.3.1 Metreleptin Monotherapy for Obesity

In addition to clinical experience with metreleptin in LD, metreleptin was administered to over 1,100 subjects in 15 clinical studies conducted as part of a clinical development program for metreleptin monotherapy in obesity (Table 5.2.3.2-1). In these studies, daily doses up to 30 mg were administered. Although overweight and obese subjects (otherwise healthy or with type 2 diabetes) represent a different patient population from LD patients, the administration of metreleptin in a much larger number of individuals than could be studied within the limited LD population provides valuable supplementary information on the safety of metreleptin, particularly for events that are common. In addition, the majority of the longer-term trials in overweight and obese subjects were placebo controlled, which can provide useful context for the evaluation of the possible relatedness of AEs to metreleptin administration.

Data from 5 of these Phase 2 studies conducted in overweight and obese subjects (3 studies in obese subjects, 2 studies in obese subjects with type 2 diabetes mellitus) involving at least 12 weeks of metreleptin treatment were integrated to provide supporting safety data (5-study ISS). In these 5 studies, 784 subjects were exposed to metreleptin, and 351 exposed to placebo, with exposure ranging from 1 day up to 42 weeks. Standard safety assessments as well as an analysis of AEs by antibody status were also performed to provide additional information on the safety (including immunogenicity) of metreleptin in obese subjects without LD.

5.2.3.2 Metreleptin in Combination with Pramlintide for Obesity

Metreleptin has also been evaluated in combination with pramlintide for the treatment of obesity in 3 Phase 2 clinical studies and an extension study. A total of 615 subjects were exposed to metreleptin (at least 1 dose of study medication) in these placebo-controlled or comparator-controlled studies. These data provide additional information on immunogenicity of metreleptin in obese subjects without LD.

Table 5.2.3.2-1 provides a summary of studies in obese subjects that provide supporting safety and/or immunogenicity data.

Table 5.2.3.2-1: Metreleptin Obesity Studies Providing Supporting Safety/Immunogenicity Data for the use of Metreleptin in LD

Study	Patient Population	Number of Metreleptin-Treated Patients	Position in BLA	Endpoints Supported
5-study ISS (metreleptin monotherapy)	Obese subjects without LD	784	Supporting	Safety (including immunogenicity)
Other 10 Obesity Studies (metreleptin monotherapy)	Obese subjects without LD	379	Supporting	Immunogenicity
Obesity Program (metreleptin-pramlintide combination)	Obese subjects without LD	615	Supporting	Immunogenicity

5.3 Extent of Exposure to Metreleptin

5.3.1 Extent of Exposure

The extent of exposure for both the NIH Studies and Study FHA101 metreleptin in years is presented in Figure 5.3.1-1.

Table 5.3.1-1: Extent of Exposure for the NIH Studies and Study FHA101 (Analysis Population)

Statistics	NIH Studies			Study FHA101		
	Age <18 y (N = 39)	Age ≥18 y (N = 33)	All (N = 72)	Age ≤18 y (N = 3)	Age >18 y (N = 25)	All (N=28)
Exposure (Years)						
n	39	33	72	3	25	28
Mean (SD)	3.88 (2.961)	3.90 (3.279)	3.89 (3.088)	1.60 (1.169)	1.19 (0.879)	1.24 (0.897)
SE	0.474	0.571	0.364	0.675	0.176	0.170
Median	2.98	2.44	2.71	1.10	1.00	1.03
Min, Max	0.3, 10.9	0.2, 10.6	0.2, 10.9	0.8, 2.9	0.1, 2.9	0.1, 2.9
Total Exposure in Patient Years (PY)	151.2	128.8	280.0	4.8	29.9	34.7

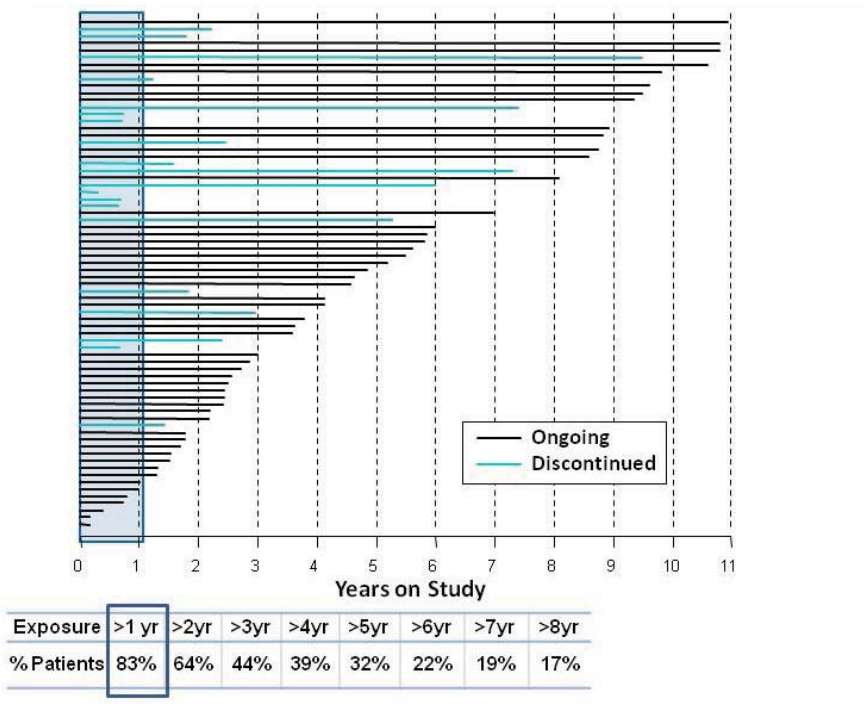
Notes: Dosing gap is defined as missing one or more days of dosing.

NIH Studies

The number and percent of individual patients exposed to metreleptin by year in the NIH studies is presented in Figure 5.3.1-1.

The total exposure to metreleptin (excluding dosing gaps) for 72 NIH patients ranged from 2 months to approximately 11 years, with a median exposure of approximately 2.7 years. A total of 60 patients (83%) had exposures longer than 1 year (Figure 5.3.1-1).

Figure 5.3.1-1: Individual Patient Extent of Exposure to Metreleptin by Year (NIH Studies, Analysis Population)



The total duration of exposure to metreleptin for 28 patients in Study FHA101 ranged from 0.1 years to approximately 3 years, with a median exposure of approximately 1 year. The total exposure to metreleptin in the FHA101 study was 34.6 patient-years. A total of 15 patients had exposure longer than 1 year and 6 patients had exposure of 2 or more years (Figure 5.3.1-1).

5.3.2 Extent of Exposure in the Obese Population Providing Supporting Safety Assessments

Table 5.3.2-1 presents the mean exposure in years and subject-years for subjects in the obese population, which provide additional supporting safety data.

Table 5.3.2-1: Extent of Exposure in the Obese Population (Supportive Controlled Safety Data)

	N on Metreleptin	Current Status	Exposure to Metreleptin: Mean (Years)	Exposure to Metreleptin: Mean (Subject Years)
5 Metreleptin Studies Integrated Safety Summary (ISS): Placebo-controlled, subcutaneous administration, at least 12 weeks in duration	**784**	**Completed**	**0.3**	**217.9**
10 Other Metreleptin Studies	379	Completed	0.3	110.1
Pramlintide-metreleptin combination studies	615	Completed	0.5	296.7
			Total Subject years:	**624.7**

5.4 Patient Demographics and Disease Characteristics

5.4.1 Demographic Characteristics at Baseline

NIH Studies

The overall population was predominantly female with the majority Caucasian. Patient age ranged from 1 to 68 years, and over half of the patients were pediatric (<18 years of age) at the time of enrollment. Approximately two-thirds of the population had generalized LD. The majority of generalized LD patients had a congenital etiology and the majority of partial LD patients were of the familial type (Table 5.4.1-1).

Study FHA101

The overall population was predominantly female and Caucasian. Unlike the NIH studies, the majority of patients were ≥18 years, consistent with the higher proportion of partial LD patients enrolled in this study, who are generally diagnosed later in life compared to patients with generalized LD (Table 5.4.1-1).

Table 5.4.1-1: Demographic Characteristics at Baseline for NIH and FHA101 Studies (Analysis Population)

Parameter	NIH Studies (N=72)	Study FHA101 (N=28)
Gender - n (%)		
Male	12 (16.7)	2 (7.1)
Female	60 (83.3)	26 (92.9)
Race - n (%)		
Caucasian	44 (61.1)	21 (75.0)
Black	9 (12.5)	3 (10.7)
Asian	3 (4.2)	0 (0.0)
Native American	2 (2.8)	1 (3.6)
Hispanic	10 (13.9)	1 (3.6)
Other	4 (5.6)	2 (7.1)
Age (years)		
Mean (SD)	23.7 (16.2)	43.6 (16.8)
Min, Max	1, 68	9, 67
Age Group n (%)		
≤12	17 (23.6)	2 (7.1)
>12 <18	22 (30.6)	1 (3.6)
<18	39 (54.2)	3 (10.7)
≥18	33 (45.8)	25 (89.3)
≥18 ≤65	32 (44.4)	23 (82.1)
>65	1 (1.4)	2 (7.1)
LD Subtype- n (%) [1]		
Acquired Generalized	16 (22.2)	4 (14.3)
Congenital Generalized	32 (44.4)	1 (3.6)
Acquired Partial	4 (5.6)	2 (7.1)
Familial Partial	20 (27.8)	21 (75.0)

Notes: Baseline is defined as the measurements collected on Day 1 (the date of the first dose of metreleptin).

5.4.2 Metabolic Characteristics at Baseline

Baseline metabolic characteristics of the Analysis Population for the NIH studies and Study FHA101 are presented in Table 5.4.2-1.

Table 5.4.2-1: Metabolic Characteristics at Baseline for NIH and FHA101 Studies (Analysis Population)

Parameter	NIH Studies (N=72)	Study FHA101 (N=28)
Body Weight (kg)		
Mean (SD)	56.3 (18.7)	78.1 (22.3)
Median	58.4	80.6
Min, Max	12, 92	36.4, 125.7
Fasting Leptin (ng/mL)[1]		
n	68	22
Mean (SD)	2.6 (2.6)	12.9 (10.7)
Median	1.4	9.2
Min, Max	0.3, 14.1	0.7, 42.9
HbA1c (%)		
n	71	28
Mean (SD)	8.2 (2.2)	8.0 (1.6)
Median	8.4	8.2
Min, Max	4.5, 13.7	5.5, 11.1
HbA1c Categories - n (%)		
< 6 (%)	15 (20.8)	4 (14.3)
≥ 6 < 7 (%)	6 (8.3)	3 (10.7)
≥ 7 < 9 (%)	24 (33.3)	12 (42.9)
≥ 9 (%)	26 (36.1)	9 (32.1)
FPG (mg/dL)		
n	72	27
Mean (SD)	176.7 (88.82)	159.2 (82.7)
Median	155.0	15.9
Min, Max	49, 478	36.0, 420.0
Fasting TG (mg/dL)		
n	71	27
Mean (SD)	1041.3 (2083.1)	823.6 (2039.6)
Median	359.0	257.0
Min, Max	49, 12697	66.0, 10623.0
Fasting TG Categories n (%)		
n	71	27
<200 mg/dL	17 (23.6)	9 (32.1)
≥200 to <350 mg/dL	16 (22.2)	10 (35.7)
≥350 to <500 mg/dL	13 (18.1)	3 (10.7)
≥500 to <1000 mg/dL	9 (12.5)	1 (3.6)
≥1000 mg/dL	16 (22.2)	4 (14.3)
HbA1c and TG Categories n (%)		
HbA1c <6% and Trig <200 mg/dL	7 (9.7)	1 (3.6)
HbA1c <6% and Trig ≥200 mg/dL	8 (11.1)	3 (10.7)
HbA1c ≥6% and Trig <200 mg/dL	10 (13.9)	8 (28.6)
HbA1c ≥6% and Trig ≥200 mg/dL	45 (62.5)	15 (53.6)
HbA1c ≥6% or Trig ≥200 mg/dL	65 (90.3)	27 (96.4)
HbA1c ≥7% or Trig ≥350 mg/dL	61 (84.7)	23 (82.1)

Notes: Baseline is defined as the measurements collected on Day 1 (the date of the first dose of metreleptin).

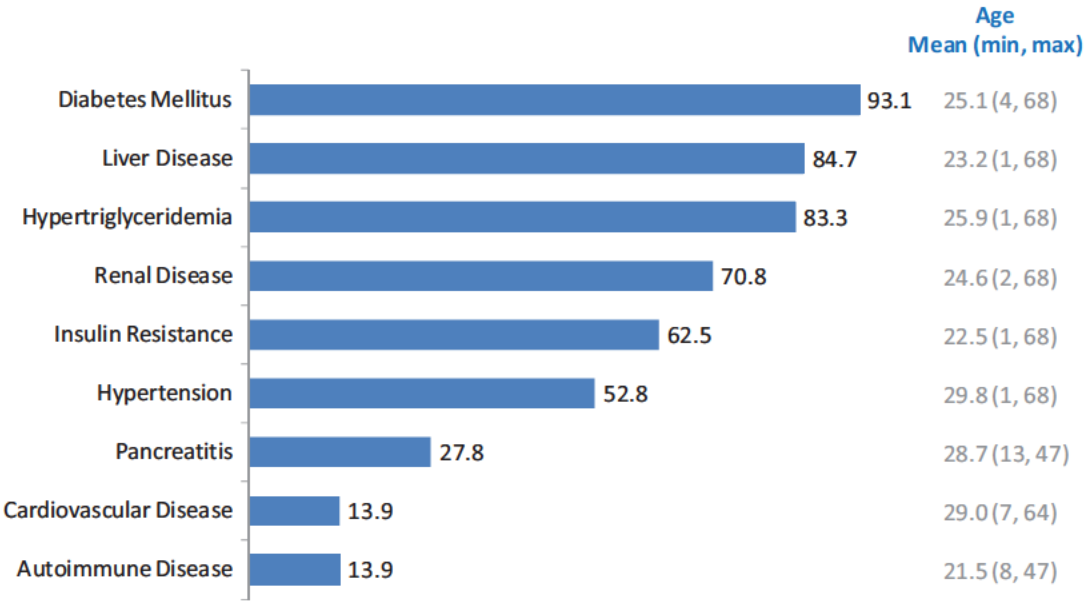
[1] For NIH Studies Lower limit of quantitation (LLOQ) for leptin concentrations is 0.3 ng/mL, thus values below LLOQ are reported as 0.3 ng/mL. For Study FHA101, LLOQ for leptin concentrations is 0.7 ng/mL, thus values below LLOQ are reported as 0.7 ng/mL.

NIH Studies

Baseline Medical Conditions

Figure 5.4.2-1 presents the percentage of patients with selected baseline medical conditions associated with LD. These patients had a high burden of co-morbid conditions associated with LD at baseline. The majority of patients in the NIH studies had a medical history of diabetes, hypertiglyceridemia and/or insulin resistance. A substantial percentage of patients had liver disease at baseline, including hepatic steatosis, steatohepatitis and/or hepatomegaly.

Figure 5.4.2-1: Percentage of Patients with Baseline Medical Conditions (NIH Studies, Analysis Population)



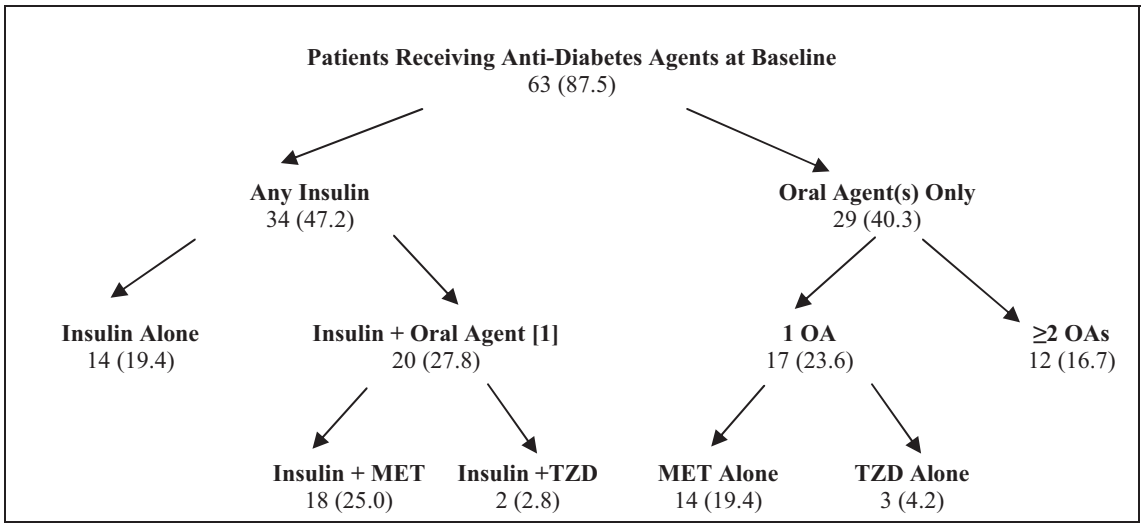
Medical condition as determined by review of medical history terms.

Concomitant Anti-diabetes and Lipid-Lowering Medications at Baseline

Anti-Diabetes Medications

Figure 5.4.2-2 summarizes the proportion of patients in the NIH Studies using concomitant anti-diabetes medications at baseline.

Figure 5.4.2-2: Proportion of Patients Receiving Baseline Anti-Diabetes Concomitant Medications (NIH Studies)



[1] All 20 patients receiving a combination of insulin and oral agent were only on 1 oral agent.

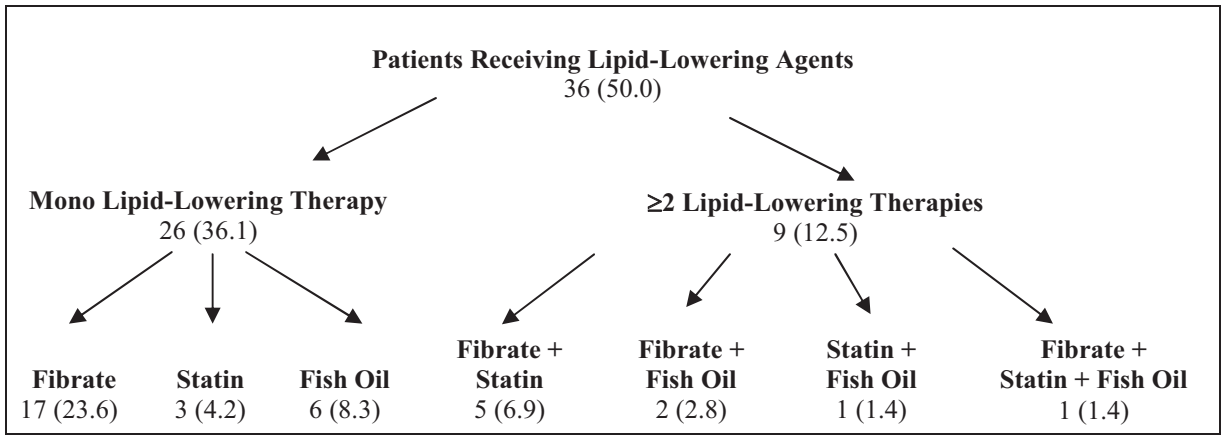
The majority of patients with LD were receiving at least 1 anti-diabetic concomitant medication at baseline. Approximately 50% of patients were receiving insulin alone or in combination with oral agents, with 40% of patients receiving oral agent(s) only. Metformin was the most commonly used oral agent in combination with insulin (25%) or alone (19%). Patients receiving any insulin had a higher mean baseline HbA1c (9.5%) as compared with patients on oral agent(s) alone (7.3%).

Lipid-Lowering Medications

Figure 5.4.2-3 summarizes the proportion of patients in the NIH Studies using concomitant lipid-lowering concomitant medications at baseline.

Half of the LD patients in the NIH studies were receiving at least 1 lipid-lowering concomitant medication at baseline. Approximately 36% of patients were receiving a single lipid-lowering agent, while 13% of patients were receiving 2 or more lipid-lowering therapies. Fibrates were the most commonly used lipid-lowering agent as a monotherapy (24%) or in combination with other therapies (11%). As expected, patients receiving any lipid-lowering agent had more severe baseline TG abnormalities (median 479 mg/dL) as compared with patients not on lipid-lowering therapies (335 mg/dL), with the most pronounced baseline abnormalities observed in patients receiving fibrates alone (471 mg/dL) or in combination (872 mg/dL).

Figure 5.4.2-3: Proportion of Patients Receiving Baseline Lipid-Lowering Concomitant Medications (NIH Studies)



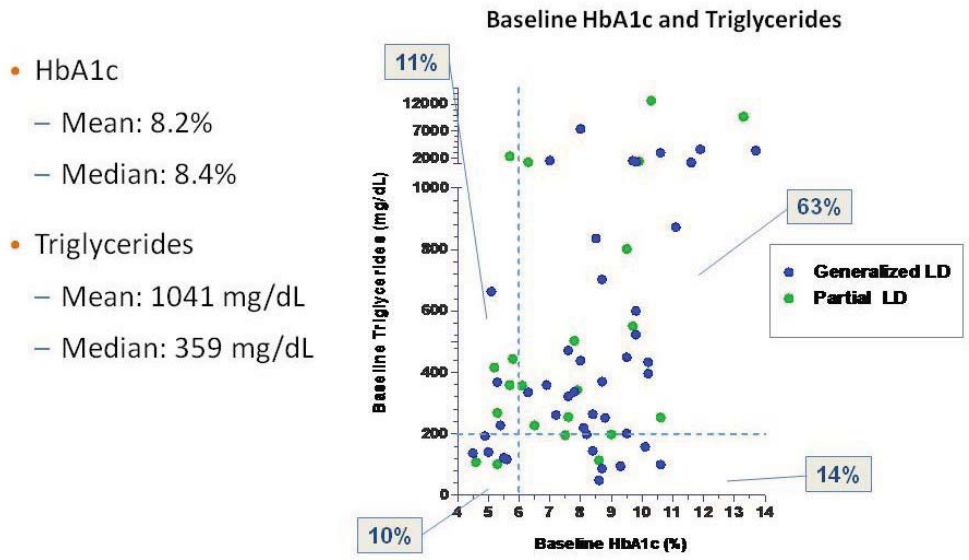
Metabolic Abnormalities: Generalized LD and Partial LD

Despite 88% of the patients being concomitantly treated with insulin and/or oral anti-diabetes medication (Section 5.4.2), the majority of patients had sub-optimal glycemic control (HbA1c ≥6%). Baseline fasting serum TG levels were markedly elevated, with mean and median concentrations of 1,041 mg/dL and 359 mg/dL, respectively. The difference in mean and median levels reflects the non-parametric distribution of TG values among the study population, with approximately 35% of patients having severe hypertriglyceridemia and TG levels over 500 mg/dL at baseline (i.e., a level that increases the risk of acute pancreatitis and that is also often not responsive to treatment with currently available, standard dyslipidemia medications).

Half of the LD patients in NIH studies were receiving at least 1 lipid-lowering concomitant medication at baseline (Section 5.4.2). The majority of these patients had hypertriglyceridemia (≥200 mg/dL). Baseline metabolic abnormalities were heterogeneous among the LD patients with the majority having HbA1c ≥ 6% and TG (≥200 mg/dL) (Table 5.4.2-1).

Figure 5.4.2-4 shows individual patient data for baseline HbA1c and TG by LD subtype, with the dotted lines indicating cut-off values for elevated HbA1c and TG. In the figure, the lower left quadrant shows data for 7 patients (10%) (6 of which were pediatric) with baseline HbA1c <6% and TG <200 mg/dL who were enrolled on the basis of insulin resistance and clinically significant liver disease. The upper right quadrant shows that 63% had both elevated HbA1c and TG. The rest of the patients had only one or the other metabolic abnormality. There was no pattern for severity of metabolic abnormality according to generalized LD vs. partial LD.

Figure 5.4.2-4: Individual Patient Data for Baseline HbA1c and TG by LD Subtype (NIH Studies, Analysis Population)



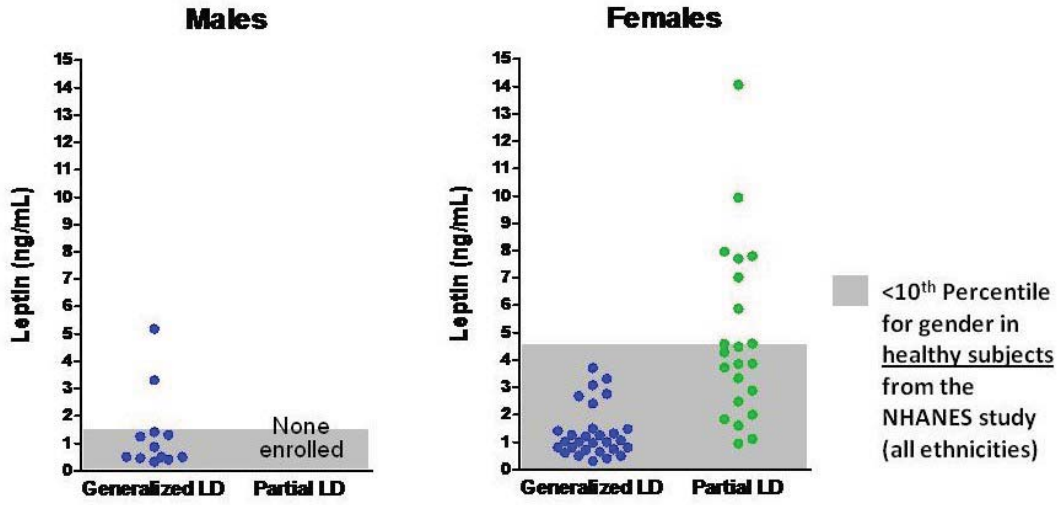
Dotted line indicates cutoff values for elevated HbA1c and TG.

Baseline Leptin levels in the NIH Studies

As mentioned previously, LD patients typically have low leptin levels. During the initial conduct of the NIH studies, the inclusion criteria for the upper limit of baseline leptin levels was 6 ng/mL for females and 4 ng/mL for males. During the course of the studies, the criteria were amended to allow patients with higher leptin levels to be enrolled (12 ng/mL for females and 8 ng/mL for males).

Figure 5.4.2-5 shows individual patient baseline leptin levels by gender and by generalized LD and partial LD. Baseline leptin levels in patients with generalized LD (shown in blue) were low; most measurements were < 5 ng/mL and also less than the 10th percentile for gender in healthy subjects without LD (gray shading).[57] The majority of patients with partial LD (shown in green) were female, and also had leptin levels in a similar low range albeit with more variability. It is important to note that significant baseline metabolic abnormalities (hyperglycemia and/or hypertriglyceridemia) were observed in patients regardless of leptin levels.

Figure 5.4.2-5: Individual Patient Baseline Leptin Levels by Gender and Generalized and Partial LD (NIH Studies, Analysis Population)



<10th percentile, in the 3rd NHANES adapted from (Ruhl CE and Everhart JE, Am J Clin Nutr 2001;74:295–301)
Females N=3366; Males N=2937; Age ≥ 20 years

1 female patient with partial LD was enrolled based on screening visit leptin level of 12 ng/mL, subsequent baseline value was above the protocol inclusion criterion of <12 ng/mL.

Study FHA101

Baseline Medical Conditions

The majority of patients in Study FHA101 had a medical history of diabetes (80.0%) and hypertiglyceridemia (64.0%). A substantial percentage of patients had liver disease at baseline, including hepatic steatosis (76%) and/or hepatomegaly (16%).

Concomitant Anti-diabetes and Lipid-Lowering Medications at Baseline

In Study FHA101, 68% of patients with LD were receiving at least one anti-diabetes concomitant medication at baseline. Approximately 40% of patients were receiving insulin alone or in combination with oral agents, with 18% of patients receiving oral agent(s) only. Metformin was the most commonly used oral agent in combination with insulin (14%).

At baseline, 68% of patients were receiving at least one lipid-lowering concomitant medication. Approximately 50% of patients were receiving a monotherapy, with 14% of patients at least 2 lipid-lowering therapies. Statins were the most commonly used lipid-lowering agent in as a monotherapy (21%) or in combination with other therapies (14%). Patients receiving any lipid-lowering agent had more elevated median baseline TG abnormalities (299 mg/dL) as compared with patients not on lipid-lowering therapies (225 mg/dL), with the most pronounced baseline abnormalities observed in patients receiving fibrates alone (398 mg/dL) or in combination (10,623 mg/dL).

Metabolic Abnormalities: Generalized LD and Partial LD

The majority (86%) of patients had an HbA1c ≥ 6%, three-quarters had an HbA1c ≥ 7%, and a third had poor glycemic control as evidenced by HbA1c ≥ 9%. The majority of patients also had hypertriglyceridemia (TG ≥ 200 mg/dL) (Table 5.4.2-1).

It is important to note that the patient population enrolled in FHA101 (with the majority of patients enrolled at 1 site) was different from the patients enrolled in NIH. Specifically, most of the FHA101 patients had partial LD (mainly FPL), whereas about two-thirds of the NIH patients had generalized LD.

6 CLINICAL EFFICACY

6.1 Introduction

The key efficacy data presented in this section examines the effect of metreleptin treatment from the NIH studies on the following parameters:

- Metabolic Control (HbA1c, FPG, and TG)
- Lipid Endpoints
- Liver endpoints
- Supportive data on the effect of metreleptin on proteinuria and food intake are also provided.

Supportive data of the effect of metreleptin treatment on metabolic control (HbA1c, FPG, and TG) and liver endpoints for Study FHA101, where the majority of patients were diagnosed with partial LD, is also presented.

6.2 Analysis Methods

NIH Studies

Key endpoints were HbA1c, FPG, TG and liver endpoints. The Sponsor focused on analysis of available metabolic data during the first year of treatment to maximize the number of patients with available data for analysis (>80% receiving treatment for >1 year) over a sufficiently long treatment duration to evaluate steady-state responses for metabolic parameters and meaningful changes in liver endpoints.

The Sponsor analysis of data was primarily descriptive, although the change from baseline with 95% confidence intervals were calculated. The Statistical Analysis Plan preserves key aspects of the protocol and its subsequent amendments, such as calculation of the 95% confidence intervals. For transparency, the Sponsor summarized “observed data” for patients with data at a particular visit, as well as at baseline.

Because not all patients have data at each time point and the duration of exposure is quite variable across patients, the data analysis was challenging. The Sponsor has however performed additional analyses using various statistical approaches and found similar results, which provides reassurance of the validity of the key conclusions from this dataset. To ensure that missing data did not impact the findings of metreleptin treatment on metabolic control, the following sensitivity analyses were conducted to supplement the above analyses using the observed cases:

1) Last Observation Carried Forward (LOCF) where subjects who did not have values at Year 1 had their last non-missing post-baseline value up to Day 365 used in the analysis.
2) Mixed-effects model with repeated measures using data at Month 4, 8, and 12 from all subjects, including covariates of age, type of LD, baseline leptin levels, and the baseline values of the response variables.
3) Worst Observation Carried Forward (WOCF) where subjects who did not have values at Year 1 had their maximum non-missing value (indicative of least response) up to Day 365 used in the analysis.

6.3 Efficacy in Patients From NIH Studies

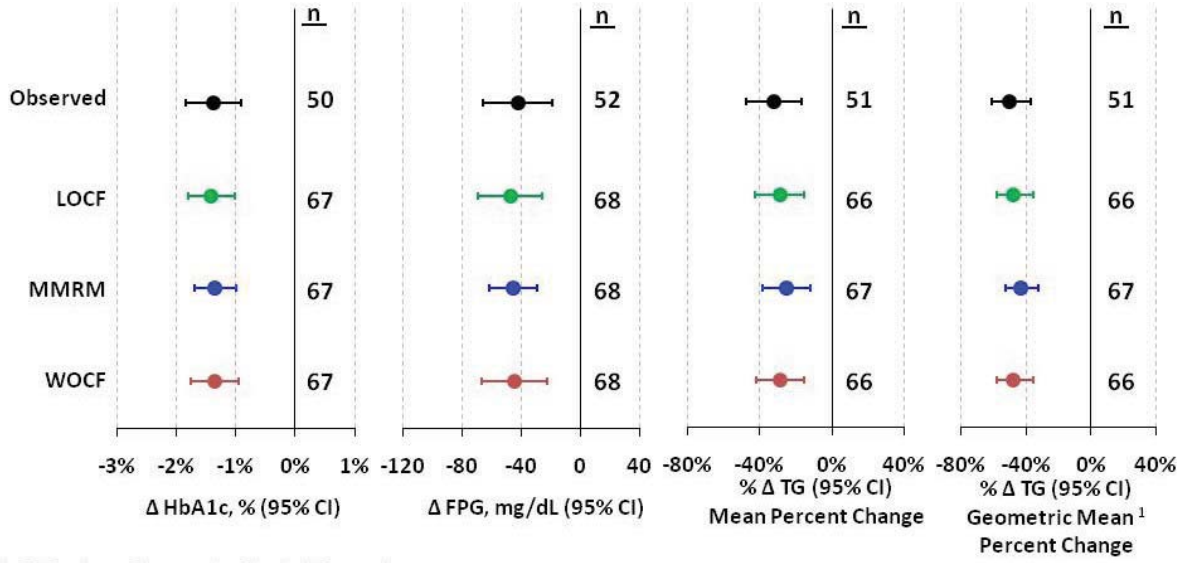
6.3.1 Effects of Metreleptin Treatment on HbA1c, Fasting Plasma Glucose, and Triglycerides

Treatment with metreleptin led to substantial reductions in HbA1c, FPG, and TG that were sustained through the first year, as measured at the Month 12 visit. Reductions in these endpoints were more pronounced in patients with elevated baseline values. Larger HbA1c, FPG, and TG reductions were observed in patients with generalized LD as compared to patients with partial LD, which appeared to correlate with greater elevations in baseline metabolic parameters.

To allow for the impact of missing data, sensitivity analyses were conducted (refer to Section 6.2) using LOCF, mixed-effects model, and worst observation carried forward (WOCF) to supplement the observed cases analyses as described above. An alternate method of analyzing change in TG values was also included to support the original methods and to generate more precise estimates in this limited dataset. In the LD patient population studied in the clinical trials for the BLA, TG values have a heavily skewed distribution (with median of 359 mg/dL, range of 49 to 12,697 mg/dL, and 22% having over 1,000 mg/dL at baseline), and log transformation of the data was performed to more closely resemble a normal distribution prior to the analysis.

There were no meaningful differences in the change from baseline in HbA1c, FPG, and TG at Month 12 for all patients with the 4 analysis methods used (Figure 6.3.1-1). For serum TG, the use of the logarithmic transformation to calculate percent change (geometric mean % change) increased the precision of the estimates with tighter confidence intervals than analyses based on non-transformed data (mean % change).

Figure 6.3.1-1: Point Estimates With 95% Confidence Intervals for the Change From Baseline to Month 12 in HbA1c, FPG, and TG for all Patients Using Sensitivity Analyses (NIH Studies)



LOCF: Last Observation Carried Forward
MMRM: Mixed-Effect Model Repeated Measures
WOCF: Worst Observation Carried Forward
% Δ TG: Mean Percent Change
[1]Change from baseline in the log values was calculated for each subject. For all the sensitivity analyses, once the point estimates and the 95% confidence intervals were calculated they were back transformed to the original scale, the value of 1 was then subtracted from these quantities and then multiplied by 100% (i.e. $(e^{y}-1)*100\%$)

Table 5.3.1-1 summarizes the key efficacy parameters at baseline and the change from baseline at Month 12 for all LD patients broken out into generalized LD and partial LD subgroup categories as well as patient subgroups with elevated baseline values. The reductions in HbA1c, FPG, and TG values were more pronounced in patients with elevated baseline values compared to all patients. Larger reductions in HbA1c, FPG, and fasting TG values were observed in patients with generalized LD as compared to patients with partial LD, which appeared to correspond with greater elevations in HbA1c and TG at baseline. A greater magnitude of response was observed in patients with partial LD who had a baseline HbA1c $\geq$ 7% and in patients with partial LD with a baseline TG $\geq$ 500 mg/dL.

Table 6.3.1-1: Key Efficacy Parameters at Baseline and Month 12 - All Patient with Elevated HbA1c (≥6%, ≥7%, and ≥8%), FPG (≥126 mg/dL), and TG (≥200 mg/dL and ≥500 mg/dL) (NIH Studies, Observed Case Population)

HbA1c (%)	All			Baseline HbA1c ≥6%			Baseline HbA1c ≥7%			Baseline HbA1c ≥8%		
Mean (SE)	n	Baseline [2]	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 ≥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 LD	30	414.5	246.5	21	600.0	432.0				12	1526.5	1117.0
Partial LD	21	357.0	74.0	16	430.0	95.5				7	1237.0	499.0

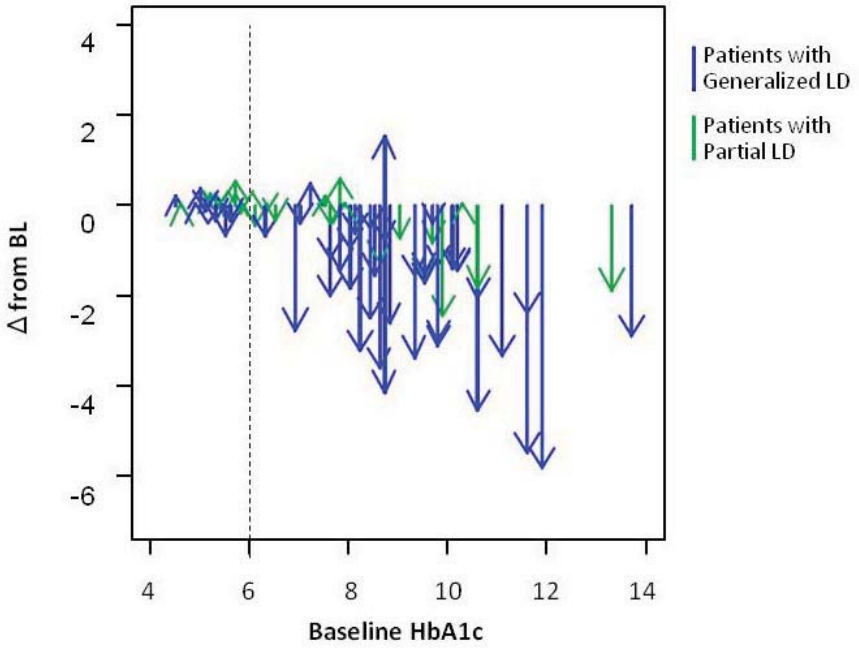
NA not applicable
In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin.

Individual Patient Data on the Effects of Metreleptin on HbA1c and Triglycerides Control

HbA1c

The average change in HbA1c during the first 12 months of metreleptin treatment for each individual patient is presented in Figure 6.3.1-2**.**

Figure 6.3.1-2: Average Change in HbA1c During the First 12 Months of Metreleptin Treatment (NIH Studies, Observed Case Population)



Dashed line denotes the upper limit of normal for HbA1c in this assay

Each arrow represents an individual patient's average change (using all available values through Month 12) in HbA1c and the X-axis display their starting baseline HbA1c. The majority of patients had improvements in HbA1c, especially patients with baseline HbA1c > 6% to the right of the dotted line. The severity of baseline metabolic abnormality appeared to be an important determinant of the magnitude of individual patient responses to treatment. Several patients had quite substantial decreases up to 6% in HbA1c% units.

To the left of the line where HbA1c was normal at baseline, there were minimal changes in individual patient HbA1c values. The larger decreases in HbA1c occurred primarily in patients with generalized LD.

Changes in Concomitant Anti-Diabetes Medications During the First 12 Months of Metreleptin Treatment

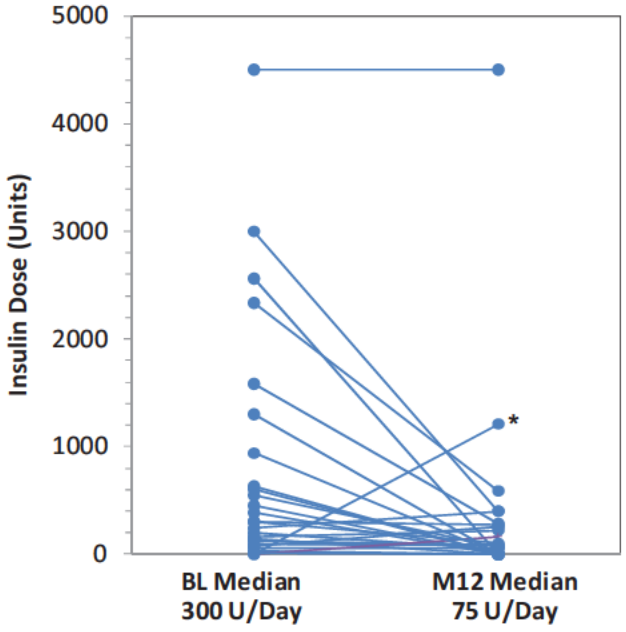
The improvements in HbA1c were particularly notable given that they occurred in the setting of substantial reductions or even discontinuation of the use of diabetes medications, especially insulin, in some patients.

As discussed in Section 5.4.2 (Metabolic Characteristics at Baseline), the majority (87.5%) of patients with LD were receiving at least 1 anti-diabetes concomitant medication at baseline. By Month 12, 23 (43%) patients discontinued or decreased antidiabetic medications. At Month 12, 16 (30%) patients maintained stable doses of their antidiabetic medications.

At baseline, approximately 50% of patients were receiving insulin alone or in combination with oral agents. Of these, data for 26 patients who were on insulin at baseline and reached Month 12 are available. Median total daily insulin doses for these individual patients (N 26) are plotted in Figure 6.3.1-3.

In these 26 patients, there was a reduction in median insulin doses by ~ 75% at Month 12. Eight of these patients were able to discontinue insulin at M12 from a median baseline of 550 U/day, reflecting substantial improvements in insulin sensitivity. One patient, shown at the top of the figure, had no change in insulin use at Month 12, but insulin use progressively decreased afterwards with continued metreleptin treatment.

Figure 6.3.1-3: Individual Patient Median Total Daily Insulin Dose at Baseline and Month 12 After Metreleptin Treatment (NIH Studies, Observed Case Population)



*After the database lock, it was clarified that the one patient with increase from 0 to 1000 u/day from baseline to M12 was actually on 1000 u/day at baseline

Includes patients taking insulin at baseline with data at Month 12 (N=26)

Triglycerides

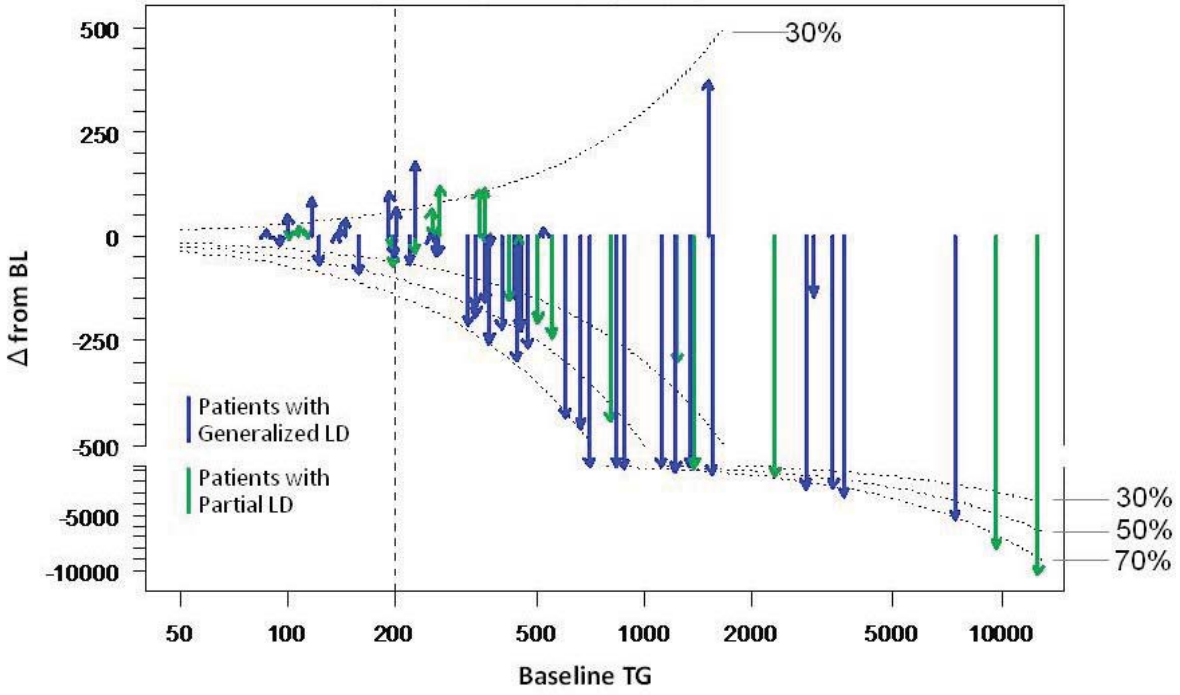
Individual patient data for the geometric mean change in TG during the first 12 months of metreleptin treatment is presented in Figure 6.3.1-4.

Each arrow represents an individual patient's average geometric mean change (using all available values through Month 12) in TG and the X-axis display their starting baseline TG. The majority of patients who had baseline TG levels over ~ 200 mg/dL (to the right of the dotted line), experienced improvement in TGs. The absolute change in TG is shown in Figure 6.3.1-4 with breaks in the Y-axis and different non-linear scales to accommodate the wide range of improvement. The dotted lines curving down represent 30%, 50%, 70% reductions for reference. Although one patient had an increase in TG of 25% from a baseline of 1500 mg/dL this patient was noted to be non-compliant for the first several months.

When baseline TG levels were less elevated, similar numbers of patients had increases compared to decreases in TG but the absolute magnitude of change was relatively small (Figure 6.3.1-4). In contrast, the magnitude of decreases in TG in patients with elevated TG at baseline was quite substantial with some patients having decreases of several 100's up to ~ 10,000 mg/dL. Nine of the 12 patients (75%) with a baseline TG > 1000 mg/dL, a value which places them at risk for pancreatitis, reached TG values substantially below < 1000 mg/dL at Month 12. The median reduction in TG value was 121 mg/dL, median percent reductions of TG were 43%, and mean (± SE) reductions in TG levels were 673 ± 223 mg/dL at Month 12.

Similar proportions of patients in each group had baseline TG values ≥ 1000 mg/dL. Large decreases in TGs were observed in both generalized and partial LD patients with elevated baseline TGs.

Figure 6.3.1-4: Geometric Mean Change in TG in Individual Patients up to 12 Months (NIH Studies, Observed Case Population)



Dotted lines represent 30, 50, and 70% reductions in TG after 12 Months of treatment.
Dashed line denotes diagnostic criteria for hypertriglyceridemia

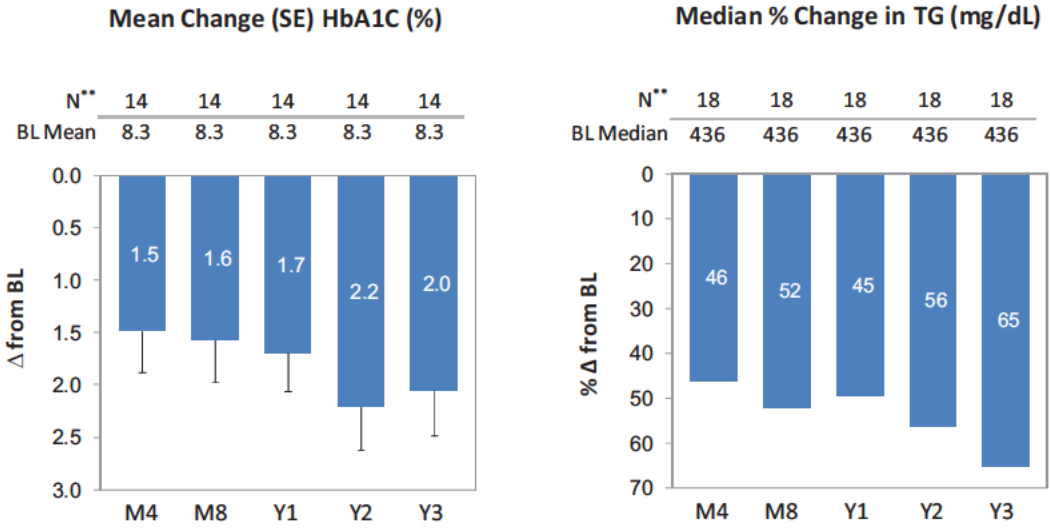
Changes in Concomitant Lipid-Lowering Medications During the First 12 Months of Metreleptin Treatment

Half of the LD patients in NIH studies were receiving at least 1 lipid-lowering concomitant medication at baseline. Given that fibrates are commonly used for lowering TG levels, changes in fibrate monotherapy, fibrates in combination (+ fish oil or + statin), and non-fibrate medications at Month 12 were analyzed. Irrespective of baseline medication category, the majority of patients maintained their lipid-lowering regimen from baseline to Month 12. Most (72%) patients' doses were unchanged at Month 12 with 17% stopping or decreasing their dose.

6.3.2 Long term Effects of Metreleptin Treatment on HbA1c and Triglycerides

The sections above presented data for the Analysis population with observed data, who may not have all received treatment for the entire time period analyzed and/or had missing data points. To address this limitation and provide further insight into the effect of metreleptin on these key efficacy parameters, Figure 6.3.2-1 presents the changes from baseline in HbA1c and fasting TG values for those patients who completed at least 3 years of treatment and had values available for visits at baseline, Month 4, Month 8, Year 1, Year 2, and Year 3 (i.e., 3-year without missing data). Changes from baseline in this population were of comparable magnitude and durability to changes seen in the Observed Case Population.

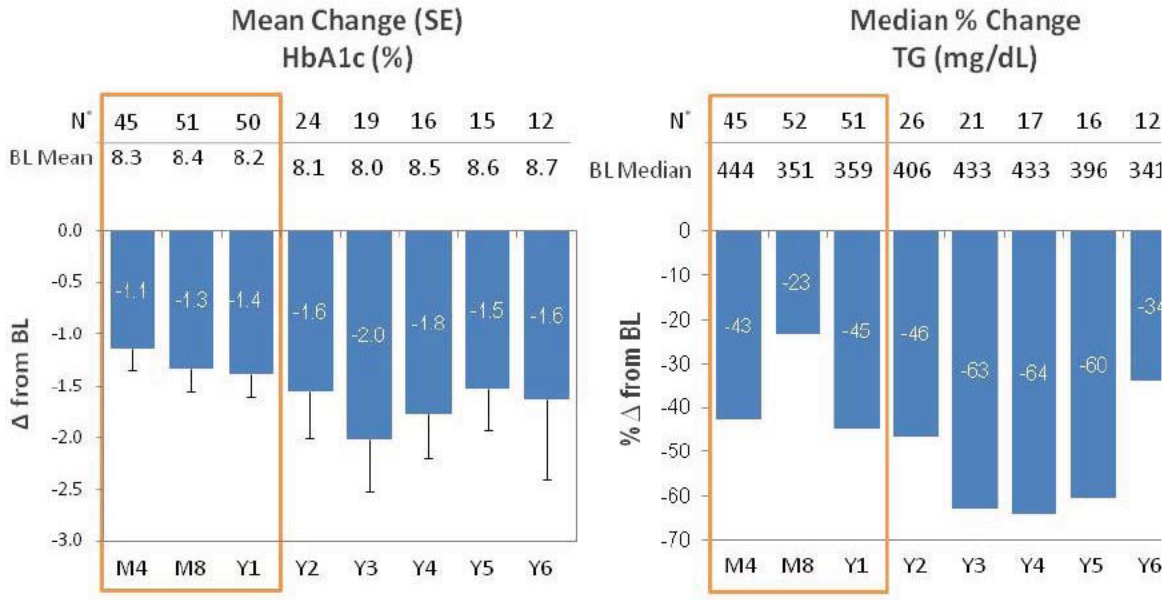
Figure 6.3.2-1: Mean (SE) Change in HbA1c and Median Change in TG From Baseline to Years 1, 2, and 3 (NIH 36-Month Complete Set Population)



N** represents patients that had data at baseline, Month 4, Month 8, Month 12, Month 24, and Month 36.
Error bars represent standard error.

More prolonged summary data for the Observed Case Population for up to 6 years of metreleptin treatment shows generally sustained efficacy over longer time frame (Figure 6.3.2-2).

Figure 6.3.2-2: Mean HbA1c and Median TG Percent Change From Baseline Over the Initial 6 Years of Metreleptin Treatment (NIH Studies, Observed Case Population)



N* represents patients with available data at baseline and that time point.
Error bars represent standard error.

6.3.3 Effects of Metreleptin Treatment by LD Subtype

Regardless of LD sub-type (i.e., CGL, n 32; AGL, n 16; FPL, n 20; APL, n 4), patients across all subtypes except APL, where there were too few patients to draw any meaningful conclusions, demonstrated improvements in HbA1c and TG with metreleptin treatment (Table 6.3.3-1). The supportive efficacy data from Study FHA101 (Section 6.4) which enrolled a greater number of patients with partial LD (n 23), including 2 APL patients, demonstrates that substantial improvements in efficacy parameters were observed for the subset of patients with partial LD and severe metabolic abnormalities.

Table 6.3.3-1: Change From Baseline to Month 12 in Key Efficacy Parameters by LD Subtype (NIH Studies, Observed Case Population)

	Mean (SE) HbA1c (%)			Median TG (mg/dL)			
	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)	51	359.0	-121.0	-44.8
LD Subtype							
CGL	20	9.0 (0.5)	-2.2 (0.4)	22	452.0	-284.0	-60.7
AGL	9	8.0 (0.6)	-1.8 (0.4)	8	348.0	-211.5	-67.4
FPL	17	7.7 (0.5)	-0.5 (0.3)	17	357.0	-74.0	-29.8
APL	4	6.7 (1.4)	-0.1 (0.2)	4	334.5	-50.5	-7.3

HbA1c treatment response was directly correlated to the degree of severity at baseline (i.e., CGL>AGL>FPL>APL). Greater improvements in TG were also observed in patients with higher baseline TG values (i.e., CGL>AGL>FPL>APL).

6.3.4 Change in HbA1c and Triglycerides Control by Baseline Leptin Levels

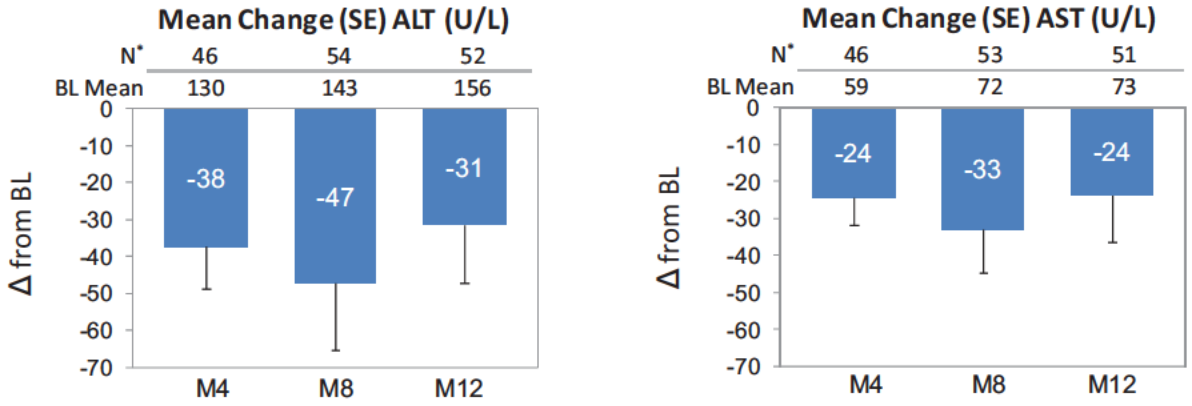
Analysis of changes in HbA1c and TG levels during the first year of treatment according to both baseline leptin levels and baseline severity of metabolic abnormalities was conducted. However, LD patients with leptin levels above the 50th percentile for gender[57] were not assessed because there were too few patients to reliably assess a relationship between response to treatment and baseline leptin level due to these limitations of the NIH study dataset. Supportive leptin data from Study FHA101, which did not have a leptin level exclusion lower limit at study entry, provide relevant information. There were demonstrated improvements in metabolic parameters with metreleptin treatment in a subset of patients with severe baseline metabolic abnormalities, and baseline leptin levels > 12 ng/mL (Section 6.4.2).

6.3.5 Liver Endpoints

Liver disease including hepatic steatosis/steatohepatitis was a frequent baseline medical condition in LD patients. Hepatic steatosis is commonly associated with elevated liver function tests, and therefore measurements of ALT, AST, and liver volume are useful surrogates for hepatic steatosis.

At baseline, mean ALT was elevated (≥ 41 U/L) in 64% of patients and AST (≥ 34 U/L) elevated in 56% of patients. Mean change in ALT and AST concentrations from baseline to Months 4, 8, and 12 are presented for the Observed Case Population in Figure 6.3.5-1. Substantial reductions in both ALT and AST occurred with metreleptin treatment, which were apparent at Month 4 and sustained through to Month 12.

Figure 6.3.5-1: Mean (SE) Change in ALT and AST Concentrations From Baseline at to Month 4, Month 8, and Month 12 (NIH Studies, Observed Case Population)



N* represents patients with available data at baseline and that time point.
Error bars represent standard error.

Table 6.3.5-1 presents the change from baseline at Month 12 for ALT and AST by generalized vs. partial LD cohorts. As observed for HbA1c, FPG, and TG, greater reductions in ALT and AST were observed in patients with generalized LD as compared to patients with partial LD, which appeared to correspond with greater elevations at baseline.

Table 6.3.5-1: Mean (SD) ALT and AST Values at Baseline and Month 12 - Patients with Baseline ALT ≥41 U/L and AST ≥34 U/L (NIH Studies, Observed Case Population)

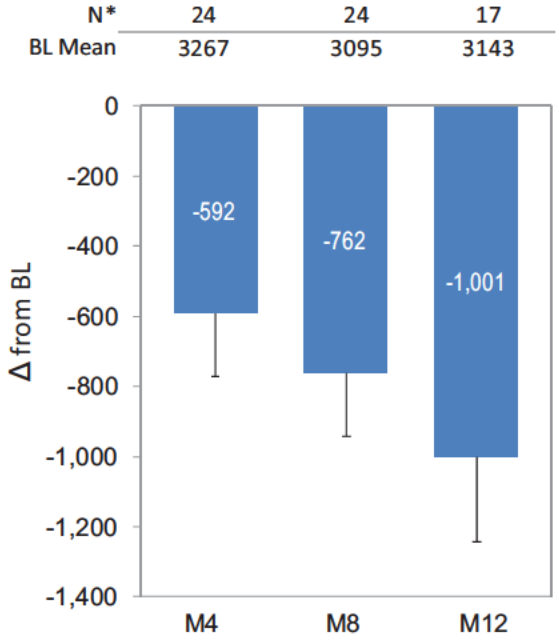
Parameter	Patients					
ALT (U/L)	All			Baseline ALT ≥41 U/L		
Mean (SE)	n	Baseline	Δ from BL at Month	n	Baseline	Δ from BL at Month
Generalized	31	130.4 (26.5)	-52.8 (25.5)	22	171.6 (33.8)	-72.0 (35.2)
Partial	21	58.4 (13.8)	0.3 (6.3)	8	114.3 (26.6)	2.3 (17.0)
AST (U/L)	All			Baseline AST ≥34 U/L		
Mean (SE)	n	Baseline	Δ from BL at Month	n	Baseline	Δ from BL at Month
Generalized	30	94.1 (17.0)	-35.7 (21.2)	20	127.8 (22.0)	-51.8 (31.5)
Partial	21	42.1 (8.6)	-6.6 (4.3)	7	81.3 (18.6)	-14.9 (12.6)

Increases in liver volume consistent with hepatomegaly (defined by the NIH investigators as liver volume > 2000 mL)[22] occurs commonly in LD due to excess lipid storage in the liver. Liver

volume measurements (based on magnetic resonance imaging [MRI]) are available in a subpopulation (N 27) of the Analysis Population (refer to Section 5.2.1. for further details).

A large mean reduction in liver volume was evident at Month 4 with further reductions observed at Month 12 (Figure 6.3.5-2).

Figure 6.3.5-2: Mean Change From Baseline to Months, 4, 8 and 12 in Liver Volume Assessed by MRI (NIH Published Data)



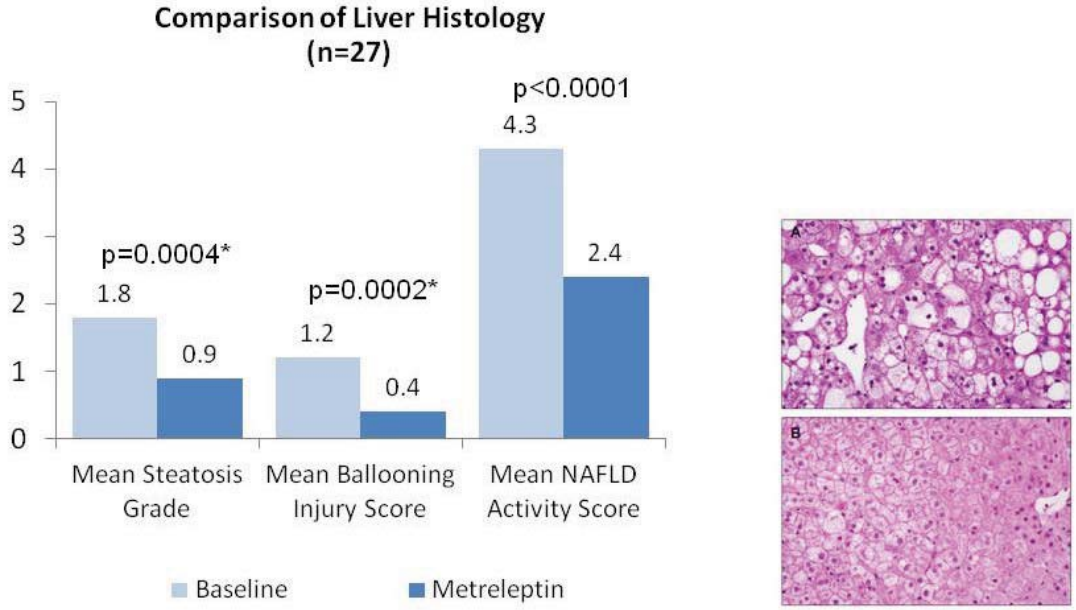
N* represents patients with available data at baseline and that time point.
Error bars represent standard error.

The mean decrease from baseline in liver volume, by LD subtype, in patients who had data available at Month 12 was 1,454 mL from a corresponding baseline of 3690 mL in patients with generalized LD (n 11) and 171 mL from a corresponding baseline of 2138 mL in partial LD patients (n 6).

The NIH investigators have also published the results from paired liver biopsies (before and after metreleptin treatment) in a subset of patients. Fifty patients with LD underwent a liver biopsy at baseline and 27 of these patients had a repeat biopsy after metreleptin treatment for an average of 26 months.[58]

A total of 85% of patients (n 27) met criteria for non-alcoholic steatohepatitis (NASH) at baseline while 67% of these cases who subsequently had repeat liver biopsies showed no steatohepatitis after metreleptin treatment. As shown in Figure 6.3.5-3, there were significant improvements in steatosis grade and ballooning injury scores, with a 44.2% reduction in mean non-alcoholic fatty liver disease (NAFLD) activity score.[58] Patients who already had evidence of fibrosis remained stable on metreleptin treatment during the assessed treatment time frame.

Figure 6.3.5-3: Liver Histology Data (NIH Published Data)



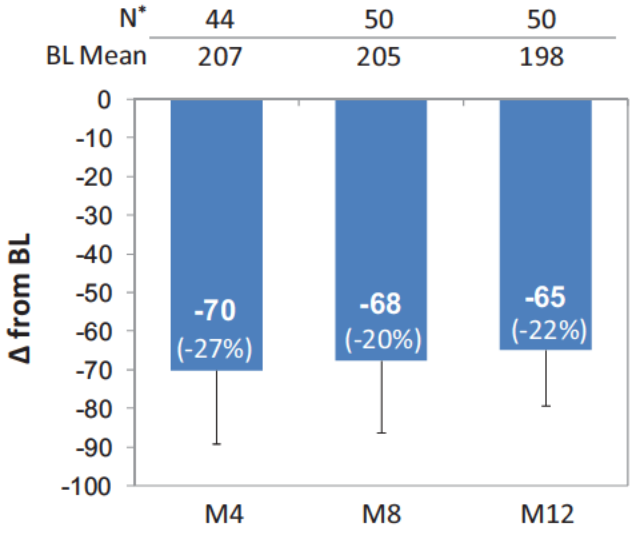
*p-value is based on Wilcoxon Signed Rank test.
NAFLD (non-alcoholic fatty liver disease)
Adapted from Zadeh et al.[58]

6.3.6 Other Lipid Endpoints

Total cholesterol and LDL cholesterol were assessed in the study, but LDL cholesterol could not be calculated in some patients due to severe hypertriglyceridemia. Non-HDL cholesterol (total cholesterol minus HDL cholesterol) was assessed and is considered a reasonable surrogate of cardiovascular risk reduction (in absence of other parameters such as ApoB).[59]

In addition to clinically meaningful reductions in TG, decreases in mean non-HDL cholesterol were observed with metreleptin treatment during the first year of treatment (Figure 6.3.6-1), with minimal changes in HDL cholesterol.

Figure 6.3.6-1: Mean Change from Baseline in Non-HDL Cholesterol at Months 4, 8 and 12 (NIH Studies, Observed Case Population)

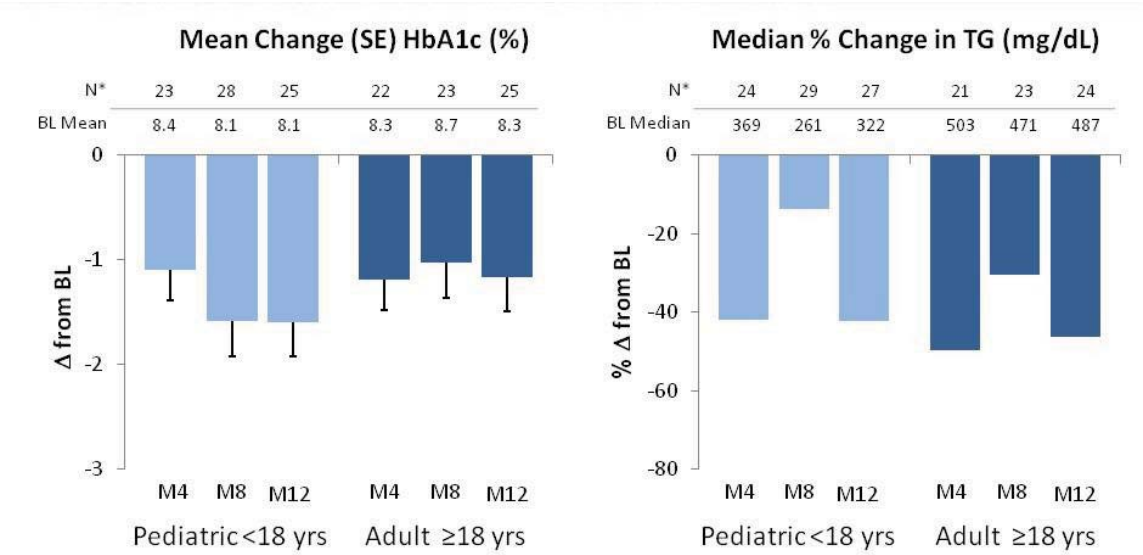


N* represents patients with available data at baseline and that time point.
Error bars represent standard error.

6.3.7 Efficacy in Pediatric and Adult Patients in the NIH Studies

Clinically meaningful improvements in HbA1c and fasting TG values were observed in the pediatric population. Overall, pediatric patients had slightly larger improvements in HbA1c compared to adult patients. For TG, a smaller absolute magnitude of improvement was observed in pediatric patients as compared to adult patients; however, comparable percent median reductions were observed. It is also important to note that although the same TG enrollment criteria (≥ 200 mg/dL) were used for pediatric as compared to adult LD patients as well as for analyses conducted herein, TG levels ≥ 200 mg/dL can be considered quite elevated for pediatric patients. This is based on recent NHANES data published in 2012 showing that the 95th percentile of TG levels for children age 12 to 19 is less than 100 mg/dL, and is 94 mg/dL to 122 mg/dL for obese children in the same age range.[60]

Figure 6.3.7-1: Mean (SE) Change in HbA1c and Median Change in TG at Months 4, 8, and 12 in Pediatric and Adult Patients (NIH Studies, Observed Case Population)



N* represents patients with available data at baseline and that time point.
Error bars represent standard error.

Effects of Metreleptin on Metabolic Control in Pediatric Patients (Age ≤ 12 Years and > 12 to < 18 Years) Patients

Analysis of the effect of metreleptin on metabolic control within the pediatric population in patients ≤ 12 years and > 12 and < 18 years was conducted. Mean baseline HbA1c and TG were very high in the > 12 and < 18 years group and improved substantially with metreleptin. Although mean baseline HbA1c was only mildly abnormal in the ≤ 12 year group, there was a small decrease with metreleptin. Both age groups had substantially elevated mean ALT and AST at baseline which decreased with metreleptin treatment.[61] In general, the beneficial effects of metreleptin were apparent within 4 months and sustained over treatment in both pediatric subgroups (Table 6.3.7-1). Overall, it is likely that the pathogenesis of LD in pediatric patients evolves as the capacity of the liver to absorb more and more lipid is saturated in the absence of normal adipose depot TG storage sites. Thus, younger patients may be able to retain better HbA1c and TG control while the liver is growing and still retains ectopic lipid storage capacity, while adolescent subjects begin to exhibit more striking metabolic abnormalities in the face of a large, lipid-engorged liver, often accompanied by other diffuse, ectopic lipid deposition sites.

Table 6.3.7-1: Change From Baseline to Month 12 in Key Efficacy Parameters for Pediatric Patients (Age ≤12 Years and >12 to < 18 Years) (NIH Published Data)

	Age ≤12 Years (n=13)				Age >12 to < 18 Years (n=14)			
	BL	Month 12	Change*	95% CI	BL	Month 12	Change*	95% CI
HbA1c (%)	6.1±1.2	5.6±0.7	0.5±0.4	1.3,0.3	10.0±1.6	7.8±1.7	2.5±0.4	3.3, 1.6
TGs (mg/dL)	239±100	225±187	0.8±20*	42,44	1461±2074	402±458	45±14*	76, 14
ALT (U/L)	182±198	147±264	35±44	130,60	109±99	59±112	50±42	141,42
AST (U/L)	112±110	84±139	28±26	86,30	92±91	60±122	32±40	119,56

Mean±SD for BL and Month 12, mean±SE for Change. Absolute change for HbA1c, ALT, AST. *Percent change for TGs.

Adapted from Brown et al.[61]

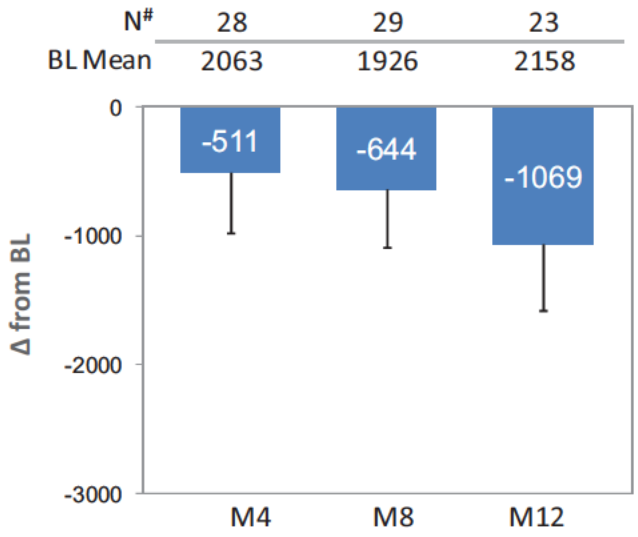
6.3.8 Proteinuria

Patients with LD often have proteinuric nephropathies, which may be related to long-standing poorly controlled diabetes. However, it is more often due to co-existing renal diseases like glomerulonephritis or glomerulosclerosis, especially with acquired forms of LD (generalized or partial).

Figure 6.3.8-1 presents the mean change from baseline in 24-hour urine protein at Month 4, 8, and 12 in patients with proteinuria at baseline. Metreleptin led to a substantial decrease in 24-hour urine protein after 1 year of treatment.

This improvement in proteinuria likely reflects the decrease in hyperfiltration associated with improvement in marked hyperglycemia. Whether metreleptin has effects on renal function independent of effects on metabolic control is unknown, but the magnitude of improvement suggests that the effect is real and not simply part of the natural history of chronic renal disease.

Figure 6.3.8-1: Mean (SE) Change From Baseline in 24-hour Urine Protein at Month 4, 8, and 12 (NIH Studies, Sub-Study Population)



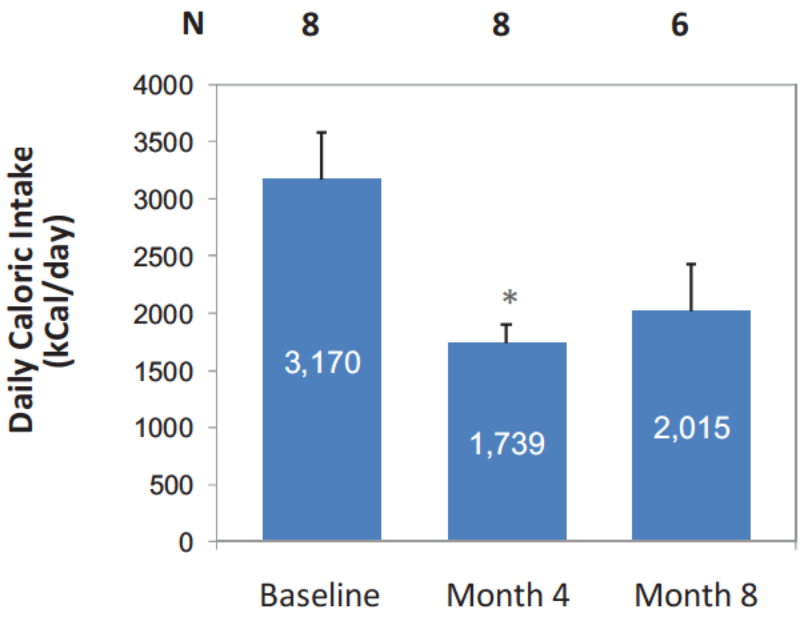
N represents patients with available data at baseline and that time point.
Error bars represent standard error.

6.3.9 *Food Intake*

One important effect of metreleptin in LD patients is to decrease the marked hyperphagia observed in both generalized and partial LD. Data published from the NIH studies in a subset of patients shows that metreleptin treatment reduces food intake in LD patients as soon as Month 4 and is sustained through Month 12.[62]

Food intake was assessed at Month 4 and Month 12 of metreleptin administration in a subset of the first 8 patients in the NIH studies. At baseline, the Block 98 food frequency questionnaire demonstrated that patients were hyperphagic, exhibiting voracious appetites and between meal food-seeking behavior. [63] Following metreleptin treatment, all patients reported a decrease in appetite with feeling of satiety after meals and hunger that became manageable. Caloric intake decreased significantly by ~ 45% at 4 months with a similar although not significant reduction at Month 12 (Figure 6.3.9-1). Over this same time frame, body weight decreased by a mean of ~ 2 kg. This weight loss may occur as hyperphagia is corrected.

Figure 6.3.9-1: Mean Change From Baseline in Daily Caloric Intake at Month 4 and Month 12 (NIH Published Data)



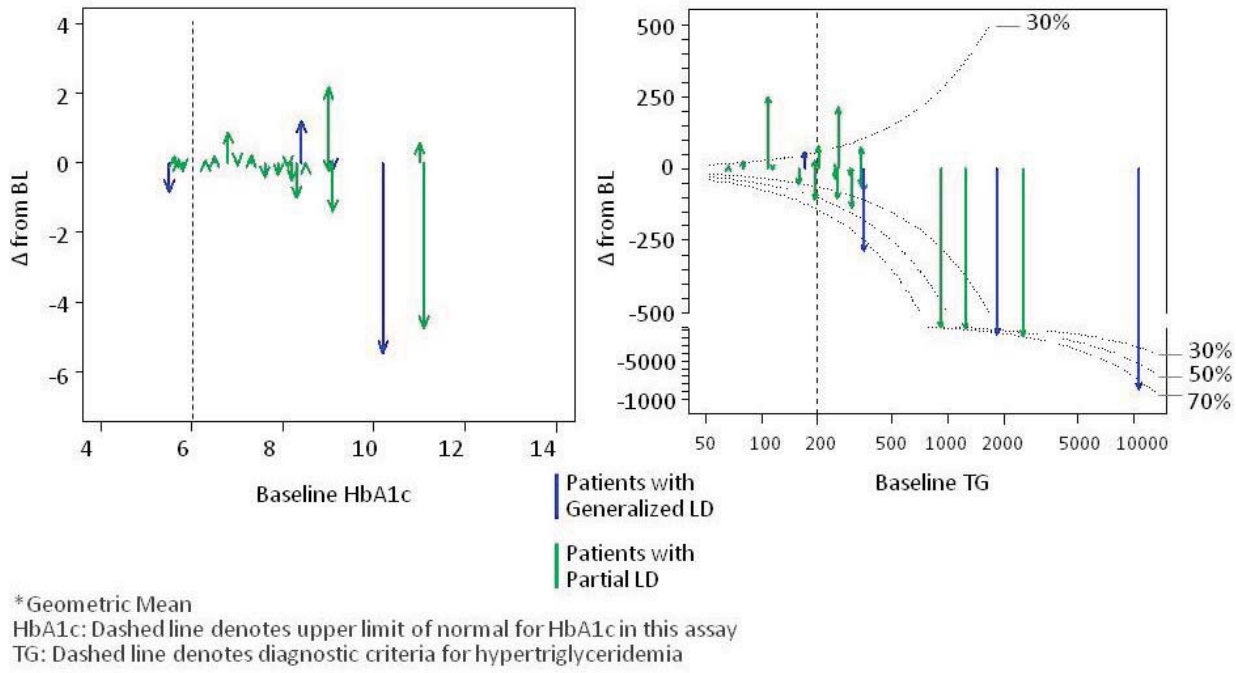
*P=0.019 vs. baseline
All values are shown as the mean ± SEM. NS=not statistically significant.
Adapted from Moran et al.[62]

6.4 Efficacy in Patients From FHA101

6.4.1 Effects of Metreleptin Treatment on HbA1c and Triglycerides

Reductions in HbA1c and TG were smaller than those observed in the NIH studies (i.e., mean change of -0.4% in Hb1Ac and median change of -16% in TG at Month 12), a finding that is not unexpected given that Study FHA101 enrolled predominantly partial LD patients i.e., 23 partial LD patients of the total 28 patients, who tended to have less severe baseline metabolic abnormalities. However, substantial improvements in efficacy parameters were observed for the subset of patients with partial LD and severe metabolic abnormalities at baseline (Figure 6.4.1-1).

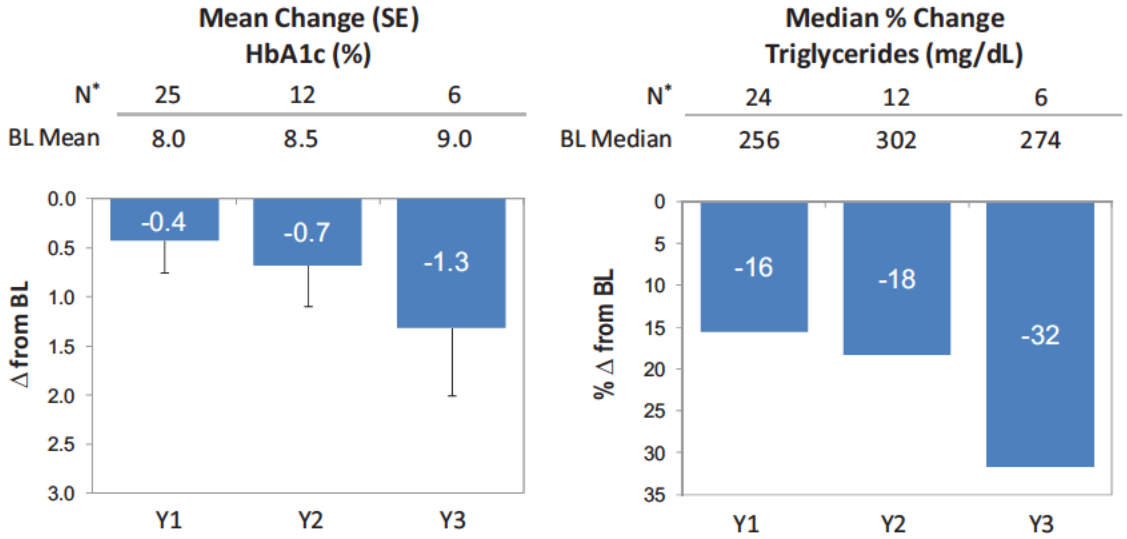
Figure 6.4.1-1: Average Change in HbA1c and TG During the First 12 Months of Metreleptin Treatment (Study FHA101, Observed Case Population)



Dotted lines represent 30, 50, and 70% reductions in TG after 12 Months of treatment.

Although the extent of patient follow-up and duration of the FHA101 study was not as long as the NIH study given its more recent starting date, the long term durability of response to metreleptin treatment in Study FHA101 was also demonstrated over 3 years of treatment (Figure 6.4.1-2).

Figure 6.4.1-2: Mean HbA1c and Median TG Percent Change From Baseline Over the Initial 3 Years of Metreleptin Treatment (Study FHA101, Observed Case Population)



Data are summarized using expanded visit windows:
Year 1 = Post baseline up to 365 + 14 days from first dose date
Year 2 = Study day 380 to 24 months + 14 days
Year 3 = 24 months +15 days to month 36 + 14 days

N* represents patients with available data at baseline and that time point.
Error bars represent standard error.

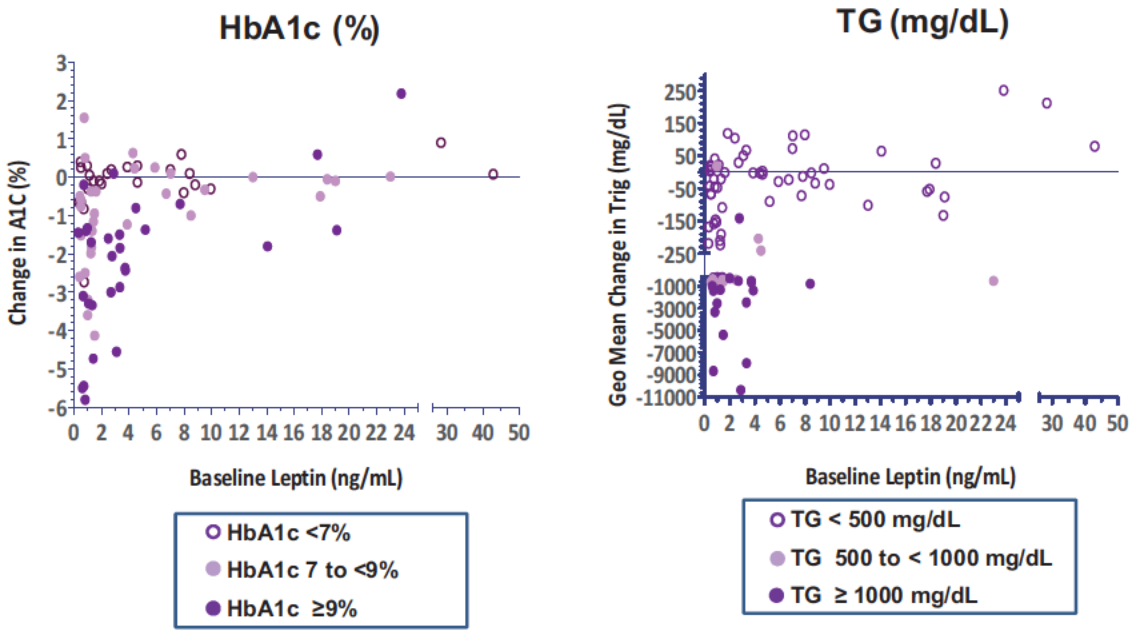
Data on the changes from baseline to Month 12 for concomitant anti-diabetes and lipid-lowering medications are limited in Study FHA101, due to the small number of patients with available data at Month 12.

6.4.2 Change in HbA1c and Triglycerides by Baseline Leptin Levels

Figure 6.4.2-1 presents the average change in HbA1c and TG during the first year of treatment in the combined NIH and FHA101 studies by both baseline leptin levels and baseline severity of metabolic abnormalities. Since Study FHA101 did not have a leptin exclusion limit, leptin levels at study entry cover a broader range. Leptin levels at baseline serve as a surrogate for the amount of adipose tissue, the fuel storage organ that secretes this hormone. The available data suggest leptin measurements can provide qualitative information on the likelihood of improvements in HbA1c or TG, but a reliable quantitative threshold cannot be defined given limited clinical data in LD patients at higher leptin levels.

The severity of baseline abnormality and the change in HbA1c and TG in patients with baseline leptin levels > 12 ng/mL (exclusion limit for the NIH studies) are more heterogeneous. For leptin levels > 24 ng/mL, there are too few patients to assess a relationship between response to treatment and baseline leptin level.

Figure 6.4.2-1: Average Change in HbA1c and TG up to 1 Year by Baseline Leptin Level and Baseline HbA1c and TG Categories in all Patients From NIH and FHA101 Studies (Observed Case Population)



6.4.3 Liver Endpoints

Since Study FHA101 was an expanded access program, liver volume and liver biopsy data were not collected. The data for liver endpoints are limited to ALT and AST parameters.

Mean baseline values for liver enzymes ALT and AST were within normal range for the 23 patients with partial LD ([mean ± SE], 32 ± 3 U/L for ALT; 28 ± 2 U/L for AST). During the initial 12 months, mean ALT and AST values remained below baseline levels and within normal ranges. Mean values for LFTs at baseline were slightly above the upper limit of normal for the total FHA study population (N 28) (ALT 54 ± 16 U/L, AST 39±8 U/L).

In 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. It should be noted that these improvements were primarly driven by two patients with AGL experiencing dramatic improvements: one patient with ALT decreasing from 419 to 89 U/L and AST from 208 to 36 U/L) at Month 6, and the other patient with ALT decreasing from 259 to 19 U/L and AST from 145 to 20 U/L at Month 6.

6.5 Overall Summary of Efficacy

Substantial and clinically meaningful improvements in HbA1c, FPG, TG, and liver endpoints were observed in the NIH studies through to Year 1 with metreleptin treatment. Reductions in these endpoints were more pronounced in patients with elevated baseline values. Larger mean reductions in HbA1c, FPG, and TG were observed in patients with generalized LD as compared

to patients with partial LD, which appeared to correlate with greater elevations in baseline metabolic parameters at baseline.

Long term durability of response to metreleptin treatment was also demonstrated. The majority of LD patients present with glycemic, lipid, and/or liver function abnormalities, although these abnormalities may be dissociated from each other in individual patients. Thus, some subjects may present primarily with hypertriglyceridemia with normal glycemic control, while others can present primarily with diabetes without hypertriglyceridemia. When the analyses of changes in HbA1c, FPG, and TG are limited to a subset of those patients with abnormalities in a specific parameter at baseline, the magnitude of response for that parameter is amplified for the subset compared to the overall study population. The magnitude of improvement appeared to correlate with the severity of the baseline abnormality, especially for TG. The primary analysis (observed data from all available subjects) was more conservative and did not restrict evaluations to subjects with abnormal values at baseline.

Efficacy was demonstrated in patients with both generalized LD and partial LD, the most important determinant of overall response to metreleptin relating to the proportion of the studied population affected and the severity of the metabolic abnormalities at baseline. Thus, larger decreases in HbA1c were observed in patients with generalized LD because a higher proportion of generalized LD patients had elevated baseline HbA1c values, and individual baseline HbA1c values were also higher in magnitude. Similar proportions of patients in each group had baseline TG values $\geq$ 1000 mg/dL. Large decreases in TGs were observed in both generalized and partial LD patients with elevated baseline TGs.

The improvements in HbA1c, FPG, and TG are particularly notable given that they occur in patients who were often uncontrolled on other anti-diabetes therapies (in some cases, extremely high doses of insulin). Moreover, many patients demonstrated concomitant substantial reductions or discontinuation in the use of anti-diabetes medications (insulin and/or oral agents) along with HbA1c reductions.

Acknowledging that there was no placebo control employed in the NIH studies, these findings suggest improvements in HbA1c, FPG, and TG was not simply due to increasing the dose amount or adding additional anti-diabetes therapies for the majority of the patients.

In addition to clinically meaningful reductions in TG, decreases in mean non-HDL cholesterol (a surrogate of cardiovascular risk reduction) were observed with metreleptin treatment during the first year of treatment, with minimal changes in HDL cholesterol.

In the NIH studies, a substantial percentage of patients had liver disease at baseline including hepatic steatosis, steatohepatitis and/or hepatomegaly. Hepatic steatosis is commonly associated with elevated liver function tests. Therefore, measurements of ALT, AST, and liver volume are a useful surrogate for hepatic steatosis. Most patients had elevated liver function tests at baseline (2 to 3 times the upper limit of normal for ALT and AST). Substantial reductions in mean ALT, AST, and liver volume, which were apparent at Month 4 and sustained through to Month 12, occurred with metreleptin treatment. There were greater mean reductions in generalized LD patients compared to patients with partial LD. These data highlight the

importance of liver disease as a clinically significant component of the spectrum of metabolic abnormalities associated with LD, as hepatic steatosis and/or steatohepatitis may be the primary metabolic manifestation of LD in certain patients, especially in the pediatric age group.

A substantial decrease from baseline in 24-hour urine protein was also noted after the first year of metreleptin treatment. This improvement in proteinuria likely reflects the decrease in hyperfiltration associated with improvement in marked hyperglycemia. It is not known whether metreleptin has effects on renal function independent of effects on metabolic control, but the magnitude of improvement suggests that the effect is real and not simply part of the natural history of chronic renal disease.

Published data from the NIH studies have shown that metreleptin treatment decreases hyperphagia (as seen with a reduction of food intake), a symptom common in LD patients. Weight loss has also been observed with metreleptin treatment, which may occur due to correction of hyperphagia and/or the decrease in hepatic steatosis.

Clinically meaningful improvements in HbA1c, fasting TG, and liver endpoints were also observed in the pediatric population. Overall, pediatric patients had slightly larger improvements in HbA1c compared to adult patients.

The majority of patients studied in the NIH studies had baseline leptin levels below the 10th percentile of the population as reported by National Health and Nutrition Examination Survey (NHANES) data. Since Study FHA101 did not have a leptin exclusion limit, leptin levels at study entry covered a broader range. The severity of baseline abnormalities and the change in HbA1c and TG in patients with baseline leptin levels > 12 ng/mL (exclusion limit for the NIH studies) are more heterogeneous. Leptin levels at baseline serve as a surrogate for the amount of adipose tissue, which is the tissue that secretes this hormone. The available data suggest that leptin measurements can provide qualitative information on the likelihood of improvements in HbA1c or TG, but a reliable quantitative threshold cannot be defined given limited clinical data in LD patients at higher leptin levels. Overall, improvements with metreleptin treatment in LD patients are related to the severity of baseline metabolic abnormalities, and not necessarily dependent upon the severity of leptin deficiency or the type of LD.

In conclusion, the efficacy of metreleptin in LD was demonstrated by improvements in HbA1c, FPG, TG, and liver endpoints in the first year of treatment for both general and partial LD patients. These improvements were most notable for patients with elevated baseline values.

7 SAFETY

7.1 Introduction

As detailed in 5.2.2 (Lipodystrophy Populations Supporting Safety and Immunogenicity), the safety analyses focuses on the Analysis population for the NIH and FHA LD studies, unless otherwise stated. The safety analysis is based on the data from the Analysis population of 72 LD patients treated with metreleptin in the NIH studies, integrated into a single analysis. The 28 LD patients from Study FHA101 are presented as a separate analysis. Data from the obesity program is also provided, where stated, to provide placebo-controlled data.

The safety sections include the following data:

- General Safety (including AEs, deaths, SAEs, AEs leading to withdrawal).
- Safety topics of Interest with metreleptin treatment (T-cell Lymphoma and immunogenicity including development of neutralizing activity to metreleptin)
- Other safety topics related to the underlying disease state and/or metreleptin treatment (pancreatitis, hypoglycemia, weight loss, generalized hypersensitivity, renal, hepatic, and cardiovascular safety)
- Other safety topics based upon leptin physiology (malignancies and immune function)
- Safety in pediatric and adult patients

7.2 General Safety

An overview of the TEAEs in patients who received at least 1 dose of metreleptin in the NIH studies and Study FHA101 is provided in Table 7.2-1.

Table 7.2-1: Overview of TEAEs in Patients who Received at Least one Dose of Metreleptin in NIH Studies and Study FHA101 (Analysis Population)

	NIH Studies (N=72)	Study FHA101 (N=28)
No. of Patients with At Least 1 TEAE	51 (70.8%)	27 (96.4%)
Total No. of TEAEs	308	185
No. of Deaths[a]	3 (4.2%)	2 (7.1%)
No. of Patients with At Least 1 Other SAE	17 (23.6%)	9 (32.1%)
Total No. of Other SAEs	40	18
No. of Patients with At Least 1 TEAE Leading to Withdrawal (AELW)[b]	2 (2.8%)	1 (3.6%)

[a] One additional death was reported after the data cutoff which is included in the 4-MSU.

[b] AELWs does not include deaths

Details on most frequent AEs, deaths and discontinuations due to AEs will be presented in the following sections.

7.2.1 Frequent Adverse Events

Lipodystrophy Population

The most frequent TEAEs (incidence ≥5% NIH studies and ≥10% in Study FHA101) are presented in Table 7.2.2-1 in order of decreasing incidence in the NIH studies. Similar types of frequent TEAEs (e.g. nausea, hypoglycemia, weight decreased) were observed among patients in the NIH studies and Study FHA101; however differences between the 2 studies were also observed. Events of hypoglycemia, urinary tract infection, vomiting, lymphadenopathy, and injection site TEAEs had a higher incidence in Study FHA101.

In the NIH studies, the overall incidences of frequent TEAES among patients with generalized (N 48) and partial (N 24) LD were generally similar with the exception of T-cell lymphoma (refer to Section 7.3.1), glomerulonephritis membranoproliferative, and weight decrease which were reported in generalized patients only. The majority of patients in the FHA study were partial LD patients, thus precluding a meaningful comparison between patients with generalized LD and partial LD.

Table 7.2.1-1: Frequent (Incidence ≥5% in NIH and ≥10% FHA101) Treatment Emergent Adverse Events in the NIH Studies and Study FHA101 (Analysis Population)

Preferred Term	NIH (N=72) n (%)	FHA101 (N=28) n (%)
Hypoglycaemia	8 (11.1)	7 (25.0)
Fatigue	7 (9.7)	--
Headache	6 (8.3)	--
Nausea	6 (8.3)	10 (35.7)
Weight decreased	6 (8.3)	--
Abdominal pain	5 (6.9)	5 (17.9)
Alopecia	5 (6.9)	--
Ovarian cyst	5 (6.9)	--
Pain in extremity	5 (6.9)	--
Upper respiratory tract infection	5 (6.9)	5 (17.9)
Arthralgia	4 (5.6)	--
Constipation	4 (5.6)	--
Diarrhoea	4 (5.6)	--
Dizziness	4 (5.6)	--
Ear infection	4 (5.6)	--
Pancreatitis	4 (5.6)	--
Renal cyst	4 (5.6)	--
Urinary tract infection	--	6 (21.4)
Vomiting	--	5 (17.9)
Injection site haematoma	--	5 (17.9)
Injection site urticaria	--	4 (14.3)
Lymphadenopathy	--	4 (14.3)
Sinusitis	--	4 (14.3)
Muscle spasms	--	3 (10.7)
Myalgia	--	3 (10.7)
Anxiety	--	3 (10.7)

Shaded events are assessed by the investigator as related to metreleptin treatment.

Obese Population (5-Study ISS: Metreleptin Monotherapy)

The most frequent TEAEs (incidence ≥5% in any treatment group) are presented in Table 7.2.1-2 in order of decreasing incidence in the placebo controlled obesity studies. The most frequently reported adverse event was injection-site reaction which was more frequent in the metreleptin vs. placebo. Other frequent AEs included headache and nasopharyngitis with similar incidences between metreleptin-treated and placebo-treated subjects. Events of nausea and fatigue reported in LD studies as related to metreleptin also had similar incidences between metreleptin-treated and placebo-treated subjects.

Table 7.2.1-2: Frequent (Incidence ≥5%) Treatment-Emergent Adverse Events in the Placebo Controlled Obesity Studies

Preferred Term	All Metreleptin N=784 n (%)	Placebo N=351* n (%)
Injection site reaction	469 (59.8)	157 (44.7)
Headache	123 (15.7)	43 (12.3)
Nasopharyngitis	95 (12.1)	44 (12.5)
Injection site erythema	85 (10.8)	2 (0.6)
Injection site pruritus	63 (8.0)	6 (1.7)
Fatigue	50 (6.4)	24 (6.8)
Influenza	48 (6.1)	24 (6.8)
Diarrhoea	42 (5.4)	17 (4.8)
Nausea	42 (5.4)	17 (4.8)
Upper respiratory tract infection	27 (3.4)	26 (7.4)

*Due to a induction period in Study LEPT 970213, 63 subjects randomized to placebo are counted in both metreleptin and placebo groups. AEs are summarized based on treatment at time of event

7.2.2 Deaths

Lipodystrophy Population

In total, 6 deaths have occurred during treatment with metreleptin among the LD patients (4 in the NIH studies, and 2 in Study FHA101) including 1 additional death in the NIH studies reported in the 4-MSU data cut (Table 7.2.2-1). None of these deaths were considered by the investigator or the Sponsor as related to metreleptin treatment.

Table 7.2.2-1: Deaths in NIH Studies and Study FHA101

Demographics	Cause of Death	Medical History
	NIH Studies	
15 yr, CGL	pancreatitis and subsequent septic shock leading to cardiac arrest	pancreatitis, diabetes, hyperlipidemia
35 yr CGL	renal failure leading to cardiac arrest	pneumonia, hyperlipidemia, diabetes, peripheral vascular disease, proteinuria
18 yr AGL	chronic hepatic failure	severe liver disease with cirrhosis, hypercholesterolemia, mild renal insufficiency, proteinuria, diabetes, and pancytopenia
27 yr, FPL	anoxic encephalopathy	Type 2 diabetes mellitus, hypertriglyceridemia, hypertension, atrial septal defect, non-alcoholic steatohepatitis, recurrent pancreatitis, acute renal failure
	Study FHA101	
67 yr, APL	loss of consciousness (subdural hematoma after fall)	hypertension, coronary artery disease, peripheral vascular disease, autoimmune overlap syndrome, and seizures
67 yr, AGL	erosive esophagitis related to her progressive adenocarcinoma	metastatic adenocarcinoma

Deaths are based on the 4-MSU (N=90, NIH and N=35, FHA101)

In the NIH studies, 3 additional deaths occurred several months after discontinuation of metreleptin treatment. These included multisystem organ failure related to peripheral T-cell lymphoma (59 yr, AGL), 7 months after stopping metreleptin, peripheral T-cell lymphoma, 8 months after stopping metreleptin (68 yr, AGL), and hepatorenal failure which occurred 9 months after stopping metreleptin (13 yr, AGL). Further details regarding each event are provided in Sections 7.3.1 and 7.5.6, respectively.

Obese Population (5-Study ISS: Metreleptin Monotherapy)

In the placebo-controlled obesity studies, 1 death was reported in a subject who was diagnosed with lymphocytic leukemia approximately 1 month after initiating treatment with metreleptin. After 29 days of treatment with metreleptin, the subject was hospitalized with pneumonia, found to have an extremely elevated white blood cell count, and diagnosed with lymphocytic leukemia. The events of lymphocytic leukemia and pneumonia were assessed by the investigator as unrelated to study medication. Although limited information is available for this case, it seems unlikely that metreleptin played a causal role in the development of lymphocytic leukemia given the relatively short duration of metreleptin exposure (~ 1 month) and the suggestion of some abnormalities in the baseline hematology data.

7.2.3 Other Serious Adverse Events

Lipodystrophy Population

In the NIH studies, 17 (23.6%) of 72 patients in the NIH study experienced a total of 40 SAEs. In Study FHA101, 9 (32.1%) of 28 patients experienced a total of 18 SAEs. The majority of the SAEs were considered by the investigator and Sponsor as unrelated to metreleptin treatment. The most prevalent SAEs in the NIH studies were pancreatitis (4 patients; 5.6%) which were considered to be related to the disease state, and not to metreleptin, as discussed in Section 7.5.1 (Pancreatitis). Other notable SAEs in which each event occurred in 1 patient only in the NIH studies are discussed in detail in subsequent sections. They included: anaplastic large cell lymphoma, T-cell lymphoma, papillary thyroid cancer, and worsening adenocarcinoma.

Obese Population (5-Study ISS: Metreleptin Monotherapy)

In the placebo controlled studies, the incidence of SAEs was similar among the metreleptin (2.0%) and placebo (3.7%) groups. Serious adverse events that occurred in more than 1 patient in the placebo controlled obesity studies included angina pectoris (2 [0.3%] for metreleptin vs. 0 placebo) and chest pain (0 for metreleptin vs. 2 [0.6%] for placebo).

The higher incidence of SAEs in LD patients is indicative of the severity of their co-morbidities.

7.2.4 Adverse Events Leading to Treatment Discontinuation

Lipodystrophy Population

As of the data cutoff for the BLA, 3 patients experienced AEs which lead to treatment discontinuation (2 in the NIH studies, and 1 in Study FHA101). The events that lead to discontinuation were: T-cell lymphoma (discussed in detail in Appendix 1) and worsening proteinuria (medical history of chronic renal failure and proteinuria) in the NIH studies and muscle spasm (medical history of muscle spasms, myopathy, and fibromyalgia) in Study FHA101. The patient who withdrew from the NIH studies due to proteinuria later re-enrolled in the same study and 7 years later transferred to a named patient program, continuing on metreleptin treatment. None of these events were considered related to metreleptin treatment.

Obese Population (5-Study ISS: Metreleptin Monotherapy)

In the placebo controlled obesity studies, AEs which lead to treatment discontinuation occurred in 79 (10.1%) of 784 metreleptin-treated subjects and 20 (5.7%) of 351 placebo-treated subjects. The majority of withdrawals due to adverse events in subjects treated with metreleptin were due to injection site reactions (incidence 38 [4.8%] vs. 1 [0.3%] for placebo) and inflammatory injection-site adverse events including the preferred terms injection site inflammation, injection site pruritis, injection site erythema, and injection site urticaria (combined incidence 11 [1.4%] vs. 0 [0.0%] for placebo).

7.3 Safety Topics of Special Interest

7.3.1 Peripheral T-Cell Lymphoma in the Lipodystrophy Program

Events of Peripheral T-Cell Lymphomas in the NIH Studies

In NIH studies, 2 cases of peripheral T-cell lymphoma (PTCL) not otherwise specified (NOS) and 1 case of a localized anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (a type of T-cell lymphoma) have been reported (all with AGL treated with metreleptin in the NIH studies). The two patients with peripheral T-cell lymphoma NOS had significant hematologic abnormalities (including abnormal bone marrow as evident from a work-up for neutropenia, leucopenia, lymphadenopathy, and/or hepatosplenomegaly) at baseline prior to initiating metreleptin. One of the two patients also had pre-existing skin lesions. Following identification of the first 2 cases of PTCL-NOS, the NIH and FHA101 protocols were amended to exclude patients with acquired LD and significant hematological abnormalities. A third case of lymphoma (ALK+ anaplastic large cell lymphoma) presenting as a localized subcutaneous mass was reported in a third patient with AGL in the NIH studies.

A summary of the lymphoma cases in the NIH studies is presented in Table 7.3.1-1.

Table 7.3.1-1: Treatment-Emergent Adverse Events of Peripheral T-cell Lymphoma (NIH Analysis Population)

Demographics, Study	Event	Time on Metreleptin Prior to Diagnosis	Relevant Past Medical History	Additional Comments
Pt 90115 68 yr M, AGL 5 yrs, NIH	Peripheral T-cell lymphoma with cutaneous involvement	8 months	Skin lesions on leg Lymphadenopathy Pancytopenia Hypercellular bone marrow	Pre-existing skin lesions, diagnosed as T-cell lymphoma during metreleptin treatment Withdrawn, death 6 months later
Pt 90147 59 yr F, AGL 3 yrs, NIH	Intraductal breast cancer	4 months	Breast fibroma	Radical mastectomy
	Peripheral T-cell lymphoma with cutaneous involvement	7 months	Neutropenia Hypercellular bone marrow Hepatosplenomegaly	Withdrawn, death 7 months later
Pt 90170 13 yr F, AGL 11 yrs, NIH	ALK+ anaplastic large cell lymphoma (Peripheral T-cell lymphoma, localized subcutaneous mass)	22 months	Severe insulin resistance Hypertriglycerdiemia Steatohepatitis	Continued metreleptin treatment after brief interruption

AGL: Acquired Generalized, CGL: Congenital Generalized, APL: Acquired Partial , FPL: Familial Partial

Detailed narratives for each of these events are provided in Appendix 1.

No patients in Study FHA101 have been identified with peripheral T-cell lymphoma.

In the placebo controlled obesity studies (most less than 6 months), there were no reported cases of lymphoma. One case of lymphocytic leukemia occurring on metreleptin treatment (refer to

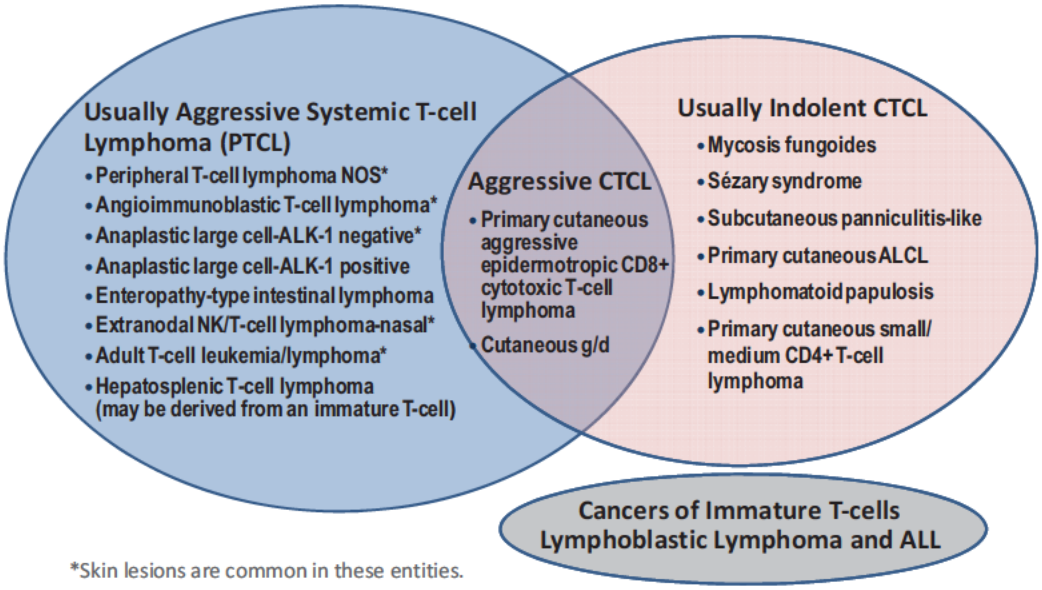
Section 7.2.2, Deaths: Obese Population) was reported in the obesity program, which was assessed by the investigator as unrelated.

Background on Peripheral T-cell lymphomas

Peripheral T-cell lymphomas (PTCL) comprise a heterogeneous group of hematological malignancies that originate from mature T-cells and constitute less than 15% of all non-Hodgkin's lymphomas (NHL) in adults.[64] The term "peripheral" does not refer to the site of involvement but rather to the immunophenotype of these tumors deriving from post-thymic (or mature) t-cells. Figure 7.3.1-1 presents an approach to categorizing mature T-cell lymphomas based on biological behavior: usually aggressive systemic T-cell lymphomas (PTCL), usually indolent cutaneous T-cell lymphoma (CTCL) (skin only or primarily skin), and aggressive CTCL (skin-only T-cell lymphomas that behave in an aggressive manner).[65]

In contrast to B-cell lymphomas, T-cell lymphomas can be difficult to diagnose because there are often no specific marker patterns (e.g. CD4+, CD8+), especially for the most common subtypes like PTCL-NOS. T-cell receptor gene rearrangements or tests for clonality of T-cells can be helpful, although there are benign clonal T-cell processes, so these alone are not sufficient for diagnosis. In addition, there are usually no specific cytogenetic abnormalities, with the exception of ALK+ anaplastic large cell lymphoma.

Figure 7.3.1-1: Categorization of Mature (Post-Thymic) T-Cell Lymphomas



*Skin lesions are common in these entities.

Horwitz 2013 Peripheral T-Cell Lymphoma CME.pdf
http://www.medscape.org/viewarticle/809373

The first two cases of lymphoma in the LD program belong to the subtype PTCL not otherwise specified (PTCL-NOS). These are PTCLs that do not fit into any of the other subtypes of PTCL in the WHO classification. PTCL-NOS is the most common subtype, usually aggressive and systemic in nature, and may have skin involvement.

The 3rd case in the LD program belongs to the subtype ALK+ anaplastic large cell lymphoma (ALCL), which is characterized by the t(2;5) translocation resulting in a nucelophosmin/anaplastic lymphoma kinase (NPM/ALK) fusion protein. ALK+ ALCL is usually a systemic disease that frequently involves extranodal sites. However, in a recent report from the Anaplastic Large Cell Lymphoma-99 trial, a subset of 6 pediatric patients out 437 with ALCL was described.[66] They had the ALK+ lymphomas restricted to the skin with a histopathological and clinical picture indistinguishable from that of the usually indolent cALCL with a median time in remission of 7 yrs. From currently available information, including clinical course, it appears that the 3rd case in the NIH study belongs to this subtype of ALK+ ALCL.

Thus, while there were 3 cases of peripheral T-cell lymphoma reported in the NIH study, it is important to note that the ALCL represents a subtype of T-cell lymphoma quite distinct from the other 2 cases of PTCL-NOS and has a different etiology (resulting from a chromosomal translocation) compared to PTCL-NOS.

Literature Reports of Lymphoma in Lipodystrophy Patients in the Absence of Metreleptin

The Sponsor has conducted a literature search to better understand the occurrence of lymphoma in LD patients in the absence of metreleptin treatment. Two cases of patients with peripheral T-cell lymphoma with cutaneous involvement who had a clinical picture of acquired LD have been identified. These patients had not been treated with metreleptin.

The first patient, a 47 year-old male, developed the lymphoma 10 years after developing panniculitis and generalized lipoatrophy.[36] The second patient, a 46-year old male, was initially diagnosed with Hodgkin lymphoma, which was later revised to peripheral T-cell lymphoma.[37] He developed the LD condition 18 months after the diagnosis of lymphoma.

A third case of lymphoma, Hodgkin's lymphoma, was reported in a 22-year old female, described as lacking subcutaneous fat when she was 3 months old and diagnosed with scleroderma at the age of 8.[39]

Thus, while the background incidence of lymphoma in LD patients has not been published and is not well understood due to the rarity of these conditions, there are 2 case reports of peripheral T-cell lymphoma occurring in patients who did not receive metreleptin and with the same type of LD (AGL) as the patients in the NIH study who developed lymphoma.

Summary:

It is the Sponsor's assessment that it is highly unlikely that metreleptin contributed to the de novo development of these lymphomas. The 2 patients with peripheral T-cell lymphoma NOS had significant hematologic abnormalities (including abnormal bone marrow as evident from a work-up for neutropenia, leucopenia, lymphadenopathy, and/or hepatosplenomegaly) at baseline prior to initiating metreleptin. In one of the patients, skin lesions were present at baseline and progressed during metreleptin treatment. The lesions were biopsied revealing the diagnosis of peripheral T-cell lymphoma. Thus, those 2 patients had some evidence of the

beginning stages of their lymphoma prior to starting metreleptin treatment, leading to the investigator's assessment of the lymphoma being unrelated to metreleptin. It should also be noted that both patients had received G-CSF treatment, which can act as a growth factor for any tumor type.

The case of anaplastic large cell lymphoma was ALK-positive, indicating the presence of a chromosomal translocation that plays an essential role in the pathogenesis of this particular type of lymphoma, and is likely not induced by metreleptin.

The nonclinical toxicology studies of metreleptin have shown no evidence of metreleptin to be mutagenic or carcinogenic, or to cause neoplastic lesions or cellular proliferation (refer to Section 3).

In addition, as discussed more in detail in section (refer to Section 7.4.1), leptin is known to inhibit the activity of T-regulatory cells and to promote effector T-cell functions. This characteristic of leptin facilitates tumor surveillance rather than promoting uncontrolled growth since it enhances effector T-cell functions (tumoricidal) while blocking T-regulatory cells (which suppress effector T-cells).[75]

It is notable that all 3 cases of lymphoma occurred in patients with acquired LD. Autoimmune diseases occur commonly in patients with acquired LD,[2] and some autoimmune diseases also have a known association with malignancies, including malignant lymphoproliferative disorders,[67] thus providing a plausible link between LD and lymphomas. In support of this notion, review of the literature has identified 2 other cases of peripheral T-cell lymphoma (occurring in the absence of metreleptin treatment) in patients presenting with lipoatrophy (in a generalized fashion)[68] or who had a diagnosis of AGL,[69] as well as a case of Hodgkin's disease in a patient with generalized LD.[70] In addition, 1 of the patients enrolled in Study FHA101 who had AGL also had a remote history of cutaneous T-cell lymphoma.

In conclusion, there is a reasonable plausibility for an independent association of lymphoma with acquired LD. It is unlikely that metreleptin contributes to the de novo development of lymphoma although the possibility of metreleptin contributing to progression of pre-existing lymphoma cannot be completely excluded.

To ensure that the appropriate patients receive treatment, the Sponsor proposes education of prescribers about the potential risk of lymphoma through physician certification as a goal of the REMS with further assessment via the metreleptin Safety Registry (refer to Section 8.2).

7.3.2 Immunogenicity Including Development of Neutralizing Activity

Development of antibodies (immunogenicity) is common with therapeutic proteins and other biologics,[71,72] including metreleptin. The clinical significance of antibodies to therapeutic proteins may vary from no clinical impact to impacting PK (and potentially efficacy) to causing potentially immune-related AEs or neutralizing activity of the drug or a related endogenous hormone, such as leptin.

As shown in Table 5.2.2-1, Section 5.2.2, assessment of binding (non-neutralizing) antibodies as well as neutralizing activity to metreleptin (based on an in vitro cell-based assay) has been performed in patients from the NIH Studies and Study FHA101. The analysis of antibody data in the NIH studies was not as comprehensive as in the FHA study due to the fact that samples for antibody testing were not available for all patients or for all time points for a given patient.

Binding (non-Neutralizing) Antibodies to Metreleptin

Nearly all individuals (> 95%) receiving metreleptin who had antibody status assessed developed binding antibodies to metreleptin. This high rate of antibody development may be related to the SC injection of a protein that likely precipitates/aggregates when injected in the SC space (because pH transitioning from 4.2 [formulation] to approximately 7.0 [SC space]). In most individuals, these binding antibodies occur at a low level (titer) and tend to decrease over time despite chronic antigen presentation (continued metreleptin therapy) but generally do not disappear completely during therapy.

Binding antibodies to metreleptin resulted in increased total plasma leptin concentrations (including endogenous leptin and metreleptin) above normal ranges during metreleptin treatment. The increase in leptin concentration is likely due to delayed clearance of metreleptin bound to antibody. These findings are consistent with data from PK and toxicology studies in mice and dogs.

Although the clinical data are limited in LD patients, the change in HbA1c or TG from baseline by titer showed no clear association between peak titer of binding antibody and efficacy response (HbA1c or TG). The most frequent AE that appeared to be associated with development of antibodies to metreleptin in the LD patients was inflammatory injection site AE. There were no other AEs associated with antibody titer (and metreleptin exposure).

Even though metreleptin treatment is associated with a relatively high incidence of development of binding antibodies in LD patients as well as obese subjects (as is common with peptide or protein therapeutics), these antibodies generally do not appear to impact clinical safety or efficacy.

Neutralizing Activity to Metreleptin

Table 7.3.2-1 presents all cases where neutralizing activity was detected, including those in studies not included in the BLA.

Table 7.3.2-1: Neutralizing Activity to Metreleptin by Indication

Condition	Total Subjects Treated	Cases of Neutralizing Activity
Lipodystrophy		
NIH Study	72	1
FHA Study	28	0
IIT Study (C. Levy-Marchal, Principal Investigator)[1]	8	1
Congenital leptin deficiency[2]	18	2
Obesity (combination program)	615	3*

*In 1 subject, neutralizing activity developed after the end of the study (between Week 28 and 3 year follow up)
[1] Beltrand et al, *EJE.* 2010; 162(6):1083 91.
[2] Farooqi et al, *JCI.* 2002;110:1093 1103.

Recently, one LD patient treated with metreleptin in the NIH studies has been identified with neutralizing activity (based on a sample collected in Jun 2013). This 16 year old patient with CGL had been on metreleptin treatment for over 3 years when neutralizing activity was identified. Follow-up data from the NIH for this patient is currently lacking since the patient has not been able to return to the site for follow-up. Data from the local laboratory show that this patient had maintained glycemic control and non-fasting TGs were similar to fasting baseline TGs. At this stage, the long term clinical consequences of neutralizing activity in this patient cannot be determined. Neutralizing activity to metreleptin has not been identified in any patients in Study FHA101.

In addition to the case identified in the NIH studies, there was one confirmed case of neutralizing activity in a LD patient reported in the literature from an investigator-initiated study.[73] This patient did not present an initial response to metreleptin therapy, and therefore the effect of neutralizing activity on response could not be assessed.

The development of neutralizing activity to metreleptin after metreleptin administration has been reported in the literature in 2 pediatric patients with congenital leptin deficiency who genetically lack the ability to produce biologically active leptin.[47] The development of neutralizing activity was transient in one child; [47]follow-up information after development of neutralizing activity was not reported in the publication for the other child. However, both these patients have remained on metreleptin with good clinical benefit (personal communication) similar to several other patients with congenital leptin deficiency, some of whom have now been on metreleptin treatment for several years.

Neutralizing activity to metreleptin (with cross-reactivity to endogenous leptin in the 2 cases tested) was identified in 3 obese subjects in the pramlintide-metreleptin for obesity program

who demonstrated weight gain compared to baseline. Long term follow-up (~ 3.5 years after identification of neutralizing activity) available to date for 1 of the 3 subjects indicates that the persistence of in vitro neutralizing activity is not associated with continuing adverse clinical sequelae (i.e. body weight returned to lower weight than pre-treatment and improved metabolic control). A second subject was identified 3 years after termination of metreleptin treatment, during which time the patient had experienced substantial weight gain. Data from 1 follow-up visit 6 months after the initial identification of neutralizing activity indicates stable body weight. No follow-up is available for the third subject.

The findings for each of the cases identified with neutralizing activity are summarized in Table 7.3.2-2. To date, there is no clear evidence of adverse clinical consequences of neutralizing activity in LD patients. In LD patients, the main potential concern of neutralizing activity would be the loss of efficacy. To ensure that the appropriate patients receive treatment, the Sponsor proposes education of prescribers about the potential risk of clinical consequences of neutralizing activity through physician certification as a goal of the REMS with further assessment via the immunogenicity follow-up program (refer to Section 8.3).

Table 7.3.2-2: Long-Term Observations in Patients With Neutralizing Activity to Metreleptin

Condition	Patient	Clinical profile at time of NAc	Comments
Congenital leptin deficiency[1]	4 yo M	Transient loss of efficacy	Clinical response resumed after disappearance of NAc Continued on metreleptin
	3 yo M	Transient loss of efficacy	Continued on metreleptin
Obesity	40 yo F BMI 43	Weight gain (26 kg)	Patient declined follow-up
	48 yo M BMI 38	Weight gain (13 kg) Diabetes Dyslipidemia	Reversal of weight gain Improved metabolic control Continued NAc
	39 yo F BMI 33	Weight gain (64 kg)	Neutralizing activity 3 yrs post study Stable body weight
Lipodystrophy, CGL			
IIT Study[2]	11 yo F	Lack of clinical response	No safety findings reported
NIH Study	16 yo F	Glycemic control maintained	>3 yrs metreleptin treatment when NAc identified Continued treatment

[1]Farooqi et al, *JCI.* 2002;110:1093–1103.
[2]Beltrand et al, *EJE*. 2010; 162(6):1083 91.

Yo=year; M=male; F=female, f/u= follow-up; NAc=neutralizing activity

7.4 Other Safety Considerations Based on Leptin Physiology

7.4.1 Malignancies Other Than Lymphoma

7.4.1.1 Literature on the Potential Role of Leptin in Malignancies and Immune Surveillance

A potential role for leptin in cancer risk has been suggested from a variety of cancer cell models.[74] In vitro studies have demonstrated that leptin can promote cell proliferation and decrease apoptosis via several intracellular signaling pathways, including the JAK/STAT, PI3K, and ERK1/2 pathways.[74] Although leptin activates the JAK/STAT signaling pathway as part of normal leptin function, there is no indication that exogenous leptin treatment induces disruption of JAK/STAT signaling. Data addressing the capacity of leptin to promote malignancies in animal models are not consistent, and in vitro models of cancer cell progression do not necessarily translate into in vivo effects in animal models.

Leptin also has an important role in modulating innate and adaptive immune responses, including effects to reduce proliferation of T-regulatory cells while inducing proliferation of T-effector cells.[75] This has relevance to the potential role of leptin in malignancies. While self-tolerance is an important mechanism to prevent development of autoimmunity, it is also a mechanism by which tumor cells can evade immune surveillance. In human breast carcinoma,

the relative number of T-regulatory cells in tumor infiltrates is inversely proportional to survival.[76]

Reduction of the proportion of T-regulatory cells in tumors in mice has been demonstrated to improve immune-mediated anti-tumor responses, which are further enhanced by the accompanying increase in T-effector cells.[77,78]

Thus, the suppression of T-regulatory cells by leptin would be expected to have a favorable effect on tumor suppression. This provides additional context for considering the literature on leptin's potential role in malignancies and underscores the importance of understanding all the various facets of a complex in vivo system, rather than relying solely on the findings from in vitro experiments.

7.4.1.2 Events of malignancies other than lymphoma reported in the metreleptin clinical studies

In addition to the 2 cases of peripheral T-cell lymphoma NOS and 1 case of anaplastic large cell lymphoma in the NIH studies, 2 other malignancies were reported in the NIH and FHA101 LD studies.

- NIH studies: One case of papillary thyroid cancer was reported in a 22 year-old female with CGL who had a history of Hashimoto's thyroiditis prior to starting metreleptin. She was found to have multiple thyroid nodules a few months later and eventually diagnosed with multifocal papillary thyroid cancer involving 1 lymph node after ~2 years of metreleptin treatment. She underwent standard treatment and was felt to have a good prognosis. The papillary thyroid cancer was assessed by the investigator as unrelated to metreleptin treatment, and the patient continued on metreleptin as of the BLA data cut.
- Study FHA101: One case of worsening metastatic adenocarcinoma was reported in a 67 year-old female with AGL who had known metastatic adenocarcinoma (unknown primary) prior to initiating metreleptin treatment. She died ~ 2 months later due to progressive adenocarcinoma.

To further evaluate any potential relationship between metreleptin treatment and development or progression of malignancies, all studies involving metreleptin treatment in any patient population were reviewed for events of malignancies. This included data from the placebo controlled obesity studies as well as other investigator studies and compassionate use treatments where available. This comprehensive review revealed no new findings suggestive of increased risk of malignancies related to metreleptin treatment. The overall incidence of malignancies was low, with a range of different tumor types reported, including common malignancies like breast cancer. Although the majority of the events in the placebo-controlled obesity studies occurred in the context of relatively short exposure to metreleptin (<6 months), there was no evidence of imbalance compared to placebo. In addition, most malignancies occurred in subjects after brief exposure to metreleptin and/or in subjects with a relevant medical history or risk factor or some evidence of the condition at baseline.

The Sponsor's nonclinical data do not support the presence of a carcinogenicity signal for metreleptin. As discussed in Section 3 (Nonclinical Development), a full battery of genotoxicity testing revealed no evidence of mutagenic or clastogenic (causing chromosomal damage) effects of metreleptin. In addition, no drug-related proliferative lesions (pre-neoplastic or neoplastic), including in lymphocytes and lymphoid organs/tissues, were observed in repeated dose toxicology studies using metreleptin treatments of up to 6 months in mice and dogs. Specific assessment of potential in vivo metreleptin-induced cellular proliferation was also conducted using an immunohistochemistry method allowing the detection of PCNA in major tissues/organs (adrenal, brain and hypothalamic subsections, colon, duodenum, kidney, liver [hepatocytes and endothelial cells], lung, mammary gland, pancreas, pituitary, spleen, stomach, testes and thyroid) in both mice and dogs. The results showed that metreleptin was not associated with increased PCNA staining in any tissues in any animal species.

In summary, there is no evidence for a causal association between metreleptin and malignancies based on the clinical experience with metreleptin across different patient populations, the non-clinical toxicology program, and review of the literature.

7.4.2 Infections

7.4.2.1 Literature on role of leptin in immune function and susceptibility to infections

Leptin has a known role in regulating immune function, a finding that is not surprising given that leptin has the structure of a cytokine and acts on specific leptin receptors that belong to the class 1 cytokine receptor superfamily. However, the role of leptin in modulating both innate and adaptive immune responses is complex. Leptin receptors are expressed on many immune cells, and some immune cells themselves secrete leptin. Furthermore, the effects of leptin can be both stimulatory and suppressive.[79]

Epidemiological studies have long suggested a link between nutritional status and immune function.[80] In populations with poor nutrition, the incidence of infections is elevated, compared to populations with better nutrition. In contrast, nutrition appears to have an opposite effect on the incidence of autoimmune disease, which occurs with greater frequency and in populations with better nutrition.[80]

Leptin has been proposed as the link between nutritional and immune status. This is supported by the observation that *ob/ob* mice with a mutation in the leptin gene have a greater risk of infection compared to normal mice. This increased risk is mitigated by administering leptin.[81] Similarly, humans with congenital leptin deficiency due to a mutation in the leptin gene have evidence of increased susceptibility to infections with a much higher rate (odds ratio of 25) of mortality due to childhood infections compared to unaffected family members.[82] In vitro studies show that leptin has a specific effect on T-lymphocyte responses, differentially regulating the proliferation of naïve and memory T-cells and promoting a shift to a proinflammatory cytokine secretion profile.[83]In vivo, leptin administration during starvation

(which is associated with low leptin levels) in normal mice reverses starvation-induced immunosuppression, as assessed by a delayed-type hypersensitivity response.[83]

Susceptibility to infections has not been described as a key feature of LD syndromes although this has not been well studied in these patients. In a subgroup of 10 generalized LD patients participating in the NIH studies, evaluation of lymphocyte subpopulations has been performed at baseline and after 4 months of metreleptin administration.[84] At baseline, total T-cell and B cell, and monocyte populations were within the normal range, and the ration of CD4 to CD8 T cells was also normal. Administration of metreleptin resulted in small mean increases in certain T-lymphocyte subsets (including CD4+ and CD8+) but well within the normal range.[84]

7.4.2.2 Events of infections reported in the metreleptin lipodystrophy and obesity clinical studies

The Sponsor reviewed cases of infections in the LD and placebo controlled obesity studies to ascertain if metreleptin had an unfavorable effect on susceptibility to infections.

In the NIH studies, TEAEs of infections occurring in 2 or more patients included upper respiratory tract infection (n 5), ear infection (n 4), sinusitis (n 3), and appendicitis, cellulitis, pharyngitis streptococcal, urinary tract infection (all n 2), and alpha haemolytic streptococcal infection (n 1). One patient (8 year old with AGL and autoimmune hepatitis, Hashimoto's thyroiditis, Kawasaki's disease) had multiple events of infections (parainfluenza pneumonia, streptococcal pharyngitis, upper respiratory infection, sinusitis, ear infection, and influenza) but also had a medical history of common variable immunodeficiency. One patient had a TEAE of mild herpes zoster. In Study FHA101, TEAEs of infections occurring in 2 or more patients included urinary tract infection (N 6), upper respiratory infection (N 5), sinusitis (N 4), and viral infection (N 2). In both studies, events of infection were usually mild and assessed by the investigator as unrelated to metreleptin treatment.

Table 7.4.2.2-1 shows TEAEs of infections occurring in ≥1% of subjects in either metreleptin or placebo treatment groups in the 5-study monotherapy ISS in obese subjects. There were no major differences between the metreleptin and placebo treatment groups for these common infections. Review of other infections not meeting the ≥1% data cut revealed 1 event of herpes zoster in a metreleptin-treated subject and 1 event in a placebo-treated subject.

Table 7.4.2.2-1: Treatment-Emergent Adverse Events of Infections Occurring in ≥1% of Subjects in the Placebo Controlled Obesity Studies

	Metreleptin, n (%) N = 784	Placebo, n (%) N = 351*
Nasopharyngitis	95 (12.1)	44 (12.5)
Influenza	48 (6.1)	24 (6.8)
Sinusitis	30 (3.8)	17 (4.8)
Upper respiratory tract infection	27 (3.4)	26 (7.4)
Bronchitis	17 (2.2)	8 (2.3)
Gastroenteritis viral	10 (1.3)	2 (0.6)
Cystitis	10 (1.3)	0
Urinary tract infection	9 (1.1)	9 (2.6)
Viral infection	9 (1.1)	3 (0.9)
Rhinitis	8 (1.0)	3 (0.9)
Gastroenteritis	8 (1.0)	0

*Due to a induction period in Study LEPT 970213, 63 subjects randomized to placebo are counted in both metreleptin and placebo groups. AEs are summarized based on treatment at time of event

In summary, leptin-deficient LD patients do not appear to experience immunosuppression and susceptibility to infections to the same degree as patients with absolute, lifelong leptin deficiency due to leptin gene mutation. There was no evidence from clinical studies of metreleptin of an unfavorable effect on susceptibility to infections, based on the lack of any imbalance for common infections compared to placebo in obese subjects, and the lack of any unusual or opportunistic infections related to metreleptin treatment.

7.4.3 Autoimmune Disease

7.4.3.1 Literature on Role of Leptin in Autoimmunity

Experimental studies suggest a potential role for leptin in autoimmunity. Leptin-deficient *ob/ob* mice are protected from induction of autoimmune disease in the experimental autoimmune encephalitis (EAE) model of multiple sclerosis,[85] but susceptibility is restored when leptin is administered. Leptin also accelerates autoimmune diabetes in a susceptible mouse model of type 1 diabetes.[86] The underlying mechanism may reflect the opposing effects of leptin on T-regulatory cells and T-effector cells, since leptin reduces proliferation of T-regulatory cells while inducing proliferation of T-effector cells.[75] T-regulatory cells play an important role in the maintenance of self-tolerance, by suppressing recognition of self-antigens as foreign, an important aspect of preventing autoimmunity. Thus, suppression of T-regulatory cells by leptin could theoretically enhance autoimmunity in susceptible models. Although the experiments in *ob/ob* mice demonstrate that leptin is necessary for restoration of "normal" autoimmune susceptibility in mice completely lacking leptin, there is no evidence that leptin can promote autoimmunity in animals not otherwise susceptible.

The potential role of leptin in enhancing autoimmunity has relevance to the use of metreleptin in LD patients, especially patients with acquired LD (AGL or APL) for whom an autoimmune basis has been proposed as a factor in the development of LD, e.g. an autoantibody against adipocytes. In the published literature, other autoimmune diseases are reported to occur frequently in both AGL and APL patients.[4,5] Although animal models suggest a low leptin state such as occurs with lipodystrophy may theoretically protect against autoimmunity, the underlying autoimmunity associated with acquired forms of lipodystrophy may predominate.

7.4.3.2 Events of Autoimmunity Reported in the Metreleptin Lipodystrophy Clinical Studies

A review of TEAEs indicative of autoimmunity in the NIH and FHA101 studies were conducted in order to understand if metreleptin exacerbates autoimmunity.

There was a high prevalence of autoimmune disease at baseline with 15 (15%) of 100 patients having a medical history of autoimmune disease. Consistent with the association between acquired lipodystrophy and autoimmune diseases, most of the patients having a medical history of an autoimmune disease had acquired LD (11 [42%] of 26 patients with acquired LD vs. 4 [5%] of 74 patients with inherited LD). In the NIH studies, most autoimmune conditions occurred only in AGL patients, including autoimmune hepatitis (N 3), type 1 diabetes (N 3), Kawasaki's disease (N 1), and vitiligo (N 1), except for Hashimoto's thyroiditis and celiac disease (both of which were reported in 1 CGL patient and 1 AGL patient). In Study FHA101, there were 4 patients with AGL (3 pediatric and 1 adult), and all 3 pediatric patients had another autoimmune disease, including dermatomyositis, autoimmune hepatitis, and Grave's disease.

Few TEAEs indicative of autoimmunity were reported during metreleptin treatment. In the NIH studies, 2 events of membranoproliferative glomerulonephritis (which can have an autoimmune basis) were reported in 2 AGL patients, 1 with a medical history of type 1 diabetes, and 1 with a medical history of proteinuria and chronic renal failure. A 3rd AGL patient with a medical history of autoimmune hepatitis and other autoimmune diseases had an event of worsening autoimmune hepatitis but has continued on metreleptin treatment for ~10 years as of the BLA data cut. Other autoimmune TEAEs not occurring in patients with acquired LD included one event of lupus anticoagulant in a FPL patient and one event of Hashimoto's thyroiditis in a CGL patient. However, there is also one case documented of improvement in a co-existing autoimmune condition during metreleptin treatment. One AGL patient in Study FHA101 who had active juvenile dermatomyositis when she initiated metreleptin treatment had improvement in her dermatomyositis with improved functional capacity and muscle inflammation (based on MRI) after 2 years of metreleptin treatment.[87]

Thus, although a role for metreleptin in exacerbating autoimmunity could be proposed based on experimental data in animal models, the clinical experience of metreleptin administration in LD patients, including patients with acquired LD and active autoimmune diseases, has not provided evidence that this is a real concern in humans.

7.4.4 Conclusions

The role of leptin in immunoregulation is complex, and the potentially dysregulated immune systems of LD patients (especially those with acquired LD and/or autoimmunity) make it difficult to ascertain the precise effects, if any, that metreleptin therapy may have on their immune function. Based on data currently available from the clinical studies of metreleptin, as well as other published data (in vitro, nonclinical, etc), there is no evidence that metreleptin has an adverse effect on immune function as it relates to promotion of malignancies, susceptibility to infections, or enhancement of autoimmunity.

7.5 Other Safety Topics Related to Underlying Disease State and/or Treatment

7.5.1 Pancreatitis

Patients with LD are predisposed to acute pancreatitis, a serious and potentially life threatening condition, due to marked hypertriglyceridemia (especially when TG levels exceed 1,000 mg/dL). Despite metreleptin's substantial effects to reduce serum TG in these patients, some patients likely remain predisposed to developing acute pancreatitis by virtue of having a history of pancreatitis and/or continuing to exhibit hypertriglyceridemia.

A summary of acute pancreatitis events reported in the LD clinical program are presented in Table 7.5.1-1. All of these events were assessed by the investigator as unrelated to metreleptin. In both the NIH and FHA studies, all patients who had a new event of pancreatitis while on metreleptin had a previous history of pancreatitis and hypertriglyceridemia.

Table 7.5.1-1: Treatment-Emergent Adverse Events of Acute Pancreatitis in the NIH Studies and Study FHA101 (Analysis Population)

	NIH N=72 n (%)	FHA N=28 n (%)
Study Population Background		
History of pancreatitis	20 (28%)	2 (8%)
Baseline TG ≥1000 mg/dL	16 (22%)	4 (14%)
AEs of Pancreatitis	5 (7%)	1 (4%)
History of pancreatitis	Yes (n 5)	Yes
Baseline hypertriglyceridemia	Yes (n 5)[1]	Yes[2]
Interruption of treatment or noncompliance	Yes (n 4)	No

[1] Baseline Hypertriglycerdemia = 359, 1669, 2324, 2984, and 7420 mg/dL
[2] Baseline Hypertriglycerdemia = 10623 mg/dl

Five of these events were SAEs. Four events were associated with withdrawal and/or noncompliance with metreleptin treatment, including one (not an SAE) that occurred in the setting of controlled withdrawal of metreleptin.[8]

One case, resulting in death, was reported in the NIH studies in a 15-year old female with generalized LD diagnosed when 4 years old and with a history of diabetes, hypertriglyceridemia, pancreatitis, hypertension, and focal segmental glomerulosclerosis. She was hospitalized due to acute pancreatitis after 3 months of metreleptin treatment, developed a ruptured pancreatic pseudocyst, septic shock, and cardiac arrest.

It is important to note that 28% of the NIH patients had a past medical history of pancreatitis or recurrent pancreatitis prior to starting metreleptin treatment and 22% of the patients had baseline TG levels higher than 1000 mg/dL. In the FHA study, 8% and 14% of patients had a history of pancreatitis or TG levels higher than 1000 mg/dL, respectively. While a precise estimate of event rate of pancreatitis prior to metreleptin treatment cannot be calculated (due to lack of details on timing and frequency of prior pancreatitis events), these data demonstrate that pancreatitis is common among LD patients. Despite this high risk for recurrent events, most of the patients with a prior history of pancreatitis did not experience any new events during metreleptin treatment.

In the placebo controlled obesity studies, one event of acute pancreatitis (an SAE) was reported in an obese subject with type 2 diabetes and baseline TG levels of 261 to 481 mg/dL who received metreleptin treatment. The TG level after the onset of symptoms was 822 mg/dL. The event was assessed as unrelated to study drug.

The available data do not indicate a causal association between metreleptin-treatment and pancreatitis. Rather, the discontinuation of metreleptin in patients with a prior history of /or risk for pancreatitis appears to be associated with a risk of recurring pancreatitis likely due to recurring hypertriglyceridemia. There are no data indicating that the discontinuation of metreleptin would have a “rebound” effect on risk of acute pancreatitis (i.e., to increase the risk beyond that pretreatment).

7.5.2 Hypoglycemia

It is common for LD patients to have severe insulin resistance and be treated with high doses of insulin. In these patients, improvement of insulin sensitivity might represent a risk for developing hypoglycemia.

A summary of hypoglycemic events reported in the LD clinical program are presented in Table 7.5.2-1.

Table 7.5.2-1: Treatment-Emergent Adverse Events of Hypoglycemia in the NIH Studies and Study FHA101: Analysis Population

	NIH N=72	FHA N=28
Incidence and events of hypoglycemia		
n (%), events	8 (11%), 9 events	7 (25%), 13 events
Mild / Moderate / Severe Events	5 / 4 / 0	11 / 1 / 1
Background Anti-Diabetes Medications*		
Oral Agents only	0	1
Insulin +/- Oral Agents	9	12

*Information for background anti diabetes medication is only provided for those patients who experienced a AE of hypoglycemia

These hypoglycemic events occurred predominantly in patients on concomitant insulin therapy (short-acting and long-acting insulins, U500 insulin) with or without oral agents for diabetes (sulfonylureas, metformin, and thiazolidinediones). The time to onset for these events varied among the patients, ranging from the first day to 2 years after administration of metreleptin. Four pediatric patients experienced hypoglycemia. Hypoglycemia events assessed as related to metreleptin were usually deemed associated with the administration of concomitant diabetes therapy together with metreleptin. Importantly, all except for 1 of the events assessed as related were mild to moderate in intensity and did not require third-party assistance for patients in the NIH studies. One patient in Study FHA101 experienced a SAE of severe hypoglycemia that did require assistance but not hospitalization. This patient recovered shortly after receiving carbohydrates.

Hypoglycemia in metreleptin-treated LD patients likely relates to the substantial improvement in insulin sensitivity with metreleptin administration, especially in patients on high-dose insulin therapy, which may not have been titrated down rapidly enough to compensate for the improved insulin sensitivity.

In the placebo-controlled obesity studies, events of hypoglycemia occurred at a low frequency (3.6% in metreleptin vs. 1.4% in placebo), and were only seen in subjects with diabetes. None of these hypoglycemic events were considered severe.

Thus, considering concomitant use of high doses of insulin in many patients, the marked improvement in insulin sensitivity with metreleptin treatment and long mean treatment duration, the number of events of hypoglycemia is low and does not appear to pose a safety concern at time of initiation of treatment or during long term follow up.

7.5.3 Weight Loss

Reduced appetite, and potentially weight loss is an expected pharmacological effect of metreleptin in leptin-sensitive individuals such as LD patients. Metreleptin treatment reduces hyperphagia in LD patients,[62] thus some weight loss may occur as hyperphagia is corrected. However, it is also possible that some of the observed weight loss may have resulted from reduction of the ectopic fat deposition, e.g. hepatic steatosis. In the data presented for the NIH studies within the BLA application, AEs of weight loss were reported in 6 (8%) patients, all of whom had generalized LD. Weight decrease was reported in 2 (7%) patients in the FHA101 study. In both studies, a decrease in mean body weight of 1 to 2 kg occurred over the first year of treatment, with body weight generally remaining stable thereafter. None of the events of weight loss were considered serious.

The potential for weight loss, especially in patients with low to normal body mass index (BMI) at baseline and/or who have generalized LD and very low leptin levels, should be considered with dose adjustments as necessary to avoid excessive weight loss. The concern for excessive weight loss is particularly relevant for pediatric patients (refer to Section 7.6.1). Most of the patients with reports of weight loss were pediatric and the dose of metreleptin was only temporarily reduced in a few of those patients, indicating that these events were not considered a major concern by the investigator.

7.5.4 Generalized Hypersensitivity

Since severe generalized hypersensitivity events tend to be rare, a search of the database for AEs with a preferred term indicative of potential generalized hypersensitivity (e.g., hypersensitivity, drug hypersensitivity, angioedema, anaphylaxis, and urticaria) was conducted. No generalized hypersensitivity events have been assessed by the investigator as related to metreleptin treatment and none were considered serious. All patients continued long term treatment with metreleptin for several years after the reported events.

There was 1 event of an anaphylactic reaction which occurred after 4 years of metreleptin treatment reported in a patient with generalized LD in the NIH studies, but this was assessed as a food-related allergy, and the patient continued treatment. There were 2 events of urticaria 1 occurring in a patient with generalized LD and 1 in a patient with partial LD. These events occurred after 1 month and 2.5 years of metreleptin treatment and both patients remained on metreleptin treatment. In Study FHA101 there were 2 events of urticaria in 1 FPL patient with IgA deficiency who had a previous history of multiple recurring episodes of urticaria.

The most common types of hypersensitivity events reported in the placebo controlled obesity studies were urticaria, hypersensitivity and drug hypersensitivity, almost all events occurring in the metreleptin-treated subjects, 20 metreleptin subjects (2.6%) vs. 2 placebo subjects (0.6 %).

In addition, there were two reports of angioedema, none associated with respiratory or circulatory compromise. One patient reported urticaria rash on arms, legs and trunk for three months; then angioedema on both arms and legs. The event resolved with prednisone and epinephrine. Concomitant meds included lisinopril and certrizine. Patient completed study per protocol. The second patient experienced urticaria and angioedema with periorbital edema and

tongue swelling after 2 weeks of treatment. The patient discontinued metreleptin treatment and the event resolved with diphenhydramine and methylprednisolone. Concomitant meds included certrizine and etanercept.

There were no events of anaphylaxis or anaphylactic reactions in the placebo controlled obesity studies. No events suggestive of a severe cutaneous reaction such as Stevens Johnson syndrome or toxic epidermal necrolysis were observed in LD patients or obese subjects treated with metreleptin. Thus, there are only a few reports of generalized hypersensitivity in patients with LD and all patients have continued metreleptin long term without recurring events.

7.5.5 Renal Safety

A high incidence of proteinuric nephropathies (e.g., MPGN and focal segmental glomerulosclerosis as well as diabetic nephropathy) have been noted in patients with generalized LD.[24] Acquired partial LD is also associated with a higher frequency of MPGN.[2] As discussed in Section 6.3.8 (Proteinuria), a substantial decrease in 24-hour urine protein excretion rate was observed with metreleptin treatment. Over two-thirds of the patients (71%) in the NIH studies had a baseline medical condition of renal disease.

A review of treatment-emergent AEs relevant to chronic renal disease in the LD clinical program is summarized in Table 7.5.1-1.

All patients who experienced TEAEs relevant to chronic renal disease had a pre-existing medical history related to renal disease. None of these AEs were considered by the investigator as related to metreleptin treatment.

Table 7.5.5-1: Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to Chronic Renal Disease in the NIH Studies: Analysis Population

Patient ID / Demog	Relevant Medical History / Baseline 24-hr Urine Protein	TEAE[a]	Time to Onset (Days)	Investigator Assessment of Relatedness / SAE
90106 35 yr F, CGL	Proteinuria (2.6 g/24 hr)	Proteinuria Kidney failure	65 3464	Unrelated – non SAE Unrelated Fatal SAE
90107 42 yr F, FPL	Focal glomerulonephritis, stage IV kidney failure, proteinuria (1.9 g/24 hr)	End stage renal disease Right renal transplant	2519[b] 2748	Unrelated - Non SAE Unrelated SAE
90109 13 yr F, AGL	Proteinuria (2.7 g/24 hr)	Membranoproliferative glomerulonephritis Worsening of proteinuria	441 422	1) Unrelated - Non SAE 2) Unrelated SAE
90113 12 yr F, CGL	Proteinuria (3.2 g/24 hr)	Focal proliferative glomerular sclerosis	327[b]	Unrelated - Non SAE
90114 35 yr M, AGL	Chronic renal failure, proteinuria (2.45 g/24 hr)	Membranoproliferative glomerulonephritis Worsening of proteinuria	270 270	1) Unrelated - Non SAE 2) Unrelated Non SAE, AELW
90163 20 yr F, CGL	Proteinuria (5536 g/24 hr)	Focal segmental glomerulosclerosis	136	Unrelated - Non SAE

[a] Verbatim term

[b] Start day unknown, calculation based on the 1st of the month and year

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

One patient, a 35-year-old with CGL died due to kidney failure leading to cardiac arrest. The patient had a medical history of pneumonia, hyperlipidemia, diabetes, peripheral vascular disease, and proteinuria. Approximately 6.5 years after discontinuing study participation, the patient resumed study participation at the NIH and restarted metreleptin treatment. At her follow-up visit, approximately 9 months after re-initiating metreleptin treatment, it was noted that her kidney disease, originally noted prior to starting study medication, had worsened, as evidenced by decreasing creatinine clearance. The patient stated she did not desire dialysis and expressed reservation about nephrology follow-up. Approximately 1.5 years after restarting metreleptin treatment the patient died from kidney failure. The event was considered by the investigator as unrelated to metreleptin treatment.

All of the events related to renal disease occurred in patients with generalized LD (either acquired or congenital), except for 1 patient who had FPL. No events indicative of chronic renal disease were reported in Study FHA101.

In the NIH population, analysis of the mean estimated Glomerular Filtration Rate (eGFR) over time, showed no major change (means of 115 to 140 mL/min/1.73 m^2, well within the normal range). Categorical shifts in renal function occurred in both directions during treatment. Clinically significant shifts to reduced renal function were generally seen only seen in patients with pre-existing renal disease.

In the placebo controlled obesity studies, the incidence of renal/urinary disorders was lower in subjects treated with metreleptin (8 subjects [1.0%]) than subjects treated with placebo (10 subjects [2.8%]).

Based on these findings, AEs related to chronic renal disease reported in the metreleptin LD studies are assessed as likely related to the underlying LD condition and not an adverse effect of metreleptin treatment.

7.5.6 Hepatic Safety

Hepatic steatosis (commonly associated with elevated liver enzymes) is a key feature of LD. Reduced capacity for TG storage in adipose tissue results in ectopic deposition of TG in non-adipose tissues such as the liver. Patients with acquired LD often have associated autoimmune diseases, including autoimmune hepatitis, which can further exacerbate the steatohepatitis associated with LD and underscoring the need for a therapy to improve the liver disease associated with LD. Consistent with the literature, the majority (85%) of patients in the LD studies had liver disease. Several other patients in the NIH studies had evidence of more advanced liver disease (with cirrhosis or hepatic fibrosis), and 3 patients (all with AGL) had a medical history of autoimmune hepatitis.

As mentioned in Section 6.4.3 (Liver Endpoints), substantial improvements in transaminase levels, liver volume, steatosis grade and ballooning injury scores, and NAFLD activity score were observed after 12 months of treatment with metreleptin. Patients, who already had fibrosis, remained stable.

Treatment-emergent AEs relevant to chronic liver disease in the LD clinical program are summarized in Table 7.5.6-1. All patients who experienced TEAEs relevant to chronic liver disease had a pre-existing medical history related to liver disease. None of these AEs were considered by the investigator as related to metreleptin treatment.

Table 7.5.6-1: Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to Chronic Liver Disease in the NIH Studies and Study FHA101: Analysis Population

Patient ID / Demog	Relevant Medical History/ Baseline LFTs	TEAE[a]	Time to Onset (Days)	Investigator Assessment of Relatedness / SAE
NIH Studies 991265/20010769				
90103 27 yr F, AGL	Autoimmune hepatitis, liver fibrosis (AST 57, ALT 128)	Increased liver enzymes	481	Unrelated SAE
90107 42 yr F, FPL	Hepatomegaly, focal glomerulonephritis (AST 28, ALT 28)	Steatohepatitis Cholecystitis	6 2370[b]	Unrelated - Non SAE
90109 13 yr F, AGL	Nonalcoholic steatohepatitis, bridging fibrosis (AST 85, ALT 79)	Chronic inflammatory hepatitis Worsening of liver disease	382 422	Unrelated- Non SAE Unrelated SAE
90110 8 yr F, AGL	Autoimmune hepatitis, mild portal fibrosis, fatty liver (AST 38-39, ALT 53-56)	Worsening autoimmune hepatitis (Hepatobiliary) Elevated ALT level of 317 U/L	2443 34	Unrelated- Non SAE Unrelated SAE
90158 18 yr F, AGL	Severe liver disease with cirrhosis (AST 142, ALT 105)	Hepatic encephalopathy Progressive end stage liver disease	344 523	Unrelated SAE Unrelated Fatal SAE
Study FHA101				
648004 30 yr F, FPL	Fatty liver, increased LFTs (AST 21, ALT 14)	Elevated AST levels	443	Unrelated – Non SAE
648016 11 yr M, AGL	Chronic active autoimmune hepatitis, history of elevated LFTs (AST 208, ALT 419)	Increased LFTs	9	Unrelated - Non SAE

[a] Verbatim term

[b] Start day unknown, calculation based on the 1st of the month and year

Yr = years; F = female; M = male; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy; LFT = liver function tests; TEAE = treatment-emergent adverse event; ALT= alanine transaminase; AST= aspartate aminotransferase

One patient, an 18-year-old Hispanic female patient with AGL died of chronic hepatic failure. This patient's medical history at study entry included severe liver disease with cirrhosis (baseline ALT 105U/L, AST 142U/L, total bilirubin 1.1 mg/dL, and alkaline phosphatase 185 U/L), elevated ammonia levels, constipation, hypercholesterolemia, mild renal insufficiency, proteinuria, diabetes, and pancytopenia. After nearly 1 year of treatment with metreleptin, the patient experienced an SAE of hepatic encephalopathy with altered consciousness related to constipation and taking pain medications for the constipation. The

only available follow-up liver enzyme data showed some increase from baseline (ALT 123 U/L, AST 198 U/L, total bilirubin 1.7 mg/dL, and alkaline phosphatase 357 U/L). The event resolved within a few days after receiving lactulose, and she was discharged in good condition. Six months after the event, the NIH study staff was notified that the patient had been hospitalized for a few weeks, was placed on life support and passed away. At the time of her death, the patient had received metreleptin treatment for approximately 1.4 years. The investigator assessed the event of chronic hepatic failure as unrelated to study medication.

All of the events related to liver disease occurred in patients with evidence or diagnoses of liver disease at baseline, and all events were assessed as unrelated to metreleptin treatment.

There were no cases of ALT or AST >3X upper limit of normal (ULN) and total bilirubin >2X ULN and thus no biochemical cases of Hy's law (drug-induced liver injury) from either the LD dataset or the placebo controlled obesity studies.

Based on these findings, the AEs reflecting chronic liver disease reported in the metreleptin LD studies are assessed as likely related to the underlying LD condition rather than an adverse effect of metreleptin treatment.

7.6 Safety in the Pediatric and Adult Patient Population

7.6.1 Frequent Adverse Events in Pediatric and Adult Patients Population

Frequent (incidence ≥5%) TEAEs in pediatric and adult patients, in order of decreasing incidence overall in the NIH studies only are presented in Table 7.6.1-1.

Table 7.6.1-1: Frequent (Incidence ≥5% in NIH) Treatment-Emergent Adverse Events by Pediatric and Adult Patients in the NIH Studies: Analysis Population

	n (%)		
Preferred Term	All Patients (N=72)	< 18 Years (n=39)	≥18 Years (n=33)
Hypoglycemia	8 (11.1)	4 (10.3)	4 (12.1)
Fatigue	7 (9.7)	2 (5.1)	5 (15.2)
Headache	6 (8.3)	3 (7.7)	3 (9.1)
Nausea	6 (8.3)	4 (10.3)	2 (6.1)
Weight decreased	6 (8.3)	4 (10.3)	2 (6.1)
Abdominal pain	5 (6.9)	5 (12.8)	0 (0.0)
Alopecia	5 (6.9)	1 (2.6)	4 (12.1)
Ovarian cyst	5 (6.9)	3 (7.7)	2 (6.1)
Pain in extremity	5 (6.9)	1 (2.6)	4 (12.1)
Upper resp. tract infection	5 (6.9)	3 (7.7)	2 (6.1)
Arthralgia	4 (5.6)	3 (7.7)	1 (3.0)
Constipation	4 (5.6)	1 (2.6)	3 (9.1)
Diarrhea	4 (5.6)	3 (7.7)	1 (3.0)
Dizziness	4 (5.6)	3 (7.7)	1 (3.0)
Ear infection	4 (5.6)	2 (5.1)	2 (6.1)
Pancreatitis	4 (5.6)	2 (5.1)	2 (6.1)
Renal cyst	4 (5.6)	2 (5.1)	2 (6.1)

In the NIH studies, the incidence of AEs was similar between adults and pediatric patients, with the exception of fatigue, alopecia, pain in extremity, and constipation which were more frequent among the adult population and abdominal pain occurring in pediatric patients only. Higher incidences of weight decreased and abdominal pain occurred in the pediatric population. Due to the small number of patients <18 years (N 3) in Study FHA101, meaningful comparisons of TEAEs by age in this study cannot be made.

A total of 7 pediatric patients reported a TEAE of weight decrease, including those reported in the 4-MSU data cut. None was reported as a SAE. A discussion of weight loss in the overall study population, including pediatric patients, is provided in Section 7.5.3.

Assessment of growth and pubertal development in pediatric patients reporting a TEAE of weight loss in the NIH studies did not reveal a consistent impact on either growth or pubertal status; 2 patients experienced normal onset of puberty and normal growth, 1 patient had puberty and growth complete prior to initiation of therapy, 1 patient had pubertal status normal for age and tall stature, and 1 subject had growth slowed. One patient had no growth or pubertal assessment reported. Further details are in Section 7.6.3 (Pubertal Development and Growth in Pediatric Patients).

7.6.2 Deaths and Other SAEs in the Pediatric Population

Deaths

Of the 4 deaths in the NIH studies, 1 death (ruptured pancreatic pseudocyst, septic shock, and cardiac arrest) occurred in a 15-year old female with CGL (refer to Section 7.5.1).

In Study FHA101, no deaths occurred in pediatric patients.

SAEs

The incidence of SAEs was lower in pediatric patients (18%) compared to the adult (30%) population. In Study FHA101, only 2 SAEs occurred in pediatric patients (1 case of constipation and 1 case of acute pancreatitis).

7.6.3 Pubertal Development and Growth in Pediatric Patients

Given the role of leptin in reproduction and the hypothesis that leptin may serve as a metabolic gate for the onset of puberty in humans,[88] pubertal development and growth in pediatric patients was assessed. Individual patient height and weight data over time for pediatric patients in NIH and FHA101, and growth expressed as a percentile according to standard growth charts, as well as Tanner staging data were collected.

The investigators provided an assessment of pubertal development in NIH pediatric patients. The majority (34 [87%] out of 39) of pediatric patients either had completed or nearly completed puberty (or likely completed) prior to metreleptin, were prepubertal before and after metreleptin (appropriate for age), or had normal pubertal onset and/or progression on metreleptin treatment. However, pubertal disorders were present at baseline in 6 [15%] out of 39 patients (2 with precocious puberty, 4 with delayed puberty).

Two patients were noted to have delayed puberty after starting metreleptin. One patient a17-year old female with AGL had complete lack of breast development before and after metreleptin treatment. However, the information available on pubertal status after starting metreleptin is limited. She was also extremely ill with other conditions (including pancreatitis, steatohepatitis, nephropathy), which may have contributed to poor pubertal development. Similarly, a 13-year old female with CGL was mid-pubertal at time of starting metreleptin with lack of apparent progression on metreleptin (though limited information on pubertal status is recorded), and also was extremely ill with other conditions (cirrhosis, hepatopulmonary syndrome), which may have contributed to poor pubertal development. It is also worthwhile to note that 2 patients had delayed puberty prior to metreleptin, but had normal pubertal progression after starting metreleptin.

These data are reassuring in demonstrating that while metreleptin treatment may help to normalize delayed pubertal progression, there is no evidence for metreleptin causing precocious puberty in these pediatric patients.[89] For the 2 patients who had possible delayed puberty on metreleptin, the poor pubertal progression appeared likely to be related to concurrent serious illness rather than metreleptin.

For evaluation of growth, each NIH pediatric patient (those with at least one growth point post baseline) was categorized into one of 3 categories of stature (short, normal, or tall) at baseline, with the majority having normal or tall stature prior to metreleptin. In addition, patients were classified into whether growth was complete or near complete prior to receiving metreleptin (N 18, 46%) or one of 3 categories of growth pattern (normal, accelerated, or decelerated) during metreleptin treatment (N 20, 51%). One patient did not have a growth pattern assessed since she died due to pancreatitis and subsequent septic shock leading to cardiac arrest about 4 months after starting metreleptin. Of 20 patients with growth pattern assessed, 9 patients had normal growth, 2 had accelerated growth, and 9 patients had growth deceleration on metreleptin. This growth deceleration likely represents a normalization (or partial normalization) of rapid growth prior to metreleptin.

Only 3 pediatric patients were enrolled in Study FHA101, there was no evidence of untoward effects of metreleptin on growth, pubertal onset or progression in these patients.

Adverse events of weight decreased occurred predominantly in pediatric patients and did not seem to affect growth or pubertal maturation.

In addition to these patients, nonclinical toxicity studies have shown no adverse effects on developmental and reproductive endpoints with metreleptin treatment (Section 3, Nonclinical Development).

7.7 Overall Summary of Safety

Metreleptin has an acceptable safety and tolerability profile in the LD patient population. In the NIH and FHA101 studies, frequent AEs considered related to metreleptin treatment included hypoglycemia, fatigue, nausea, decreased body weight, abdominal pain, injection site hematoma, and injection site urticaria. None of the events considered related to treatment led to discontinuation. One event of hypoglycemia and one event of abdominal pain were reported as SAEs.

Two cases of peripheral T-cell lymphoma and 1 case of a localized anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (a type of T-cell lymphoma) have been reported in the NIH studies. All 3 events occurred in patients with AGL known to be associated with autoimmune disease. There was evidence of pre-existing lymphoma and/or bone marrow abnormalities in the 2 patients with peripheral T-cell lymphoma before metreleptin treatment. The third case of anaplastic large cell lymphoma occurred in the context of a specific chromosomal translocation. Based on these observations, it is unlikely that metreleptin contributed to de novo development of the 3 lymphomas. It is also unlikely that metreleptin contributed to any progression of pre-existing lymphoma, although the latter cannot be excluded with certainty. In addition, 2 cases of peripheral T-cell lymphoma have been reported in the literature in patients with a clinical picture of acquired LD, who have not been treated with metreleptin.

Most patients in the NIH and FHA101 studies developed drug binding antibodies, which is not an unusual finding with biologic therapeutics. Assessment of binding (non-neutralizing) antibodies as well as neutralizing activity to metreleptin (based on an in vitro cell-based assay)

has been performed in the NIH and FHA101 studies, as well the obesity program. Development of these binding antibodies had no apparent impact on overall efficacy or safety. In a small number of subjects, development of high-titer drug antibodies was coincident with detection of neutralizing activity.

From the available data, there is no clear evidence of adverse clinical consequences of in vitro neutralizing activity in patients with LD. As loss of efficacy represents the main potential concern of neutralizing activity, testing for neutralizing activity should be considered in patients in whom loss of efficacy is suspected and no other causes can be identified, such as noncompliance with treatment.

A thorough review of AEs reported in the LD studies (supplemented by placebo-controlled studies of metreleptin in obesity) suggests that the majority of serious AEs (e.g., chronic renal or liver disease, cardiovascular events, acute pancreatitis, etc) were related to the underlying disease state and do not result from metreleptin therapy. There were no major differences in the safety profile of patients with partial LD compared to patients with generalized LD independent of the baseline co-morbidities and underlying metabolic abnormalities. Similarly, the safety profile of metreleptin was similar among the adult and pediatric LD population. Adverse events of decreased weight and abdominal pain occurred at a higher incidence in pediatric patients compared to adult patients. There was no evidence of an adverse effect of metreleptin on growth or pubertal maturation in pediatric patients.

In the LD studies, TEAEs of acute pancreatitis were reported in 5 patients. All of these patients who had a new event of pancreatitis while on metreleptin had a previous history of pancreatitis and hypertriglyceridemia. The events were considered to be related to severe hypertriglyceridemia, consistent with the underlying LD disease state. The risk of recurrent pancreatitis is increased in patients who discontinue metreleptin treatment or are noncompliant with treatment, particularly in patients with a previous history of pancreatitis. Dose tapering is recommended if metreleptin treatment is discontinued in patients with risk factors for pancreatitis.

Pharmacological effects of metreleptin (such as potential weight loss or hypoglycemia, particularly in combination with insulin as down titration becomes necessary) were manageable. Although hypoglycemia is not evident with metreleptin treatment alone, hypoglycemia may occur in the setting of rapid improvement in insulin sensitivity with metreleptin treatment in patients on high doses of insulin, and possibly in patients on insulin secreatogues. The risk for hypoglycemia can be managed by appropriate monitoring of blood glucose in patients on concomitant insulin secretagogues or insulin therapy and dose adjustment of concomitant diabetes therapies as needed.

No events of generalized hypersensitivity were assessed by the investigator as related to metreleptin treatment in the LD clinical studies. Events of generalized hypersensitivity were reported in obese subjects (without LD) treated with metreleptin but were infrequent, and no events with respiratory or circulatory compromise have been reported.

Leptin has a known role in regulating immune function that is complex. This has relevance given the potentially dysregulated immune systems of LD patients (especially those with acquired LD and/or autoimmunity). However, based on the available data from clinical studies of metreleptin, as well as other published data (in vitro, nonclinical, etc), there is no evidence that metreleptin has an adverse effect on immune function as it relates to promotion of malignancies, susceptibility to infections, or enhancement of autoimmunity.

Overall, metreleptin has a favorable safety profile with the majority of patients studied as part of this BLA remaining on treatment, some for over 11 years. This long term data provides important safety information for a therapy intended for chronic administration.

8 RISK MANAGEMENT AND POST-MARKETING SAFETY ASSESSMENTS

Metreleptin has been studied in LD patients up to 11 years through ongoing clinical studies. To ensure the continued assessment of the benefit-risk profile of metreleptin, proactive safety surveillance and evaluation in the post-marketing period is planned. The Sponsor has developed Risk Management activities, such as labeling, educational materials, Risk Evaluation and Mitigation Strategy (REMS) to address identified and potential risks associated with metreleptin treatment. Post-marketing safety assessments include routine pharmacovigilance surveillance activities along with targeted questionnaires to gather additional information on adverse events of special interest.

To further evaluate long-term safety and efficacy of metreleptin in patients with LD, the Sponsor is initiating a prospective metreleptin Safety Registry, an immunogenicity follow-up program, and a pregnancy and lactation exposure follow-up program.

8.1 Proposed REMS Program

The Sponsor is committed to ensure safe and appropriate use of metreleptin by the implementation of risk mitigation activities as part of a proposed Risk Evaluation and Mitigation Strategies (REMS) that was submitted in the BLA. The proposed goals of the metreleptin REMS are:

1) To educate prescribers about:
   - the potential risk of lymphoma associated with the use of metreleptin
   - the potential risk of loss of efficacy due to the development of neutralizing activity to metreleptin; and
   - the need to monitor patients during treatment with metreleptin as per product labeling
2) To restrict access to therapy with metreleptin to pediatric and adult patients with inherited or acquired LD.

The REMS will include the following elements to assure safe use:

Healthcare providers (HCPs) will be required to be specially certified to prescribe metreleptin.

1) In order for HCPs to be certified, they must undergo an educational program and enroll in the metreleptin REMS program by acknowledging an understanding of the potential risks of metreleptin and the appropriate patient population for metreleptin therapy.
2) Metreleptin will be dispensed by a single pharmacy provider that are certified and that agree to follow the REMS requirements.
3) Certified pharmacies will need to have systems in place to ensure that only certified prescribers prescribe metreleptin to patients in whom therapy with metreleptin is medically appropriate.
4) Metreleptin will be dispensed only to patients with evidence or other documentation of safe-use conditions.
5) The prescriber will need to attest on a prescription authorization form, for each prescription, that he/she is aware and understands the metreleptin indication and that the drug is medically appropriate for the patient.

The Sponsor will facilitate prescriber certification by communicating information to prescribers and professional organizations through Dear Healthcare Provider (DHCP) Letters, Dear Professional Organization Letters (e.g., American Association of Clinical Endocrinology, The Endocrine Society), the Prescribing Information (PI), and a metreleptin REMS Program website.

8.2 Metreleptin Safety Registry

While the clinical development program for LD has provided important data about the benefit-risk profile of metreleptin, the Sponsor will continue to assess the safety profile of metreleptin in the clinic through a prospective observational study (Metreleptin Safety Registry). The Registry will monitor the occurrence of known and potential risks in the post-marketing environment.

The Registry will start recruitment within the first year after approval of metreleptin for the treatment of LD patients in the U.S. The sponsor will implement a comprehensive operating procedure to offer enrollment to all prescribing physicians and treated patients into the Registry. The study will have a 5 year enrollment period and each patient will be followed for at least 2 years capturing data on parameters of standard clinical practice. The actual duration of follow-up will vary depending upon when metreleptin treatment was initiated. Patients with metreleptin treatment for LD prior to the Registry start date will be eligible to retrospectively enroll into the study. Thus, some patients will have more than 7 years of follow up information.

The prescriber at the Registry study sites will be trained on data collection forms which include medical history, concomitant medication use, occurrence of adverse event of special interest (AESIs) and associated risk factors. This data will be collected twice a year, via a clinic visit with the treating physician. The registry study will continue to monitor patients who discontinue metreleptin therapy if feasible. Source data verification will be conducted to ensure data accuracy and to validate occurrence of study outcome.

The Sponsor will continue to work with the FDA to finalize the overall scope and design of the Metreleptin Safety Registry.

8.3 Immunogenicity Follow-up Program

The potential risk of development of metreleptin neutralizing activity in metreleptin treated LD patients warrants further assessment based on the limited data. To further evaluate the presence of metreleptin neutralizing activity and clinical consequences in the post marketing setting, the Sponsor has implemented an *Immunogenicity Testing and Safety Follow-Up Program for Patients who Received Treatment with Metreleptin and Developed Metreleptin Neutralizing Activity*. The program consists of 2 components:

- To test for in vitro metreleptin neutralizing activity in patients with inherited or acquired LD who received treatment with metreleptin and have evidence of clinical symptoms suggestive of a loss of efficacy and for whom there is a request for immunogenicity testing in the post marketing setting.
- To follow up with patients identified with metreleptin neutralizing activity.

The primary objectives of this program are: 1) to provide a method for testing for neutralizing activity to metreleptin in patients with LD who received treatment with metreleptin and for whom testing is requested by the treating physician or by the BMS Safety physician based on the patient's adverse event profile; 2) to perform safety follow-up in those patients who are tested positive for neutralizing activity to metreleptin in clinical trial or post marketing setting, in order to obtain long term clinical information and possible adverse reactions associated with development of metreleptin neutralizing activity.

The Safety follow-up program will follow these patients every 3 to 6 months for up to 12 months. However, at the end of the safety follow-up (Month 12), the Safety physician will determine whether the patient needs further follow-up based on the patient's safety profile (adverse reaction [type and severity]) and status of neutralizing activity to metreleptin.

8.4 Pregnancy and Lactation Exposure Follow-up Program

There are limited human data on the effects of pregnancy or lactation exposure to metreleptin on infants and pregnant women. Clinical trials exclude pregnant and lactating women due to ethical considerations regarding the usually unknown effects of an investigational agent on the fetus and the infant, as was the case for the metreleptin LD clinical development program.

The purpose of the *Post marketing Pregnancy and Lactation Exposure Safety Follow-Up Program* is to examine and describe the impact of metreleptin therapy on pregnancy and lactation outcomes in infants and pregnant women after exposure to metreleptin: 1) during pregnancy; 2) approximately 6 months prior to pregnancy; 3) lactation or approximately 6 months prior to breastfeeding. The program will also gather data on metreleptin treatment from the male sexual partners of women with LD exposed to metreleptin up to approximately 6 months prior to conception.

The program will include a maternal observation period starting at enrollment and continuing until the end of pregnancy. The Lactation Exposure Safety Follow-Up Program will consist of an observation period from the time of live birth to 12 months after birth. The duration of the study will be open-ended and is contingent on enrollment. The pregnancy follow-up program is an optional safety surveillance program. Physicians and patients will be informed and educated

about the needs to report all pregnancies via product label, medication guide, and product website and through pharmacy. In addition, pregnancy reports received from all metreleptin related programs (e.g., customer service call center, medical information group, metreleptin Safety Registry, or the immunogenicity follow-up program), will be triaged to the Sponsor's pharmacovigilance group and followed up per pregnancy follow-up procedure.

9 SUMMARY AND BENEFIT–RISK ASSESSMENT

9.1 Benefits of Metreleptin

The main benefits of metreleptin treatment in patients with LD can be summarized as follows:

- Substantial and clinically meaningful improvements in HbA1c (mean improvement of 1.1% at 4 months, which were generally sustained throughout the first year of treatment) consistent with improvement in insulin sensitivity. Long term data for over 6 years in patients treated early during the conduct of the NIH studies demonstrates sustained benefit without loss of efficacy.
- Marked improvement in hypertriglyceridemia (mean and median improvement of approximately 472 mg/dL and 188 mg/dL, respectively, at 4 months, which was generally sustained throughout the first year of treatment).
- Efficacy was demonstrated in patients with both generalized LD and partial LD, the most important determinant of overall response to metreleptin relating to the proportion of the studied population affected and the severity of the metabolic abnormalities at baseline.
    - Thus, larger decreases in HbA1c were observed in patients with generalized LD because a higher proportion of generalized LD patients had elevated baseline HbA1c values, and individual baseline HbA1c values were also higher in magnitude.
    - Similar proportions of patients in each group had baseline TG values ≥ 1000 mg/dL. Large decreases in TGs were observed in both generalized and partial LD patients with elevated baseline TGs.
- Clinically meaningful improvements in elevated hepatic enzymes AST and ALT (approximately 40% at 4 months and 30% at 12 months) and hepatomegaly, commonly used surrogate measures of hepatic steatosis. Reduction in liver volume was demonstrated in a sub-population, and histological improvement in steatohepatitis has also been reported.
- Reduction in concomitant medication, including discontinuation of insulin treatment for some patients after the first year.
- Improvement in hyperphagia driven by relative leptin deficiency, which helps to break the vicious cycle of excess food consumption that further exacerbates metabolic abnormalities as ingested fats are directed towards ectopic locations.
- Clinically meaningful improvements in 24-hour proteinuria which may, at least in part, reflect the decrease in hyperfiltration associated with improvement in marked hyperglycemia.

9.2 Risks of Metreleptin

9.2.1 Potential Risks

- Lymphoma represents a potential risk with metreleptin treatment. Three patients, all with AGL, were diagnosed with lymphoma following metreleptin treatment. An independent association between LD (especially acquired forms of LD, which are associated with underlying immune dysregulation, including autoimmune diseases) and malignancies, especially hematologic malignancies like lymphoma, is suggested by the limited literature and case reports on these rare patients. It is unlikely that metreleptin contributed to the de novo development of the lymphomas observed. The potential benefits and risks of metreleptin therapy should be considered in patients with significant hematologic abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy) and/or in patients with acquired forms of LD. The Sponsor proposes to include the potential risk of lymphoma in the warnings and precautions section of the Prescribing Information. In order to help ensure that the appropriate patients receive treatment, the Sponsor also proposes education of prescribers about the potential risk of lymphoma through physician certification as a goal of the REMS with further assessment via the metreleptin Safety Registry (refer to Section 8.2).
- Development of neutralizing activity to metreleptin and endogenous leptin, which could potentially impact efficacy. The potential impact of neutralizing endogenous leptin is inducing a phenotype of severe leptin deficiency characterized by severe hyperphagia and weight gain reminiscent of congenital leptin deficiency. However, the clinical consequences of developing neutralizing activity to metreleptin and (endogenous leptin) in LD patients who are already leptin deficient (in most cases markedly so) as compared to leptin-replete obese individuals is unclear. Specifically, it is unclear whether hyperphagia would worsen, or whether excessive weight gain is likely to occur in LD patients who lack the capacity to expand adipose depots by the very nature of their disease. In the product label, the Sponsor proposes to include the potential risk of clinical consequences associated with developing neutralizing activity in the warnings and precautions section, and to provide guidance to prescribers that testing for neutralizing activity to metreleptin may be considered in patients who experience loss of efficacy during metreleptin treatment. In order to help ensure that the appropriate patients receive treatment, the Sponsor also proposes education of prescribers about the potential risk of clinical consequences of neutralizing activity through physician certification as a goal of the REMS with further assessment via the immunogenicity follow-up program (refer to Section 8.3).

9.2.2 Identified Risks

- Hypersensitivity events have been observed in a small percentage of overweight/obese subjects without LD who were treated with metreleptin, but no cases of anaphylaxis with respiratory or hemodynamic compromise have been observed. In addition, no hypersensitivity events assessed as related to metreleptin treatment by the investigator have been reported in LD patients to date. The Sponsor proposes to include hypersensitivity in the warnings and precautions section of the product label as a means of managing the risk of hypersensitivity.

- Acute pancreatitis may occur as a result of withdrawal and/or noncompliance with metreleptin therapy, especially in patients at increased risk of pancreatitis (e.g., prior history of pancreatitis, severe hypertriglyceridemia) who have substantial improvements in hypertriglyceridemia with metreleptin therapy. It would be expected that discontinuation of effective therapy for hypertriglyceridemia could be associated with return of hypertriglyceridemia (possibly rapid) and therefore return to baseline elevated risk for pancreatitis. The risk for pancreatitis can be managed by appropriate education of prescribers and patients regarding compliance/ avoidance of interruption of metreleptin treatment. Specifically, the Sponsor proposes to provide guidance in the product label recommending tapering (if needed) of the metreleptin dose over one week when discontinuing therapy in patients at risk for pancreatitis, with recommendation for monitoring of triglyceride levels and adjustment of lipid lowering medications as indicated.
- Although hypoglycemia is not evident with metreleptin treatment alone, hypoglycemia may occur in the setting of rapid improvement in insulin sensitivity with metreleptin treatment in patients on high doses of insulin, and possibly in patients on insulin secreatogues. The risk for hypoglycemia can be managed by appropriate monitoring of blood glucose in patients on concomitant insulin secretagogue or insulin therapy and dose adjustment of concomitant diabetes therapies as needed. The Sponsor proposes to provide guidance in the product label that dose adjustment, including possible large reductions, of insulin or insulin secretagogues (e.g., sulfonylurea) may be necessary in some patients to minimize the risk of hypoglycemia and to advise regular blood glucose monitoring in patients on such therapies.
- Weight loss may occur in leptin-sensitive patients with LD as an expected pharmacological effect of metreleptin. The risk for weight loss (especially relevant in pediatric patients who are still growing) can be managed by careful monitoring of body weight and dose adjustments of metreleptin as appropriate. The Sponsor proposes to provide recommendations for dose adjustments based on clinical response and considerations such as excessive weight loss in the product label.
- Inflammatory injection site AEs (representing primarily a tolerability issue rather than a safety risk for the patient) may occur in some patients.

9.2.3 Benefit-Risk Summary and Discussion

Lipodystrophy is a heterogeneous disease that is associated with significant morbidity and mortality, and metreleptin is a unique therapy that treats the associated metabolic abnormalities and relative leptin deficiency due to the loss of SC adipose tissue. In the metreleptin clinical studies, LD patients with metabolic abnormalities (including diabetes, hypertriglyceridemia, and/or liver dysfunction) treated with metreleptin experienced clinically meaningful, and often substantial, improvements in these abnormalities. Metreleptin was efficacious in the majority of patients with metabolic abnormalities (including diabetes, hypertriglyceridemia, and/or liver dysfunction) with an acceptable safety and tolerability profile, established over a period of 11 years.

The current proposed draft indication for metreleptin cited in Section 2.1 of this briefing book, which is changed from the initial draft indication has been refined to better identify patients with LD who will gain the most benefit from metreleptin treatment.

At a fundamental level, there are three primary interrelated types of metabolic abnormalities in LD patients that arise as a consequence of ectopic lipid accumulation: diabetes, hypertriglyceridemia, and liver dysfunction. These disease elements all contribute to current co-morbidities in LD patients, and predispose patients to risks for future morbidities and mortality, and help define the need for metreleptin treatment in individual LD patients. The clinically meaningful improvements in metabolic abnormalities seen with metreleptin treatment in the LD clinical program may lead to reduced risks of serious complications such as acute pancreatitis, end stage liver disease, and accelerated cardiovascular disease. Responses in hepatic disease are not limited to reductions in serum transaminases, and include improvements in hepatic steatosis and/or hepatosteatosis. In pediatric patients with predominant fatty liver disease who otherwise have few alternatives for treatment and face a grave prognosis for progressive liver disease without intervention, metreleptin represents a potential treatment option.

Metreleptin treatment in LD patients over several years indicates an overall favorable safety profile. The main known or identified potential risks are lymphoma and the potential risk for loss of efficacy if neutralizing activity to metreleptin develops. In order to help ensure that the appropriate patients receive treatment, the Sponsor proposes education of prescribers about the potential risk of lymphoma and clinical consequences of neutralizing activity through physician certification as a goal of the REMS with further assessment via a metreleptin Safety Registry and immunogenicity follow-up program.

The benefits of metreleptin treatment apply to LD syndromes considered as a whole, but there are important distinctions to note for the individual LD subtypes. Overall, the treatment decision regarding use of metreleptin for patients with generalized LD can be more straightforward. Generalized LD, whether congenital or acquired, is a condition associated with substantial morbidity and mortality due to complications from severe metabolic abnormalities (which are often not responsive or suboptimally controlled on standard, currently available therapies). Both subtypes of generalized LD patients are typically diagnosed early in life, adding to their risk of developing severe morbidity and pre-mature mortality. As a consequence of marked SC adipose tissue deficiency, patients with generalized LD have leptin levels below the 10^{th} percentile of measured concentrations observed in the normal population, and are indeed both adipose tissue and leptin deficient. Treatment of generalized LD patients with metreleptin has been demonstrated to improve the patient's metabolic abnormalities and the magnitude of improvement correlates with the severity of the specific baseline metabolic abnormalities present.

The treatment decision in patients with AGL must also consider two potential concerns, i.e. the potential risk of T-cell lymphoma and the concern of worsening autoimmune disease through pro-inflammatory effects. Available evidence from nonclinical studies supports the conclusion that metreleptin is unlikely to cause T-cell lymphoma de novo. The clinical assessment of the

potential role of metreleptin in contributing to progression of lymphoma is limited by the lack of placebo control. Thus, a potential role cannot be fully excluded. The potential for metreleptin to worsen autoimmune disease in patients with AGL is also of hypothetical concern but within the available dataset, autoimmune progression in AGL patients on metreleptin treatment is consistent with that reported in the literature. Balanced with this, by the nature of their extensive loss of SC adipose tissue, AGL patients tend to have very significant metabolic abnormalities which present in childhood or adolescence. This combination puts them at especially high risk of and morbidity and mortality associated with these complications. Therefore, the potential for these patients to achieve benefits which are particularly important needs to be taken into consideration for this population.

Patients with partial LD are more heterogeneous in presentation due to the varying degree of SC adipose tissue loss demonstrated at presentation. These patients can experience similar severe metabolic abnormalities and serious co-morbidities as generalized LD patients, although there is greater variability in the severity of metabolic abnormalities at presentation. Clinical diagnosis of significant loss of SC adipose tissue in regional distribution patterns based on thorough physical examination, combined with the presence of more severe metabolic abnormalities (including hypertriglyceridemia, diabetes mellitus with marked insulin resistance, and/or hepatic steatosis or hepatomegaly) are important considerations guiding a treatment decision in partial LD patients. Evidence of refractoriness to conventional treatment (for example anti-diabetic and lipid-lowering therapies) is another consideration. Overall, improvements with metreleptin treatment in partial LD patients are related most reliably to the severity of baseline metabolic abnormalities. Leptin measurements can provide qualitative information on the likelihood of improvements in HbA1c or TG, but a reliable quantitative threshold cannot be defined given limited clinical data in LD patients at higher leptin levels. In such patients who have no other effective means to effectively control their metabolic abnormalities, metreleptin fulfills an important unmet need.

10 CONCLUSIONS

The benefit-risk assessment for metreleptin must be placed in the context of existing therapies as well as individual patient needs. Current diabetes and lipid-lowering medications are often sub-optimally effective, especially for LD patients with severe metabolic abnormalities. In addition, these conventional therapies do not address the underlying pathophysiology of LD, whereby aberrant, ectopic lipid storage in the absence or relative deficiency of leptin drives these many metabolic abnormalities. In addition, conventional anti-diabetic therapies and insulin, especially at high doses, do not treat hepatic steatosis or steatohepatitis, and may actually accelerate the accumulation of lipid in the liver. Finally, conventional therapies do not address the hyperphagia that makes adherence to dietary restriction difficult. Metreleptin therapy uniquely designed to address many of these deficiencies and can be effective in many patients with LD. By targeting the control of metabolic abnormalities, and limiting ectopic lipid deposition, metreleptin should positively impact the co-morbidities leading to organ damage in patients with LD.

11 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
4-MSU	4-Month Safety Update
AE	Adverse event
AGL	Acquired generalized LD
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
APL	Acquired partial LD
ASA	Active systemic anaphylaxis
AST	Aspartate aminotransferase
AZ	AstraZeneca
BLA	Biologics License Applications
BL	Baseline
BID	Twice daily
BMI	Body mass index
BMS	Bristol-Myers Squibb
BW	Body weight
CGL	Congenital generalized LD
CTCL	Cutaneous T-cell lymphomas
CKD	Chronic kidney disease
CNS	Central nervous system
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FPL	Familial partial LD
GLP	Good laboratory practice
HbA1c	Hemoglobin HbA1c
HDL	High-density lipoprotein
IND	Investigational New Drug Application
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
IV	Intravenous
LD	lipodystrophy
LDL	Low-density lipoprotein
LOCF	Last observation carried forward

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of action
MPGN	Membranoproliferative glomerulonephritis
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin's lymphomas
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NK-cells	Natural killer cells
NOAEL	No observed adverse effect level
PCA	Passive cutaneous anaphylaxis
PD	Pharmacodynamic
PK	Pharmacokinetic
PTCL	Peripheral T-cell lymphomas
QD	Once daily
REMS	Risk Evaluation and Mitigation Strategies
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TG	Triglycerides
ULN	Upper limit of normal
WHO	World Health Organization
Yr	Year

12 LIST OF REFERENCES

1 Chan JL, Oral EA. Clinical classification and treatment of congenital and acquired lipodystrophy. Endocr Pract. 2010;16(2):310-323.

2 Garg A. Acquired and inherited lipodystrophies. N Engl J Med. 2004;350(12):1220-1234.

3 Garg A. Lipodystrophies: Genetic and acquired body fat disorders. J Clin Endocrinol Metab. 2011;96(11):3313-3325.

4 Misra A, Garg A. Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. Medicine (Baltimore). 2003;82(2):129-146.

5 Misra A, Peethambaram A, Garg A. Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. Medicine (Baltimore). 2004;83(1):18-34.

6 Hubler A, Abendroth K, Keiner T, et al. Dysregulation of insulin-like growth factors in a case of generalized acquired lipoatrophic diabetes mellitus (Lawrence Syndrome) connected with autoantibodies against adipocyte membranes. Exp Clin Endocrinol Diabetes. 1998;106(1):79-84.

7 Haque WA, Shimomura I, Matsuzawa Y, et al. Serum adiponectin and leptin levels in patients with lipodystrophies. J Clin Endocrinol Metab. 2002;87(5):2395.

8 Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. N Engl J Med. 2002;346(8):570-578.

9 Hegele RA. Premature atherosclerosis associated with monogenic insulin resistance. Circulation. 2001;103(18):2225-2229.

10 Van Maldergem L, Magre J, Khallouf TE, et al. Genotype-phenotype relationships in Berardinelli-Seip congenital lipodystrophy. J Med Genet. 2002;39(10):722-733.

11 Garg A. Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). J Clin Endocrinol Metab. 2000;85(5):1776-1782.

12 Bolan C, Oral EA, Gorden P, et al. Intensive, long-term plasma exchange therapy for severe hypertriglyceridemia in acquired generalized lipoatrophy. J Clin Endocrinol Metab. 2002;87(1):380-384.

[13] Yadav D and Pitchumoni CS. Issues in hyperlipidemic pancreatitis. J Clin Gastroenterol. 2003;36(1):54-62.

[14] UK guidelines for the management of acute pancreatitis. Gut. 2005;54 Suppl 3:iii1-9.

[15] Smith PM, Morgans ME, Clark CG, et al. Lipodystrophy, pancreatitis, and eosinophilia. Gut. 1975;16(3):230-234.

[16] Bulbul M, Erdogan O, Demircin G, et al. Acute pancreatitis in a patient with partial lipodystrophy and membranoproliferative glomerulonephritis. Nephrol Dial Transplant. 2001;16(9):1930-1931.

[17] Haque WA, Vuitch F, and Garg A. Post-mortem findings in familial partial lipodystrophy, Dunnigan variety. Diabet Med. 2002;19(12):1022-1025.

[18] El-Zayadi AR. Hepatic steatosis: a benign disease or a silent killer. World J Gastroenterol. 2008;14(26):4120-4126.

[19] Federico A, Trappoliere M, and Loguercio C. Treatment of patients with non-alcoholic fatty liver disease: Current views and perspectives. Digestive & Liver Disease. 2006;38(11):789-801.

[20] Festi D, Colecchia A, Sacco T, et al. Hepatic steatosis in obese patients: clinical aspects and prognostic significance. Obes Rev. 2004;5(1):27-42.

[21] Ludtke A, Genschel J, Brabant G, et al. Hepatic steatosis in Dunnigan-type familial partial lipodystrophy. Am J Gastroenterol. 2005;100(10):2218-2224.

[22] Javor ED, Ghany MG, Cochran EK, et al. Leptin reverses nonalcoholic steatohepatitis in patients with severe lipodystrophy. Hepatology. 2005;41(4):753-760.

[23] Savage DB, Semple RK, Clatworthy MR, et al. Complement abnormalities in acquired lipodystrophy revisited. J Clin Endocrinol Metab. 2009;94(1):10-16.

[24] Javor ED, Moran SA, Young JR, et al. Proteinuric nephropathy in acquired and congenital generalized lipodystrophy: baseline characteristics and course during recombinant leptin therapy. J Clin Endocrinol Metab. 2004;89(7):3199-3207.

[25] Alchi B, Jayne D. Membranoproliferative glomerulonephritis. Pediatr Nephrol. 2010;25(8):1409-1418.

[26] Iseki K, Kinjo K, Kimura Y, et al. Evidence for high risk of cerebral hemorrhage in chronic dialysis patients. Kidney Int. 1993;44(5):1086-1090.

[27] Wakefield MA. The interrelationship between hypocomplementaemia, partial lipodystrophy and mesangiocapillary glomerulonephritis. Postgrad Med J. 1976;52(612):651-652.

[28] McNally M, Mannon RB, Javor ED, et al. Successful renal transplantation in a patient with congenital generalized lipodystrophy: a case report. Am J Transplant. 2004;4(3):447-449.

[29] Casali RE, Resnick J, Goetz F, et al. Renal transplantation in a patient with lipoatrophic diabetes. A case report. Transplantation. 1978;26(3):174-177.

[30] Chopra S, Isaacs R, Mammen K, et al. Renal transplantation in a patient with Barraquer-Simons disease and mesangiocapillary glomerulonephritis type II. Nephrol Dial Transplant. 2000;15(10):1723-1724.

[31] Lenane P, Murphy G. Partial lipodystrophy and renal disease. Clin Exp Dermatol. 2000;25(8):605-607.

[32] Meyrier A. The patient with glomerulonephritis and lipodystrophy. Nephrol Dial Transplant. 1997;12(1):226-227.

[33] Lupsa B, Sachdev V, Lungu A, et al. Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. Medicine (Baltimore). 2010;89(4):245-250.

[34] Subramanyam L, Simha V, and Garg A. Overlapping syndrome with familial partial lipodystrophy, Dunnigan variety and cardiomyopathy due to amino-terminal heterozygous missense lamin A/C mutations. Clin Genet. 2010;78(1):66-73.

[35] Bingham A, Mamyrova G, Rother KI, et al. Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. Medicine (Baltimore). 2008;87(2):70-86.

[36] Yiannias JA, DiCaudo DJ, Maskin E. Peripheral T-cell lymphoma presenting as lipoatrophy and nodules. Int J Dermatol. 2006;45(12):1415-1419.

[37] Aslam A, Savage D, Coulson I. Acquired generalized lipodystrophy associated with peripheral T-cell lymphoma with cutaneous infiltration. Br J Dermatol. 2012;167:S1-14-15.

[38] Franceschini P, Barisone E, Signorile F, et al. Pre-B acute lymphoblastic leukemia in a patient with partial lipodystrophy and acanthosis nigricans. Panminerva Med. 1995;37(4):248-251.

[39] Hall SW, Gillespie JJ, Tenczynski TF. Generalized lipodystrophy, scleroderma, and Hodgkin's disease. Arch Intern Med. 1978;138(8):1303-1304.

[40] Friedman JM and Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395(6704):763-770.

[41] Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372(6505):425-432.

[42] Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334:292-295.

[43] Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA. 1999;282(16):1568-1575.

[44] Ahima RS, Prabakaran D, Mantzoros C, et al. Role of leptin in the neuroendocrine response to fasting. Nature. 1996;382(6588):250-252.

[45] Chan JL, Heist K, DePaoli AM, et al. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest. 2003;111(9):1409-1421.

[46] Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med. 1999;341(12):879-884.

[47] Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. J Clin Invest. 2002;110(8):1093-1103.

[48] Saad M, Damani S, Gingerich R, et al. Sexual dimorphism in plasma leptin concentration. J Clin Endocrinol Metab. 1997 Feb;82(2):579-84.

[49] Kelesidis T, Kelesidis, I, Chou, S et al. Narrative Review: The role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 2010;152:93-100.

[50] Shimomura I, Matsuda M, et al. Decreased IRS-2 and Increased SREBP-1c Lead to Mixed Insulin Resistance and Sensitivity in Livers of Lipodystrophic and ob/ob Mice. Molecular Cell, 2000; 6, 77 86,

[51] Snel, M, Jonker,J, Schoones J, et al. Ectopic Fat and Insulin Resistance: Pathophysiology and Effect of Diet and Lifestyle Interventions. J Endocrinology 2012; Article ID 983814.

[52] Miyamoto L, Ebihara K, Kusakabe T, et al. Leptin Activates Hepatic 5-AMP-activated Protein Kinase through Sympathetic Nervous System and α1-Adrenergic Receptor. JBC 2012;. 287, 48, pp. 40441 40447.

[53] Shimomura I, Hammer RE, Ikemoto S, et al. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature. 1999;401(6748):73-6.

[54] Gavrilova O, Marcus-Samuels B, Graham D, et al. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. J Clin Invest. 2000 Feb;105(3):271-8.

[55] Colombo,C. Cutson,J Yamauchi,T et al. Transplantation of adipose tissue lacking leptin is unable to reverse the metabolic abnormalities associated with lipoatrophy. Diabetes 2002; 51:2727 2733.

[56] Novartis Pharmaceuticals Corporation. ILARIS® Injection for Subcutaneous use. [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2012.

[57] Ruhl E and Everhat J. Leptin concentrations in the United States: relations with demographic and anthropometric measures. Am J Clin Nutr 2001;74:295 301

[58] Zadeh ES, Lungu AO, Cochran EK, et al. The Liver Diseases of Lipodystrophy: The Long-term Effect of Leptin Treatment. Journal of Hepatology. 2013;Vol. 59,(1): 131-137.

[59] Robinson JG, Wang, S, and Jacobson, TA. Meta-Analysis of Comparison of Effectiveness of Lowering Apolipoprotein B Versus Low-Density Lipoprotein Cholesterol and Nonhigh-Density Lipoprotein Cholesterol for Cardiovascular Risk Reduction in Randomized Trials. Am J Cardiology 2012:110: 1468 1476

[60] Kit BK, Carroll MD, Lacher DA, et al. Trends in serum lipids among us youths aged 6 to 19 years, 1988-2010. JAMA: The Journal of the American Medical Association. 2012;308(6):591-600.

[61] Brown R, Cochran E, Miller S, et al. Clinical effects of metreleptin treatment in pediatric patients with lipodystrophy. Pediatric Endocrine Society (PES) Annual Meeting 2013; May 4-7. Abstract 3490.3

[62] Moran SA, Patten N, Young JR, et al. Changes in body composition in patients with severe lipodystrophy after leptin replacement therapy. Metabolism. 2004;53(4):513-519.

[63] Block GH, Hartman AM, Dresser CM, et al: A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124 (3):453-469.

[64] Rodriguez -Abreu D, Filho V and Zucca E. Peripheral T-cell lymphomas, unspecified (or not otherwise specified): a review. Hematol Oncol 2008; 26: 8 20

[65] Horwitz. Pheripheral T-cell Lyphoma CME. 2013 http://www.medscape.org/viewarticle/809373.

[66] Oschlies,I Lisfeld J, Lamant, L et al. ALK-positive anaplastic large cell lymphoma limited to the skin:clinical, histopathological and molecular analysis of 6 pediatric cases. A report from the ALCL99 study. Haematologica 2013;98(1).

[67] Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas--an update. J Intern Med. 2008;264(6):514-527.

[68] Yiannias JA, DiCaudo DJ, Maskin E. Peripheral T-cell lymphoma presenting as lipoatrophy and nodules. Int J Dermatol. 2006;45(12):1415-1419.

[69] Aslam A, Savage D, Coulson IH. Acquired generalized lipodystrophy associated with peripheral T-cell lymphoma with cutaneous infiltration. British Journal of Dermatology. 2012;167:14-15.

[70] Hall SW, Gillespie JJ, Tenczynski TF. Generalized lipodystrophy, scleroderma, and Hodgkin's disease. Arch Intern Med. 1978;138(8):1303-1304.

[71] Schnabel CA, Fineberg SE, Kim DD. Immunogenicity of xenopeptide hormone therapies. Peptides. 2006;27(7):1902-1910.

[72] Mire-Sluis AR, Barrett YC, Devanarayan V, et al. Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology products. J Immunol Methods. 2004;289(1-2):1-16.

[73] Beltrand J, Lahlou N, Charpentier T el al. Resistance to leptin-replacement therapy in Berardinelli Seip congenital lipodystrophy: an immunological origin. European Journal of Endocrinology 2010; 162 1083 1091

[74] Housa D, Housová J, Vernerová z et al. Adipocytokines and Cancer. Physiol. Res. 2006; 55: 233-244.

[75] De Rosa V, Procaccini C, Calı`G, et al. A Key Role of Leptin in the Control of Regulatory T Cell Proliferation. Immunity 2007; 26, 241 255.

[76] Menetrier-Caux C, Gobert M, Caux C. Differences in tumor regulatory T-cell localization and activation status impact patient outcome. Cancer Res 2009;69:7895 7898

[77] Quezada SA, Peggs KS, Curran MA, et al. CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells. J Clin Invest 2006;116:1935 1945

[78] Marabelle A, Kohrt H, Sagiv-Barfi I, et al.Depleting turmo-specific Tregs at a single site eradicates disseminated tumors. J Clin Invest. 2013;123(6):2447 2463

[79] Bernotiene E, Palmer G and Gabay C. The role of leptin in innate and adaptive immune responses. Arthritis Research & Therapy 2006, 8:217-226

[80] Matarese G, La Cava A, Sanna V, et al. Balancing susceptibility to infection and autoimmunity: a role for leptin? TRENDS in Immunology 2002;Vol.23 No.4.

[81] Howard JK, Lord GM, Matarese G, et al. Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. J Clin Invest. 1999 Oct;104(8):1051 1059

[82] Ozata M, Ozdemir IC, Licinio J. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects . J. Clin. Endocrinol. Metab. 1999; 84:3686 3695.

[83] Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature. 1998;394(6696):897-901.

[84] Oral EA, Javor ED, Ding L, et al. Leptin replacement therapy modulates circulating lymphocyte subsets and cytokine responsiveness in severe lipodystrophy. J Clin Endocrinol Metab. 2006;91(2):621-628.

[85] Matarese G, Di Giacomo A, Sanna V, et al. Requirement for leptin in the induction and progression of autoimmune encephalomyelitis. J Immunol. 2001 May 15;166(10):5909 5916.

[86] Matarese G, Moschos S, Mantzoros CS. Leptin in immunology. Journal of Immunology. 2005;174(6):3137-3142.

[87] Ajluni N, Neidert A, Tapiador, C, et al. Metrelptin treatment in aquired generalized lipodystropgy: Consistent metabolic effects in three patiens presenting with disctinct autoimmune conditions. Endocr Rev. 2012; 33 MON-167.

[88] Farooqi IS and O'Rahilly S. Leptin: a pivotal regulator of human energy homeostasis. American Journal of Clinical Nutrition. 2009;89(3):980S-984S.

[89] Mantzoros CS, Flier JS, and Rogol AD. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. V. Rising leptin levels may signal the onset of puberty. J Clin Endocrinol Metab. 1997;82(4):1066-1070.

Appendix 1: Individual Narratives on Cases of T-Cell Lymphoma

4 page(s) excluding cover page

APPENDIX 1: INDIVIDUAL NARRATIVES ON CASES OF T-CELL LYMPHOMA

Case 1:

The 59-year-old woman is a patient from Spain who was first seen at the NIH in May 2008 for evaluation and treatment of acquired generalized lipodystrophy that had developed over the past 10 years. She had a recent history of neutropenia diagnosed in December 2007 for which she was briefly treated with G-CSF (Neupogen) with normalization of her neutrophil count. However, the neutropenia recurred in January 2008, and the G-CSF was restarted. She had a bone marrow biopsy in Spain in January 2008 and brought the slides with her to the NIH, which were evaluated by pathologists at NIH. The diagnosis was hypercellular bone marrow with marked atypical T-cell lymphocytosis and myeloid maturation with left shift. At her baseline visit at the NIH in May 2008, her WBC was normal at 7,240/uL with a normal neutrophil count of 2,150/uL and elevated lymphocyte count of 4200/ul (on G-CSF treatment). She was started on metreleptin on 04 June 4 2008, and returned home to Spain to continue metreleptin treatment. This was her only visit to the NIH.

In (b) (6), the patient's husband informed the NIH that she had just undergone a mastectomy for breast cancer. The patient had apparently had a history of a breast lesion in the past (preceding metreleptin treatment). Of note, this part of the medical history was not communicated to the NIH at the time of initial evaluation, and thus they were not aware of this diagnosis when they initiated metreleptin treatment. According to information provided to the NIH by the patient's husband, the patient had a long history of a benign fibroma in her breast. During an annual exam (unclear when), some calcifications were noted, and a biopsy was performed that revealed "cancerous cells." She had a radical mastectomy performed. The breast cancer was localized, and all of her lymph nodes were clear. The husband communicated to the NIH that the final diagnosis was intraductal carcinoma.

According to the husband, the patient subsequently developed ulcers/wounds in her throat accompanied by a persistent cough, as well as corneal ulcers, and a nodule on her left ankle that became inflamed. When the nodule appeared to have become infected, she was hospitalized with an initial diagnosis of infectious cellulitis. Over the next several days, she had progression of nodules on her right forearm and on her ankle. A diagnosis of "nodus erythema" was considered. Culture of these ulcers was negative. Bone marrow biopsy and biopsy of nodules on the forearm and leg were performed in January 2009 and led to a diagnosis of peripheral T-cell lymphoma. PET scan showed no evidence of internal organ involvement. She was subsequently started on chemotherapy and was doing well after the first 2 sessions. The patient was due for a 6 month follow-up at the NIH around January 2009 but given the intervening diagnosis of peripheral T-cell lymphoma, she was discontinued from metreleptin treatment, and thus never returned for follow-up at the NIH. Of note, the information above is based primarily on communication from the patient's husband to the NIH.

Case 2:

The 68-year-old man is a patient from the US who developed acquired generalized lipodystrophy in 1997 with loss of subcutaneous fat over a few months and development of metabolic abnormalities, including severe insulin resistance and hypertriglyceridemia. He was diagnosed with diabetes in December 1997. In 1997, he was also noted to have abnormal liver function tests, and an abdominal ultrasound in September 1997 showed hepatosplenomegaly. A few months prior in July 1997, he was evaluated for leukopenia (WBC 2000/ul) with relative neutropenia by a hematologist and was diagnosed with chronic idiopathic neutropenia. A lymph node biopsy and bone marrow biopsy in 1998 were nondiagnostic. Erythropoietin was prescribed starting 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 4-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 8-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 AE at that time.

Case 3:

NIH patient 90170 is a 13 year old female with acquired generalized lipodystrophy (AGL) who was 11 years of age upon initiation of metreleptin treatment who had a relevant medical history of hypertriglyceridemia, hyperlipidemia, severe insulin resistance, and non-alcoholic steatohepatitis with possible cirrhosis (based on liver biopsy). 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 anti-nuclear Ab, anti-ENA, thyroid peroxidase Ab, anti-thyroglobulin Ab, GAD65 Ab, anti-cardiolipin Ab, anti-mitochondrial 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 10$_3$/µL (50% neutrophils, 34% lymphocytes, 14% monocytes, 2% eosinophils, 1% basophils), hemoglobin 13.2 g/dL, hematocrit 36.8%, platelet 188 x 10^3/µL. Routine chemistry was normal.

She was initiated on metreleptin treatment on 22 Feb 2011 based on severe insulin resistance and significant liver disease with possible cirrhosis on liver biopsy. Follow-up labs at month 4 (M4, on 27 Jun 2011) and month 12 (M12, on 22 Feb 2012) showed stable HbA1c, improvement in TG to 113 mg/dL at M4 and 253 mg/dL at M12, reduction in insulin level to 10.3 uIU/mL at M4 and 115 uIU/mL at M12, decrease in AST and ALT to 10 and 20 U/L at M4 with increase to 43 and 126 U/L at M12. CBC and chemistries remained normal at M4 and M12.

The patient presented to the NIH on 12 Dec 2012 for an unscheduled visit for evaluation of a mass around her right breast. She reported a 2 week history of a mass around her right breast that was tender only when she slept on her right side and without erythema, and no history of fevers. (b) (6) prior to the NIH visit, she was seen by her primary care physician for evaluation of this mass and referred to the local emergency department where an ultrasound was performed suggesting that the mass was a reactive lymph node with no suspicious solid, shadowing, or cystic mass identified. She was treated with Augmentin for a presumed lymphadenitis, but had no improvement in the mass and was thus arranged for follow-up at the NIH. On evaluation at the NIH on 12 Dec 2012, 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.

Laboratory data on 12 Dec 2012 showed stable HbA1c (4.9%), insulin increased from M12 but below baseline (153 uIU/mL), TG similar to baseline (363 mg/dL), AST decreased from M12 and similar to baseline (26 U/L), ALT decreased from M12 but above baseline (62 U/L). CBC

remained normal with WBC 10.9 x 10^3/µL (69% neutrophils, 19% lymphocytes, 6% monocytes, 4% eosinophils, 1% basophils), hemoglobin 11.9 g/dL, hematocrit 35.1%, platelet 460 x 10^3/µL). A MRI performed 12 Dec 2012 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, she had 2 core needle biopsies performed of the mass. 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%). She returned home after the biopsy with arrangements to return for staging and possible excisional biopsy.

On 25 Dec 2012, she 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 that the mass had decreased in size. She had continued on metreleptin treatment after the Dec 12 visit until this admission when metreleptin was stopped (on 25 Dec 2012). 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 26 Dec 2012, she had a PET scan that showed mild enhancement of the primary lesion (SUVmax 2.31) and only minimal uptake in the right axilla. Examination of CSF on 27 Dec 2012 was negative for malignant cells. A bone marrow biopsy performed 27 Dec 2012 showed normocellular marrow with progressive trilineage hematopoiesis and no evidence of lymphoma. On 27 Dec 2012, she underwent an 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. This patient's case was discussed at the NIH Tumor Board on 15 Jan 2013.

On 23 January 2013, the patient was readmitted to 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 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 node / chest wall mass were no longer visualized.