# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125390Orig1s000

# SUMMARY REVIEW

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | February 23, 2014 |
| **Subject** | Deputy Division Director Summary Review |
| **BLA #** | 125390 |
| **Applicant Name** | Bristol-Myers Squibb |
| **Date of Submission** | April 3, 2012 |
| **PDUFA Goal Date** | February 24, 2014 |
| **Proprietary Name /Established Name** | MYALEPT/metreleptin |
| **Dosage Forms / Strength** | Subcutaneous injection/11.3 mg per vial |
| **Indication:** | Treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy |
| **Action for NME:** | Approve |

| **Material Reviewed/Consulted** OND Action Package, including: | |
|---|---|
| Medical Officer Review | Julie Golden, MD |
| Statistical Review | Bradley McEvoy, DrPH |
| Pharmacology Toxicology Review | Federica Basso, PhD |
| OBP Review | Laura Salazar, PhD |
| Biotech Manufacturing/Product Quality | Steven Fong, PhD and Kalavati Suvarna, PhD |
| Microbiology Review | Kalavati Suvarna, PhD |
| Clinical Pharmacology Review | Jaya Vaidyanathan, PhD |
| OPDP | Kendra Jones |
| OSI | Cynthia Kleppinger, MD |
| OSE/DMEPA | Reasol Agustin, PharmD, Yelena Maslov, PharmD |
| OSE/OPVE | Patricia Bright, PhD |
| OSE/DRISK | Suzanne Robottom, PharmD |
| QT-IRT | Monica Fiszman, MD |
| Pediatrics | Donna Snyder, MD |
| Maternal Health | Tamara Johnson, MD |
| Division of Hematology Products | Karen McGinn, MSN, CRNP |
| Office of Combination Products | Patricia Love, MD |
| DPARP | Tracy Kruzick, MD |
| DGIEP | Lauren Weintraub, MD |

OND=Office of New Drugs
OBP=Office of Biological Proteins
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
OPVE=Office of Pharmacovigilance and Epidemiology
DRISK=Division of Risk Management
QT-IRT=QT-Interdisciplinary Review Team
DPARP=Division of Pulmonary, Allergy, and Rheumatology Products
DGIEP=Division of Gastroenterology and Inborn Errors Products

# 1. Introduction

This memorandum provides the regulatory recommendations from various review disciplines and details the metreleptin clinical efficacy and safety data and the proposed risk evaluation and mitigation strategy (REMS).

# 2. Background

Leptin is an adipocyte-derived hormone that plays a critical role in energy homeostasis and regulation of body weight. Metreleptin is a non-glycosylated 16 kDa recombinant analog of human leptin. Metreleptin differs by one amino acid compared with native human leptin.

Soon after the discovery of the hormone leptin in the early 1990s, Amgen initiated a development program for the treatment of obesity. Data from five clinical trials, however, failed to demonstrate adequate weight loss with metreleptin, leading Amgen to terminate the obesity program. More recently, encouraging results from animal models led Amylin, who acquired the metreleptin application in 2006, to conduct clinical trials of metreleptin plus pramlintide in obese patients. Despite favorable weight-loss data, this development program was discontinued due to "commercial considerations."

Lipodystrophy is a heterogeneous group of disorders characterized by selective loss of adipose tissue. The underlying pathophysiology of lipodystrophy includes deficiency of leptin and other adipokines with ectopic lipid deposition in muscle and the liver. The physiological consequences of lipodystrophy include insulin resistance with resultant hyperinsulinemia and diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and severe hypertriglyceridemia (HTG). The latter predisposes patients to episodes of acute pancreatitis.

Lipodystrophy can be classified as genetic or acquired and subclassified as generalized or partial. Generalized lipodystrophy is usually associated with very low levels of leptin and severe metabolic disease; partial lipodystrophy is associated with a range of leptin levels and may or may not be accompanied by metabolic disease. Acquired lipodystrophies are associated with immunological abnormalities including dermatomyositis, autoinflammatory disorders, tissue specific autoimmunity, and myeloid disorders (e.g., myelosuppression and lymphoma). The clinical diagnosis of lipodystrophy is based on history and physical examination.

The prevalence of lipodystrophy is estimated to be several thousand patients worldwide. Metreleptin for lipodystrophy was granted orphan drug status in 2001.

Also in 2001, metreleptin received fast track designation for the treatment of patients with lipodystrophy and metabolic disorders. This decision was based on data from a small group of patients with lipodystrophy, low leptin levels, and at least one of the following: diabetes mellitus, fasting serum TG > 200 mg/dl, and/or fasting serum insulin > 30uU/ml. Four months of treatment with metreleptin led to impressive reductions in levels of HbA1c (even with most of the subjects coming off anti-diabetic therapy) and serum TGs.

There are no drugs or biologics approved for the treatment of generalized or partial (non-HIV related) lipodystrophy.

The sponsor is requesting approval of metreleptin for the treatment of patients with generalized lipodystrophy and for the treatment of metabolic complications associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis.

This biologic licensing application (BLA) was granted a priority review; however, the PDUFA goal date was extended three months following the sponsor's submission of a major amendment.

# 3. Product Quality

According to Drs. Salazar, Fong, and Suvarna, there are no outstanding product quality or inspection issues that would preclude approval of this BLA. I agree.

# 4. Nonclinical Pharmacology/Toxicology

Dr. Basso notes that *in-vitro* and *in-vivo* data from published literature indicate that leptin promotes proliferative and anti-apoptotic responses in human cancer cells. Data also exist indicating that leptin is permissive in support of lymphopoiesis and autoimmunity.

In mice and dogs treated with metreleptin for six months, no proliferative or pre-neoplastic lesions were observed. In addition, metreleptin was not mutagenic when tested in *in-vivo* or *in-vitro* assays.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

# 5. Clinical Pharmacology/Biopharmaceutics

There are limited data on the pharmacokinetics of metreleptin in lipodystrophy patients. The median $T_{max}$ of metreleptin is 4 hours (range 2-8 hours) and renal clearance is the major route of elimination. No drug-drug interaction studies were conducted in lipodystrophy patients. However, because leptin is a cytokine, metreleptin has the potential to alter the formation of CYP450 enzymes. This may affect the metabolism of drugs with a narrow therapeutic index.

Based on clinical response (e.g., inadequate metabolic control) or other considerations (e.g., tolerability issues, excessive weight loss [especially in pediatric patients]), metreleptin dosage may be decreased or increased to the maximum dosage listed in the following table.

**Metreleptin Recommended Dosage**

**Metreleptin Recommended Dosage**

| Baseline Weight | Starting Daily Dose (injection volume) | Dose Adjustments (injection volume) | Maximum Daily Dose (injection volume) |
|---|---|---|---|
| Less than or equal to 40 kg (males and females) | 0.06 mg/kg (0.012 mL/kg) | 0.02 mg/kg (0.004 mL/kg) | 0.13 mg/kg (0.026 mL/kg) |
| Males greater than 40 kg | 2.5 mg (0.5 mL) | 1.25 mg (0.25 mL) to 2.5 mg (0.5 mL) | 10 mg (2 mL) |
| Females greater than 40 kg | 5 mg (1 mL) | 1.25 mg (0.25 mL) to 2.5 mg (0.5 mL) | 10 mg (2 mL) |

Based on review of non-clinical and clinical (e.g., ECGs) data provided in the BLA, the QT inter-disciplinary review team agreed with the decision to waive the requirement for a thorough QT study.

I concur with the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

# 6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewers that there are no outstanding clinical microbiology or sterility issues that preclude approval of the metreleptin BLA.

# 7. Clinical/Statistical-Efficacy

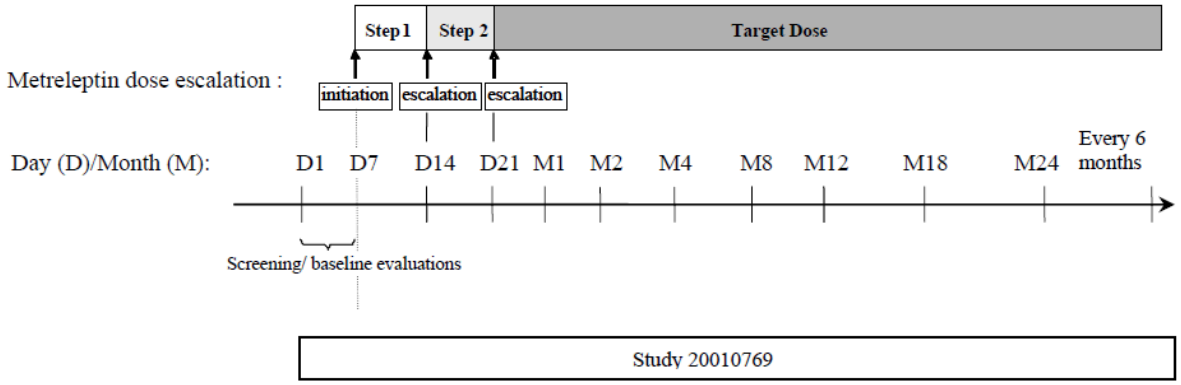
The metreleptin-lipodystrophy development program began in 2000 with a proof-of-concept study (991265) conducted under an investigator IND. This initial evaluation involved a small number of patients, most of whom had generalized lipodystrophy, low leptin levels, and severe metabolic disorders. Metreleptin treatment in this select group of patients led to impressive reductions in serum glucose and TG levels. Given these dramatic results and the rarity of lipodystrophy, the Division agreed with continued study of metreleptin in an open-label single-arm fashion. Over time, however, the study population broadened to include patients with partial lipodystrophy, higher leptin levels, and less severe metabolic disorders. As emphasized by Dr. Golden and discussed further below, the inherent limitations of single-arm, open-label studies made it challenging to assess metreleptin's efficacy and safety, particularly in patients with partial lipodystrophy.

The BLA submission includes efficacy data from 72 patients treated in studies 991265/20010796 at the NIH, and 28 patients from study FHA101 conducted under a treatment IND opened in 2008.

Study 991265 was initially designed as a four-month, open-label single-arm study with the primary objectives to determine: 1) if metreleptin can be safely administered to a group of patients with generalized lipodystrophy, and 2) if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with lipodystrophy.

Entry criteria included males and females > 14 years of age, clinically-significant lipodystrophy, circulating leptin levels < 4.0 ng/ml in females and < 3.0 ng/ml in males, and the presence of at least one of the following metabolic abnormalities: diabetes mellitus, fasting insulin > 30 uU/ml, or fasting TG > 200 mg/dl. Metreleptin was to be injected subcutaneously at doses predicted to achieve 50%, 100%, and 200% of normal leptin concentrations based on a normal body fat content of 30% in females and 20% in males. Patients were started at 50% of the predicted dose and maintained at this dose for one month. The dose was then increased to 100% of the predicted dose for another month. If this dose was tolerated, the dose was to be increased to 200% of the predicted dose. The total daily dose was to be administered in two equal injections separated by 12 hours. In a protocol amendment, the duration of treatment was extended to eight months. In a second amendment, patients were offered the opportunity to take part in a withdrawal trial, which required an inpatient admission and controlled diet. Afterwards, metreleptin therapy was resumed in the long-term extension trial 20010796.

Study 20010796 was designed to continue and expand study 991265 by lowering the inclusion age from 14 years to 5 years and by including patients with less severe leptin deficiency. An additional protocol amendment allowed patients to enter the study as young as 6 months of age. An overview of the study design is provided in the below figure from Dr. Golden's review.




[1] In the initial protocol metreleptin target dose was to be achieved via a 2-step dose escalation. As the study evolved over time patients who initiated later started at higher doses and required minimal dose escalation.

[2] Following the first metreleptin dose on Day 7, patients were observed as inpatients for at least 48 hours. Patients were not required to visit the site on Day 14 or Day 21

[3] Patients in Study 20010769 who continued treatment beyond 2 years were scheduled to return for follow-up visits every 6 months.

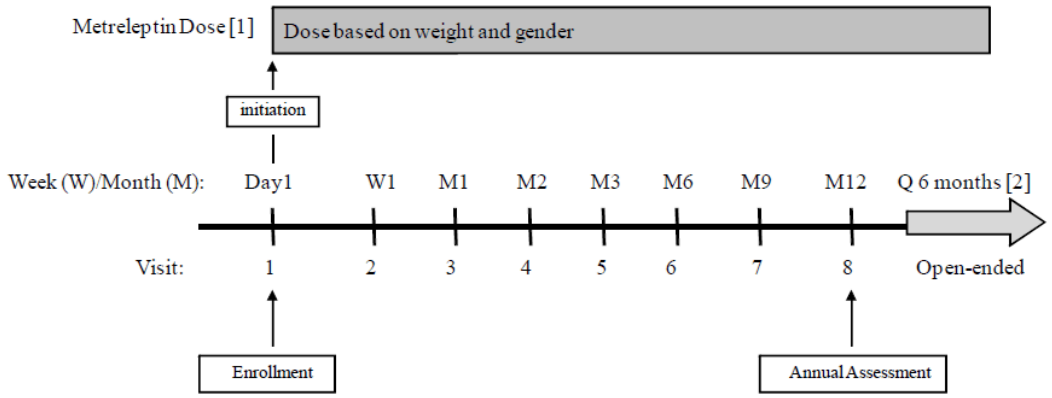
The baseline characteristics of the patients in the NIH studies 991265 and 20010769 are shown in the below table.

**Baseline Demographic Characteristics**

| | Study 991265 | Study 20010769 |
|---|---|---|
| | | |
| Generalized lipodystrophy | 89% | 63% |
| Female | 100% | 81% |
| Caucasian | 67% | 60% |
| Age < 17 years | 56% | 54% |
| Diabetes mellitus | 100% | 81% |
| Baseline HbA1c > 7% | 100% | 65% |
| Baseline TG > 500 mg/dl | 66% | 31% |
| Low leptin (< 3 males, < 4 females) | 100% | 70% |

As of a July 2011 cutoff date, seven of nine subjects enrolled into study 991265 continued into study 20010796. Of 72 subjects enrolled into study 20010796, 52 remained under active treatment. Reasons for withdrawal included non-compliance (n=5), death (n=3), adverse events (n=2), deemed ineligible (n=2), entry into non-US compassionate use program (n=6), and other health issues (n=1).

Study FHA101 was conducted under a treatment IND opened in 2008. The majority of patients in this study had partial lipodystrophy who could be enrolled regardless of leptin concentration. An overview of the study design is provided in the below figure from Dr. Golden's review.




[1] Daily recommended dose: subjects ≤40 kg (0.06 mg/kg), male subjects >40 kg (2.5 mg [0.5 mL]), females >40 kg, (5.0 mg [1.0 mL]). Based on clinical response (e.g., inadequate metabolic control or excessive weight loss or tolerability issues), metreleptin dose may be adjusted in increments or decrements of 0.02 mg/kg for subjects ≤40 kg and 1.25 (0.25 mL) to 2.5 mg (0.5 mL) for subjects >40 kg.

[2] Following evaluation at the end of approximately 1 year of treatment, subjects should return to the treatment site every 6 months or as directed by the investigator until metreleptin treatment is discontinued or until the protocol is terminated for administrative or safety reasons.

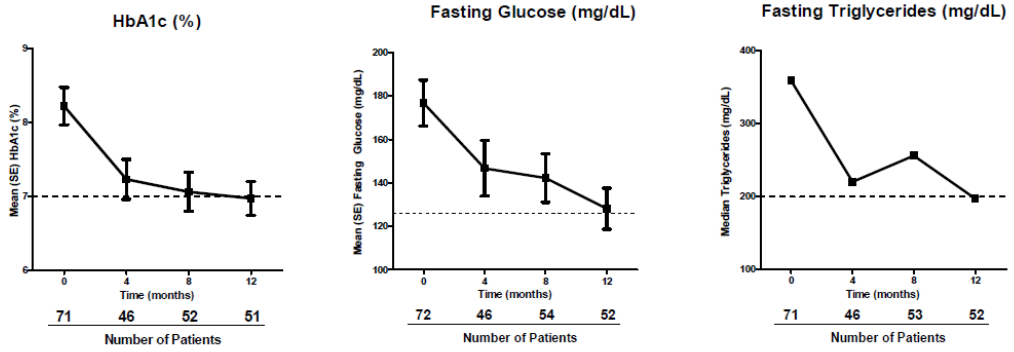
Baseline demographic characteristics of patients from study FHA101 included generalized lipodystrophy (18%), female (93%), Caucasian (75%), age < 17 years (11%), diabetes mellitus (75%), baseline HbA1c ≥ 7% (68%), baseline TG > 500 mg/dl (19%), and low leptin concentration (23%).

As of a March 2012 cutoff date, 20 of 28 patients enrolled into FHA101 remained under active treatment. Reasons for withdrawal included death (n=2), adverse event (n=1), withdrew consent (n=3), investigator decision (n=1), and loss to follow up (n=1).

The changes in metabolic parameters over the course of one year from the NIH trials are shown in the following table and figure adapted from Dr. Golden's review.

**Changes in Metabolic Parameters – NIH Studies**

| Parameter | | Month 4 | Month 8 | Month 12 |
|---|---|---|---|---|
| HbA1c (%) | N | 45 | 51 | 50 |
| | Baseline Mean (SD) | 8.3 (2.0) | 8.4 (2.1) | 8.2 (2.2) |
| | Change from Baseline | | | |
| | Mean (SE) | -1.1 (0.2) | -1.3 (0.2) | -1.4 (0.2) |
| | 95% CI | -1.6, -0.7 | -1.8, -0.9 | -1.8, -0.9 |
| Fasting Glucose (mg/d) | N | 46 | 54 | 52 |
| | Baseline Mean (SD) | 192 (97) | 176 (86) | 170 (89) |
| | Change from Baseline | | | |
| | Mean (SE) | -46 (12) | -34 (10) | -42 (12) |
| | 95% CI | -69, -22 | -54, -14 | -65, -18 |
| Fasting TG (mg/dl) | N | 45 | 52 | 51 |
| | Baseline Mean (SD) | 959 (1331) | 1175 (2378) | 1016 (1780) |
| | Change from Baseline | | | |
| | Mean (SE) | -471 (172) | -585 (285) | -673 (223) |
| | % Change from Baseline | | | |
| | Mean (SE) | -38 (6) | -11 (9) | -32 (8) |
| | 95% CI | -50, -26 | -29, 8 | -47, -17 |




The mean changes in HbA1c, fasting glucose, and fasting TG levels were favorable and of nominal statistical significance (aside from percent change in TG at Month 8) over the course of one year of treatment.

The changes in metabolic parameters over the course of one year for the patients with partial lipodystrophy in study FHA101 are shown in the below table adapted from Dr. Golden's review.

**Changes in Metabolic Parameters – FHA101, Subset of Patients with Partial Lipodystrophy**

| Parameter | | Month 3 | Month 6 | Month 12 |
|---|---|---|---|---|
| HbA1c (%) | N | 19 | 14 | 8 |
| | Baseline Mean (SD) | 7.9 (1.6) | 7.7 (1.5) | 8.7 (1.7) |
| | Change from Baseline | | | |
| | Mean (SE) | -0.2 (0.3) | -0.2 (0.4) | -0.9 (0.6) |
| | 95% CI | -0.8, 0.4 | -1.2, 0.7 | -2.3, 0.6 |
| Fasting Glucose (mg/d) | N | 18 | 14 | 8 |
| | Baseline Mean (SD) | 139 (51) | 146 (53) | 173 (50) |
| | Change from Baseline | | | |
| | Mean (SE) | 24 (25) | -26 (14) | -42 (22) |
| | 95% CI | -28, 77 | -56, 3 | -95, 11 |
| Fasting TG (mg/dl) | N | 18 | 14 | 8 |
| | Baseline Mean (SD) | 310 (298) | 333 (337) | 339 (255) |
| | Change from Baseline | | | |
| | Mean (SE) | -38 (64) | -61 (63) | -120 (84) |
| | % Change from Baseline | | | |
| | Mean (SE) | 12.3 (18) | 5.1 (13) | -23 (15) |
| | 95% CI | -26, 51 | -24, 34 | -59, 12 |

In contrast to the results from the NIH studies, the changes in metabolic parameters from study FHA101, while numerically favorable at some time points, they were not of nominal statistical significance.

With the exception of one patient who was prematurely discontinued from the study FHA101 for noncompliance and other issues, limited data from patients with generalized lipodystrophy in this trial were for the most part consistent with generalized lipodystrophy patients from the NIH trials.

The majority of patients in the NIH trials with generalized lipodystrophy on concomitant anti-diabetic medication(s) at baseline discontinued or had a significant reduction in the doses of anti-diabetic agents by Month 12. In contrast, a sizable proportion of patients with partial lipodystrophy initiated anti-diabetic medications or had their dose of anti-diabetic medication increased by Month 12.

Lipodystrophy is associated with non-alcoholic fatty liver disease (NAFLD) or hepatic steatosis, which can progress to non-alcoholic steatohepatitis (NASH), hepatic fibrosis, and ultimately cirrhosis. The sponsor proposed [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

Dr. Golden and I agree with this overall assessment.

Summary of Efficacy

As summarized by Drs. Golden and McEvoy, the quantification of metreleptin's efficacy was limited by a number of factors including: 1) single-arm, uncontrolled study designs, 2) the heterogeneity and ill-defined natural history of lipodystrophy, particularly partial lipodystrophy, 3) multiple changes to concomitant anti-diabetic and lipid-altering drug therapy, and 4) missing data.

Nevertheless, even with these limitations in mind, I believe that one can conclude with reasonable confidence that metreleptin effectively improves glycemic control and lowers serum TG levels in patients with generalized lipodystrophy. In patients with partial lipodystrophy, however, the data in the BLA do not provide adequate evidence of efficacy.

# 8. Safety

The safety assessment of metreleptin is based principally on data from the lipodystrophy and the Amgen and Amylin obesity development programs (see the below table from Dr. Golden's review).

**Studies Supporting the Efficacy and Safety of Metreleptin**

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

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

Unless indicated otherwise, data from the "other 10 Amgen obesity studies" were consistent with the data from the Amgen 5-trial Integrated Summary of Safety (hereafter "obesity ISS").

Deaths and Serious Adverse Reactions

There were eight deaths reported from the NIH and FHA101 clinical studies as of 2013. Six of these deaths occurred while the patient was receiving metreleptin or within one month of discontinuing treatment. The causes of death included pancreatitis, T-cell lymphoma, hepatorenal failure, renal failure, hepatic failure, anoxic encephalopathy, loss of consciousness, and adenocarcinoma.

One patient from the obesity ISS reportedly died from lymphocytic leukemia one month after initiating metreleptin therapy. One patient from the placebo group from one of the Amylin obesity studies died from adenocarcinoma of the lung 36 days after the first dose of study drug.

As of 11 July 2011, 24% of the patients in the NIH trials reported a total of 40 serious adverse reactions. Gastrointestinal disorders – including 4 patients with pancreatitis – and infections and infestations were the most frequently cited system organ classes. As of 11 January 2013, 27.8% of patients from the NIH trials reported a total of 58 serious adverse reactions. As of 7 March 2012, 32% of the patients in study FHA101 reported a total of 18 serious adverse reactions. As of 9 January 2013, 28.6% of patients from study FHA101 reported a total of 27 serious adverse reactions.

As shown in the following table from Dr. Golden's review, the incidence of serious adverse reactions from the obesity ISS was low, with 3.7% of patients randomized to placebo and 2.0% of patients randomized to metreleptin reporting a serious adverse reaction.

| **All Serious Adverse Reactions – Obesity ISS** | Placebo N=351 n (%) | Metreleptin N=784 n (%) |
|---|---|---|
| | 13 (3.7) | 16 (2.0) |
| | | |
| Cardiac disorders | 0 | 4 (0.5) |
| Angina pectoris | 0 | 2 (0.3) |
| Atrial fibrillation | 0 | 1 (0.1) |
| Ventricular arrhythmia | 0 | 1 (0.1) |
| | | |
| Gastrointestinal disorders | 2 (0.6) | 1 (0.1) |
| Abdominal pain upper | 1 (0.3) | 1 (0.1) |
| Pancreatitis | 0 | 1 (0.1) |
| Diverticulum intestinal | 1 (0.3) | 0 |
| Rectal hemorrhage | 1 (0.3) | 0 |
| | | |
| General disorders and administration site conditions | 4 (1.1) | 1 (0.1) |
| Injection site erythema | 0 | 1 (0.1) |
| Chest pain | 2 (0.6) | 0 |
| Pyrexia | 1 (0.3) | 0 |
| Vessel puncture site reaction | 1 (0.3) | 0 |
| | | |
| Hepatobiliary disorders | 1 (0.3) | 0 |
| Cholelithiasis | 1 (0.3) | 0 |
| Jaundice | 1 (0.3) | 0 |
| | | |
| Infections and infestations | 3 (0.9) | 4 (0.5) |
| Chronic sinusitis | 0 | 1 (0.1) |
| Pneumonia | 1 (0.3) | 1 (0.1) |
| Sinusitis | 0 | 1 (0.1) |
| Upper respiratory tract infection | 0 | 1 (0.1) |
| Injection site abscess | 1 (0.3) | 0 |
| Meningitis meningococcal | 1 (0.3) | 0 |
| | | |
| Injury, poisoning and procedural complications | 1 (0.3) | 2 (0.3) |
| Arthropod bite | 0 | 1 (0.1) |
| Tendon rupture | 0 | 1 (0.1) |
| Road traffic accident | 1 (0.3) | 0 |
| | | |
| Investigations | 2 (0.6) | 1 (0.1) |
| Heart rate irregular | 1 (0.3) | 1 (0.1) |
| Blood pressure increased | 1 (0.3) | 0 |
| | | |
| Metabolism and nutrition disorders | 1 (0.3) | 0 |
| Hyperglycemia | 1 (0.3) | 0 |
| | | |
| Musculoskeletal and connective tissue disorders | 0 | 1 (0.1) |
| Pain in extremity | 0 | 1 (0.1) |
| | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (0.6) | 3 (0.4) |
| Lymphocytic leukemia | 0 | 1 (0.1) |
| Metastatic malignant melanoma | 0 | 1 (0.1) |
| Uterine leiomyoma | 0 | 1 (0.1) |
| Breast cancer stage III | 1 (0.3)* | 0 |
| Cervix carcinoma | 1 (0.3)* | 0 |
| | | |
| Nervous system disorders | 0 | 3 (0.4) |
| Cerebrovascular accident | 0 | 1 (0.1) |
| Cubital tunnel syndrome | 0 | 1 (0.1) |

| **All Serious Adverse Reactions – Obesity ISS** | Placebo N=351 n (%) | Metreleptin N=784 n (%) |
|---|---|---|
| Headache | 0 | 1 (0.1) |
| | | |
| Renal and urinary disorders | 0 | 1 (0.1) |
| Stress urinary incontinence | 0 | 1 (0.1) |
| | | |
| Reproductive system and breast disorders | 1 (0.3) | 0 |
| Ovarian cyst | 1 (0.3) | 0 |
| | | |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 (0.1) |
| Asthma | 0 | 1 (0.1) |
| | | |
| Surgical and medical procedures | 1 (0.3) | 0 |
| Cholecystectomy | 1 (0.3) | 0 |
| *Note: these events occurred in study 980236 (notably not during the randomized portion of study 970213, in which all patients received metreleptin during a run-in period; therefore, neither of these patients were exposed to metreleptin). | | |

There was a similarly low incidence of serious adverse reactions reported by patients from the Amylin metreleptin + pramlintide obesity program, with no overarching patterns of concern.

Commonly-Reported Adverse Reactions

The most commonly-reported adverse reactions from the lipodystrophy program included headache (13%), hypoglycemia (13%), decreased weight (13%), and abdominal pain (10%).

Adverse Reactions of Special Interest

Lymphoma

As aforementioned in section 4.0, *in-vitro* and *in-vivo* data indicate that leptin, through activation of tumor-associated leptin receptors, can influence the growth and progression of malignant cells. Perhaps the use of "replacement doses" of metreleptin in lipodystrophy patients would not be expected to increase the risk for malignancy; yet, any clinical evidence to the contrary would be worrisome.

The proportion of patients with malignancies was similar in the metreleptin and placebo groups from the Amgen or Amylin metreleptin obesity programs. However, three cases of T-cell lymphoma were reported in patients from the NIH the FHA101 lipodystrophy clinical studies. All three cases occurred in patients with acquired generalized lipodystrophy.

According to our colleagues in the Division of Hematology Products, the incidence of T-cell lymphoma in the general population from the United States is 2.3 per 100,000 for males and 1.4 per 100,000 for females.

While the incidence of lymphoma in patients from the NIH and FHA101 clinical studies was 5900 per 100,000 in males and 1900 per 100,000 in females, these crude estimates are based on a very small sample of patients and therefore have very wide confidence intervals. Moreover, in addition to not knowing if lipodystrophy itself may be associated with an

increased risk for lymphoma, two of the three cases of lymphoma were confounded by histories of neutropenia and treatment with G-CSF. Nevertheless, the clinical review team considers the T-cell lymphoma data sufficient to warrant a boxed warning. I agree with this assessment.

Immunogenicity

Metreleptin is highly immunogenic; almost all patients, including those from the obesity development programs, treated with this protein developed binding antibodies. Of greatest immunogenic concern is the potential development of neutralizing antibodies, with resultant inhibition of endogenous leptin activity or loss of efficacy in patients with lipodystrophy or inhibition of endogenous leptin activity in patients without lipodystrophy (e.g., obese patients treated off-label with metreleptin alone or in combination with pramlintide).

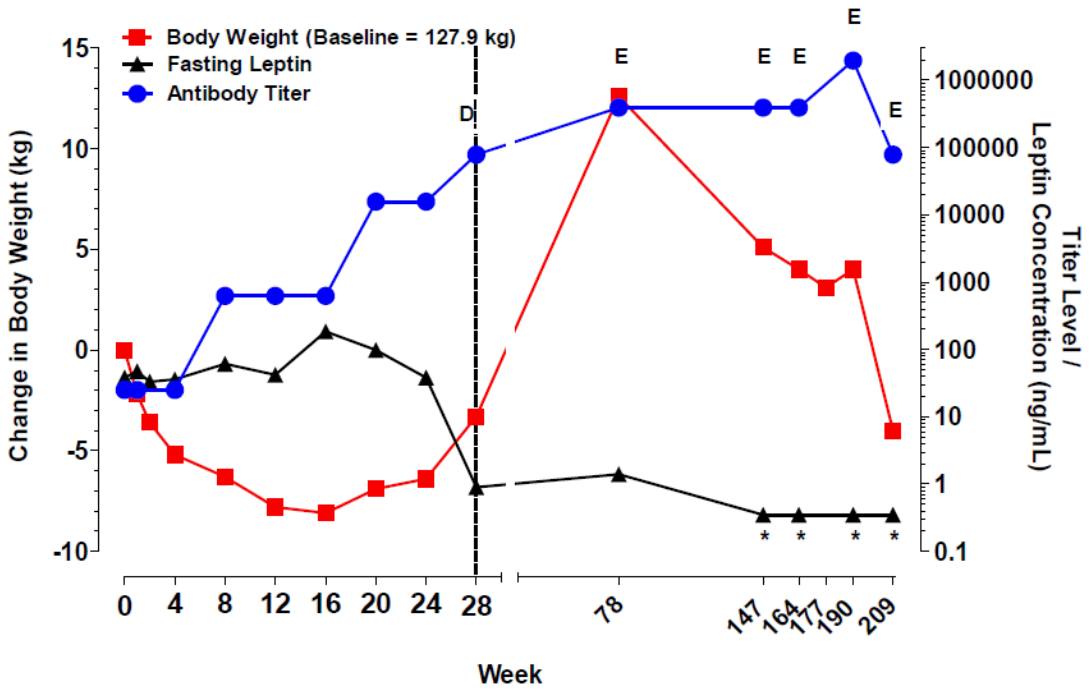
The sponsor used the following categorization for neutralizing activity from their *in-vitro* assay: Category A: result is less than the assay cut-point on initial testing; Category B: result is higher than the assay cut-point on initial testing, but less than assay cut-point on repeat testing; Category C: result is higher than the assay cut-point on initial testing and re-testing, but is less than the assay cut-point after additional 1:10 dilution; Category D: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 dilution but not after 1:100 dilution; and Category E: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 and 1:100 dilutions. Categories D and E represent high potency neutralizing activity to metreleptin.

Seven patients from the NIH and FHA101 studies developed neutralizing antibody activity (categories D or E). One of these patients had loss of efficacy, as indicated by an increase in HbA1c concentrations, and five hospitalizations due to bacterial infections. A second patient, also with a history of hospitalization for sepsis and worsening glycemic control, was recently reported to have developed neutralizing activity. These cases raise concern that development of neutralizing antibodies to metreleptin could impair metabolic control and immune function.

No patient from the obesity ISS was known to have developed neutralizing antibodies, although the assay used may have been less sensitive than the assay used for the lipodystrophy program.

Three patients out of 579 who participated in Amylin's metreleptin-pramlintide obesity program were identified with Category D or E antibodies. All of these patients presented with high antibody titer, low leptin concentrations, and excessive body weight gain. The following figure from Dr. Kruzick's immunogenicity consult, depicts the changes in levels of antibody titer, fasting leptin, and body weight in one of these patients.

Figure 19. Change in Body Weight, Fasting Leptin Concentration, and Antibody Titer over Time for Subject 130019




Note: Antibody data generated using the Amylin assay methods as described in Sections 4.1.1.1 (binding antibody) and 4.1.1.2 (metreleptin neutralizing activity). D, E indicate category of in vitro neutralizing activity.

* Indicates plasma leptin concentration below the lower limit of quantification (LLOQ) (<0.7 ng/mL).

- Week 177 antibody/plasma leptin samples were lost.

Cross-references: CSR DFA102 Appendices 3.9.2, 3.9.3, and 3.19; and MedWatch form 2011AM004395.

The clinical ramifications of developing neutralizing antibodies are not well characterized; yet, the potential risks of worsening metabolic control and/or severe infections in metreleptin-treated patients with lipodystrophy led the clinical review team to recommend that this information be included in a boxed warning. I agree with this recommendation. The labeling will direct healthcare providers to test for neutralizing activity to metreleptin in lipodystrophy patients who develop severe infections or show signs of loss of efficacy. Furthermore, use of metreleptin to treat obesity – where neutralizing antibodies could induce a leptin deficiency-like syndrome - will be contraindicated in the labeling.

There were four pregnancies reported from the NIH studies – two resulted in live births, one ended with a premature birth and delivery of a non-viable fetus, and one ended in miscarriage. One of the live births had complications of shoulder dystocia and Erb's palsy. There were no reported pregnancies in study FHA101. One patient who took part in the obesity development program was reported to have become pregnant while receiving metreleptin, although no follow-up information was provided by the sponsor.

Dr. Golden appropriately raises concern about the theoretical risk of neutralizing antibodies crossing the placental and inducing a leptin deficiency-like syndrome in children born to

mothers who are exposed to metreleptin during pregnancy. The sponsor will be required to conduct post-marketing studies to assess this potential risk.

Hypoglycemia

Hypoglycemia of either mild or moderate intensity was the most commonly-reported adverse reaction in the lipodystrophy trials: 11% of patients from the NIH trials and 25% of the patients from FHA101. In the NIH trials, only those patients using insulin therapy with or without oral anti-diabetic medication reported events of hypoglycemia. None of the hypoglycemic events were severe enough to require assistance of another individual. In study FHA101, one patient had a severe episode of hypoglycemia; another patient had five hypoglycemic events. As with the NIH trials, most cases of hypoglycemia in FHA101 occurred in patients who were using insulin with or without oral anti-diabetic therapy.

In the obesity ISS, 3.6% of patients randomized to metreleptin and 1.4% of patients randomized to placebo reported events of hypoglycemia. These events occurred exclusively in patients with type 2 diabetes.

The labeling will include hypoglycemia in the Warnings and Precautions section so that healthcare providers will be apprised of this risk in patients with lipodystrophy using metreleptin with insulin and/or insulin secretagogues.

Pancreatitis

By virtue of their severe hypertriglyceridemia, patients with lipodystrophy are at increased risk for pancreatitis. In the NIH trials, 22% of the patients had a history of at least one episode of pancreatitis and 5.6% had a history of recurrent episodes of pancreatitis. In FHA101, 8% of the patients had a history of at least one episode of pancreatitis.

The below table from Dr. Golden's review provides the cases of pancreatitis reported during the lipodystrophy studies.

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

| Patient ID<br>Age / Sex / Type | Relevant Medical History / Baseline TG | Verbatim Term / SAE? | Time to Onset (Days) |
|---|---|---|---|
| | TG 359 mg/dL | | |
| 648001<br>9 / F / AGL | Acute pancreatitis<br>High triglycerides<br>TG 10623 mg/dL | Acute pancreatitis / Y | 191 |
| | | Pancreatitis / Y | 1205 |

All but one of these cases occurred in patients with extremely elevated levels of baseline TG. The sponsor argues that the patients who developed pancreatitis were either non-compliant or they discontinued metreleptin therapy too rapidly and induced a rebound in serum TG levels. Dr. Golden was unable to confirm the sponsor's assertion and rightly points out that the lack of a control group and the small size of the lipodystrophy database leave unanswered the question of metreleptin's role in the cases of pancreatitis.

(Historically, the Division has approved therapies to treat severe hypertriglyceridemia based on a statistically significant reduction in serum TG levels, as it is not feasible to conduct a study with episodes of pancreatitis as the primary efficacy endpoint. This certainly holds true for the lipodystrophy population.)

In the event that a patient needs to discontinue metreleptin therapy, the sponsor has proposed labeling language to inform healthcare providers of the need to closely monitor patients' TG levels and perhaps adjust lipid-altering therapy as the dose of metreleptin is tapered over the course of one week. This seems reasonable.

Autoimmunity

Acquired lipodystrophies are associated with autoimmune disorders such as autoimmune hepatitis and membranoproliferative glomerulonephritis. Because leptin plays a role in the regulation of the immune system, it is concerning that some patients with acquired generalized lipodystrophy treated with metreleptin in the NIH trials experienced progression of pre-existing autoimmune hepatitis and membranoproliferative glomerulonephritis (see table below from Dr. Golden's review).

**Autoimmune Disease Reported during NIH Trials**

| Patient ID | Age (years) and Gender (M/F) | LD Subtype | Relevant Medical History | Relevant Adverse Events |
|---|---|---|---|---|
| 90107 | 42 yr F | FPL | No relevant medical history | Lupus anticoagulant |
| 90109 | 13 yr F | AGL | Type 1 diabetes mellitus | Chronic inflammatory hepatitis, Membranoproliferative glomerulonephritis |
| 90110 | 8 yr F | AGL | Hashimoto's thyroiditis, Kawasaki's disease, Autoimmune hepatitis, Common variable immunodeficiency | Elevated ALT, Worsening autoimmune hepatitis, Parainfluenza pneumonia, streptococcal pharyngitis, URI, sinusitis, ear infection, flu |
| 90113 | 12 yr F | CGL | No relevant medical history | Hashimoto's thyroiditis |
| 90114 | 35 yr M | AGL | Chronic renal failure, Proteinuria | Membranoproliferative glomerulonephritis |

Based on Sponsor review of TEAEs.

However, the small size of the lipodystrophy database, the lack of a placebo control, and a heighted risk for autoimmune disease associated with acquired lipodystrophy preclude determination of the nature of the relationship between use of metreleptin and exacerbation of autoimmune disease. Nonetheless, I agree with including autoimmunity in the Warnings and Precautions section of the metreleptin labeling.

Other Immune-Related Adverse Reactions (hypersensitivity)

In the NIH trials, 15% of patients experienced 13 reactions that could be considered immune-related. These included urticaria (2.8%), anaphylactic reaction (1.4%), and papular rash (1.4%). In study FHA101, 32% of patients experienced 13 reactions that could be considered immune-related. These included urticaria, swelling face, rash, pruritus, injection site inflammation, injection site pruritus, and injection site urticaria.

In the obesity ISS, the most-commonly reported adverse reaction in both metreleptin- and placebo-treated patients was injection-site reaction (60% versus 45%). The percentages of patients experiencing events of anaphylactic reaction, angioedema, and potential hypersensitivity-related cutaneous reactions were 6.1% of metreleptin-treated patients versus 5.7% of placebo-treated patients. One patient from the metreleptin + pramlintide program who received metreleptin reported a serious adverse event of hypersensitivity.

Liver-Related Events

Patients with lipodystrophy are at increased risk for developing NAFLD, with some patients progressing to NASH and cirrhosis. Furthermore, patients with acquired forms of lipodystrophy are at increased risk for autoimmune hepatitis.

In the NIH trials, 44% of the patients had a history of NASH and 19% had a history of NAFLD. Eight percent of the patients had cirrhosis and 6% had hepatic fibrosis. In the FHA101 study, 76% of the patients had a history of NAFLD and 4% had a history of autoimmune hepatitis.

Shown in the below table from Dr. Golden's review are liver-related adverse events reported in the lipodystrophy trials.

| **Patient ID Age / Sex / Type** | **Relevant Medical History (Baseline AST / ALT)** | **Verbatim Term / SAE?** | **Time to Onset (Days)** |
|---|---|---|---|
| 90103<br>27 / F / AGL | Autoimmune hepatitis, liver fibrosis (AST 57, ALT 128) | Increased liver enzymes / Y | 481 |
| 90107<br>42 / F / FPL | Hepatomegaly, focal glomerulonephritis (AST 28, ALT 28) | Steatohepatitis / N | 6 |
| 90109<br>13 / F / AGL | Nonalcoholic steatohepatitis, bridging fibrosis (AST 85, ALT 79) | Chronic inflammatory hepatitis / N | 382 |
| | | Worsening of liver disease / Y | 422 |
| 90110<br>8 / F / AGL | Autoimmune hepatitis, mild portal fibrosis, fatty liver (AST 38-39, ALT 53-56) | Elevated ALT level of 317 U/L / Y | 34 |

| Patient ID Age / Sex / Type | Relevant Medical History (Baseline AST / ALT) | Verbatim Term / SAE? | Time to Onset (Days) |
|---|---|---|---|
| | | Worsening autoimmune hepatitis / N | 2443 |
| 90158 18 / F / AGL | Severe liver disease with cirrhosis (AST 142, ALT 105) | Hepatic encephalopathy / Y | 344 |
| | | Progressive end stage liver disease / Y (fatal) | 523 |
| 648004 30 / F / FPL | Fatty liver, increased LFTs (AST 21, ALT 14) | Elevated AST levels (AST 78, ALT 33) / N | 443 |
| 648016 11 / M / AGL | Chronic active autoimmune hepatitis, history of elevated LFTs (AST 208, ALT 419) | Increased LFTs / N | 9 |

No liver-related adverse events were reported in metreleptin-treated subjects from the obesity ISS. The following information related to the liver was provided from the metreleptin + pramlintide trials and the Amgen obesity trials other than the 5 included in the ISS: One case of blood bilirubin increased in a metreleptin-treated patient; three cases of ALT increased in metreleptin-treated patients and one case in a placebo-treated patient; and three cases of AST increased in metreleptin-treated patients and one case in a placebo-treated patient. There were no reports of Hy's law in the lipodystrophy or obesity development programs.

Summary of Safety

The principal safety concerns with metreleptin are T-cell lymphoma and anti-metreleptin antibodies with neutralizing activity. These concerns are of sufficient magnitude to require REMS, as described below. Other safety findings that warrant inclusion in the Warning and Precautions section of the metreleptin labeling include hypoglycemia, autoimmunity, and hypersensitivity.

Risk Evaluation and Mitigation Strategy

To ensure that the benefits of metreleptin outweigh its risks, this BLA will be approved with a REMS. The goal of the REMS is to mitigate (1) the risks of serious adverse sequelae such as severe infections, excessive weight gain, glucose intolerance, and diabetes mellitus due to the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT, and (2) the risk of lymphoma by:

- Educating prescribers about the development of neutralizing antibodies, the serious adverse sequelae that may result from these antibodies, and the risk for lymphoma associated with metreleptin
- Limiting the population exposed to metreleptin by requiring prescriber certification, pharmacy certification, and prescriber attestation that each patient has a diagnosis consistent with the approved indication

The Elements to Assure Safe Use (ETASU) include: 1) Healthcare providers who prescribe metreleptin will be specially certified; 2) Pharmacies that dispense metreleptin will be

specially certified; and 3) Metreleptin will be dispensed only to patients with evidence or other documentation of safe-use conditions through healthcare provider attestation.

Post-Marketing Requirements and Commitments

The sponsor will be directed to conduct seven studies as post-marketing requirements (PMR) and eight studies as post-marketing commitments (PMC).

The PMRs include a long-term prospective observational study (product exposure registry) of patients treated with metreleptin to assess for potential serious risks such as pancreatitis, severe hypoglycemia, serious infections, and pregnancy outcomes; a study to assess the immunogenicity of metreleptin; and an enhanced pharmacovigilance program to assess and analyze spontaneous reports of serious risks associated with metreleptin use such as pancreatitis, severe hypoglycemia, serious infections, new diagnoses of autoimmune disorders (e.g., autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, and pregnancy outcomes.

The PMCs will examine various aspects of product quality (e.g., test the stability of metreleptin drug product reconstituted in bacteriostatic water, develop, validate, and implement the quantitative polymerase chain reaction (qPCR) method to detect *E.coli* DNA impurities in drug substance lots).

# 9. Advisory Committee Meeting

The metreleptin BLA was discussed at an 11 December 2013 EMDAC meeting. For the most part, the committee did not believe that the sponsor had provided adequate evidence that the benefits of metreleptin outweighed the risks for the treatment of pediatric and adult patients with metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on current therapy, and/or evidence of hepatic steatosis (Vote: Yes=2, No=10). In contrast, the majority of the committee agreed that the benefits of metreleptin outweighed the risks for the treatment of pediatric and adult patients with generalized lipodystrophy (Vote: Yes=11, No=1). The committee agreed that lymphoma and immunogenicity were significant safety concerns, but they did not believe that they should preclude approval of metreleptin for the treatment of generalized lipodystrophy.

# 10. Pediatrics

The Pediatric and Maternal Health staff was consulted to obtain the appropriate language for the Pregnancy, Nursing Mothers, and Pediatric Use sections of the labeling. Because metreleptin contains benzyl alcohol when reconstituted with bacteriostatic water for injection (BWFI) and benzyl alcohol has been associated with serious adverse reactions (including gasping syndrome) and death in pediatric patients, particularly neonates and premature infants, the metreleptin labeling with include a warning directing prescribers to use preservative-free water for injection in neonates and infants.

Since lipodystrophy is an orphan indication, the sponsor is not required to comply with the Pediatric Research Equity Act (PREA).

# 11. Other Relevant Regulatory Issues

Following inspections of two domestic investigative sites, as well as a contract research organization, the Office of Scientific Investigation issued a No Action Indicated (NAI). Facility inspections were similarly deemed acceptable.

The sponsor had originally proposed (b) (4)

This is an acceptable alternative.

Dr. Yelena Maslov, reviewer from the Division of Medication Error Prevention and Analysis, has confirmed that the human factors study conducted by the sponsor provides adequate evidence to support approval of metreleptin and its safe and effective use as directed in the final labeling.

The NIH confirmed that their investigators for the two NIH lipodystrophy trials did not have any reportable financial conflicts of interest. Similarly, none of the investigators for study FHA101 had reportable financial conflicts of interest. Several investigators/sub-investigators of the Amylin metreleptin-pramlintide obesity program reported disclosed financial interests. I agree with Dr. Golden that the potential impact of these financial interests is minimized by the fact that the clinical trials had multiple investigative sites and investigators/sub-investigators. Because the Amgen metreleptin obesity program was conducted prior to 1999, the sponsor had no obligation to collect financial disclosure information.

There are no other unresolved relevant regulatory issues

# 12. Labeling

The proposed proprietary name, MYALEPT, was considered acceptable by DMEPA. I agree with this assessment.

The BLA lacked sufficient evidence to support approval of metreleptin for the treatment of patients with partial lipodystrophy. Hence, the Indications and Usage section of the labeling will read: MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Important limitations of use will include:

- The safety and effectiveness of MYALEPT for the treatment of complications of partial lipodystrophy have not been established.
- The safety and effectiveness of MYALEPT for the treatment of liver disease, including non-alcoholic steatohepatitis (NASH), have not been established.
- MYALEPT is not indicated for use in patients with HIV-related lipodystrophy.
- MYALEPT is not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy.

# 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I concur with Dr. Golden's recommendation that the metreleptin BLA be approved as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

- Risk-Benefit Assessment

Taking into account the required REMS, the risk-benefit assessment of metreleptin is favorable when used to treat the complications of leptin deficiency in patients with generalized lipodystrophy. Because the sponsor has not provided sufficient evidence of metreleptin's efficacy in patients with partial lipodystrophy, the benefit-risk assessment in this population is unfavorable and does not support approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The goal of the metreleptin REMS is to mitigate (1) the risks of serious adverse sequelae such as severe infections, excessive weight gain, glucose intolerance, and diabetes mellitus due to the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT, and (2) the risk of lymphoma by:

- Educating prescribers about the development of neutralizing antibodies, the serious adverse sequelae that may result from these antibodies, and the risk for lymphoma associated with metreleptin
- Limiting the population exposed to metreleptin by requiring prescriber certification, pharmacy certification, and prescriber attestation that each patient has a diagnosis consistent with the approved indication

The Elements to Assure Safe Use (ETASU) include: 1) Healthcare providers who prescribe metreleptin will be specially certified; 2) Pharmacies that dispense metreleptin will be specially certified; and 3) Metreleptin will be dispensed only to patients with evidence or other documentation of safe-use conditions through healthcare provider attestation.

- Recommendation for other Postmarketing Requirements and Commitments

The sponsor will be obligated to conduct seven studies as post-marketing requirements and eight studies as post-marketing commitments. See the metreleptin approval letter for details of the PMRs and PMCs.

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/s/

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ERIC C COLMAN
02/24/2014