CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	February 24, 2014
From	Mary H. Parks, M.D.
Subject	Office Deputy Director Summary Review
NDA/BLA # **Supplement #**	BLA 125390
Applicant Name	Bristol-Myer Squibb/Astra-Zeneca
Date of Submission	March 27, 2013 (final submission to rolling BLA)
PDUFA Goal Date	February 24, 2014 (including 3 month extension)
Proprietary Name / **Established (USAN) Name**	Myalept (metreleptin) – recombinant leptin analog
Proposed Indication(s)	Originally proposed for the treatment of metabolic disorders associated with lipodystrophy including diabetes mellitus and/or hypertriglyceridemia in pediatrics and adults with inheritied or acquired lipodystrophy.
Action/Recommended Action for NME:	Approval

Signatory Authority Review

1. Introduction

This biologic licensing application (BLA) is for metreleptin, an analog of the human protein leptin, a 167-amino acid protein secreted primarily by white adipose tissue that plays an important role in the regulation of energy homeostasis, neuroendocrine function, and metabolism. Complete leptin deficiency resulting from a homozygous mutation of the leptin gene results in marked hyperphagia, obesity, and neuroendocrine abnormalities including hypogonadotropic hypogonadism. Administration of leptin in this very rare disorder reduces food intake and normalizes body weight. However, the clinical application of leptin in the treatment of common obesity, where patients have relatively high leptin levels have not yielded promising results.

This BLA is for the treatment of another group of rare medical conditions called lipodystrophy. Lipodystrophy is characterized by complete or partial loss of adipose tissue and abnormal redistribution of fat in other tissues such as muscle or liver. It is categorized according to etiology (congenital or acquired) and pattern of fat loss (generalized or partial). The clinical presentation across the different subtypes of lipodystrophy is heterogeneous but signs and symptoms of severe insulin resistance (diabetes and hypertriglyceridemia) predominate among patients.

Patients with the generalized forms of lipodystrophy (congenital or acquired) have very low levels of the hormones leptin and adiponectin, as a result of near total lack of body fat or severely reduced subcutaneous adiposity. Diagnosis may be made at birth (congenital) or during childhood or adolescence (acquired). Patients with generalized lipodystrophy have very distinguishable features due to the marked loss of subcutaneous adipose tissue. In addition, hepatic steatosis is common, which may progress to cirrhosis. Acquired generalized lipodystrophy may be associated with other autoimmune disorders.

Like the generalized form, partial lipodystrophy can be inherited (referred to in this BLA as familial lipodystrophy) or acquired. As implied in its name, the loss of adipose tissue in these patients is not as severe as in the generalized forms, which can account for less-severe insulin resistance. Circulating levels of leptin tend to be higher which may also be due to the less-extensive lipoatrophy. Due to the pattern of subcutaneous fat loss in some of these patients, the physical features, particularly of males, may resemble those of an athlete with increased muscularity. Infections and autoimmune disease have been linked to the development of acquired partial lipodystrophy (APL), and there is an association between APL and membranoproliferative glomerulonephritis.

Despite summarizing lipodystrophy neatly into these four subtypes, the clinical presentation of these patients is far from being clearly delineated. Instead, the highly variable presentation of

this condition contributes to the complexity in reviewing this BLA, as will be noted throughout this memo.

2. Background

Use of metreleptin under an IND for the treatment of lipodystrophy began in 2000 with a single open-label trial in nine patients with lipodystrophy, hypoleptinemia, and severe insulin resistance. The sponsor at that time was Amgen and the investigation was conducted by researchers at the National Institutes of Health (NIH). The early promising results from this trial led to an agreement that results from this single study would be sufficient as a single pivotal trial for a marketing application. In 2001, orphan and fast track designations were granted for metreleptin in the treatment of metabolic disorders secondary to lipodystrophy.

In 2006, sponsorship of the metreleptin IND was transferred to Amylin. Over the years, the clinical investigation of metreleptin had evolved such that the eligibility criteria under the initial clinical protocol had been modified to expand the age and patient population based on higher leptin levels permitted under a new clinical protocol. Many of the patients under the original protocol continued into this new clinical protocol for long-term therapy. In 2008, Amylin opened a treatment IND to allow expanded access to metreleptin. The protocol under this treatment IND was less restrictive than previous protocols, eliminating leptin levels as an eligibility criterion.

All along, these trials were open-label and uncontrolled in design. The protocols' objectives were to investigate the effectiveness of metreleptin; however, the execution of these studies did not fully prohibit the use of other therapies by well-meaning investigators. Such concomitant therapies introduced confounders that complicate interpretation of the study results. The collection of data and its compilation were not of the quality typically received by FDA review staff. The following example statements from Dr. Golden under Section 3 of her clinical review highlight the challenges she faced:

- "Furthermore, given the nature of the disease (rare, with heterogeneous presentation), the development program (evolving over time, open-label), and the regulatory program under which this was submitted (fast track, utilizing a rolling review), the application was very challenging to review."

- "Unfortunately, some of the data from earlier cuts were not available for later data cuts, and finding earlier data was challenging, since it could have been included in various documents from a variety of submission dates."

Section 3, page 20 through 23 of her review, goes further to list the limitations of the development program. It is against the backdrop of these limitations in the setting of a rare disorder that the review disciplines considered their interpretation of the data and final recommendations.

3. CMC/Device

Metreleptin is an analog of the human protein leptin, produced by recombinant technology in E. coli. It is a non-glycosylated, 147-amino acid polypeptide that differs from the human protein by the addition of methionine at the amino-terminal end.

The drug product is supplied as a sterile, lyophilized cake to be reconstituted with either bacteriostatic water, which contains 0.9% benzyl alcohol, or preservative-free sterile water. The latter is to be used as the diluent when treating neonates and infants.

All deficiencies identified during the review have been addressed by the company.

4. Nonclinical Pharmacology/Toxicology

Please see reviews of Dr. Basso (primary) and Bourcier (secondary) for detailed discussions of the pharmacology/toxicology program for metreleptin. Both recommend approval without required postmarketing studies. Main concerns identified were carcinogenic potential, immunogenicity, and possible dystocia in pregnancy. Regarding carcinogenicity, it should be noted that standard 2-year carci studies were not required for this indication; however, genotoxicity assays and chronic mouse and dog studies did not identify a signal for concern. Nonetheless, the pharm/tox reviewers believe there remains a theoretical risk given the evidence supporting leptin as a promoter of cell growth. The three cases of T-cell lymphoma in the clinical program do little to abate these concerns (see Section 8.0 of this memo).

5. Clinical Pharmacology/Biopharmaceutics

Please see review authored by Drs. Vaidyanathan and Zadezensky. Recommendation is made for approval with no post-marketing requirements.

No tQT study was conducted for this BLA. CDER's QT-IRT (interdisciplinary review team) was consulted and, based on review of nonclinical and clinical evidence, there was agreement that no tQT study was needed for metreleptin.

There are limited PK data in patients with lipodystrophy. Cmax occurs at approximately 4 hrs after a single-dose subcutaneous injection in both healthy and lipodystrophic patients. Half-life is approximately 4 hrs with renal clearance expected to be the major route of elimination.

6. Clinical Microbiology

Please see reviews by Drs. Survana and Hughes for CMC microbiology issues of drug substance and Dr. Stephen Fong for CMC microbiology issues of drug product. The application can be approved from their standpoint.

7. Clinical/Statistical-Efficacy

Two clinical studies were considered pivotal in the assessment of efficacy of metreleptin for the treatment of lipodystrophy (LD). These studies were Study 991265 and Study 20010769, hereafter referred to as Study 265 and Study 769. A third study, FHA101, was conducted under a treatment IND to allow expanded access to metreleptin. This study and its results were considered supportive in the review of this BLA and will not be considered in this section of my memo.

The critiques of the study design and conduct of all three studies are well-documented in the reviews of Drs. Golden (clinical) and McEvoy (statistics). I concur with them that the open-label, uncontrolled nature of these studies, alongside with numerous confounding factors, make interpretation of the study results very challenging. Furthermore, these studies were designed and executed as research protocols or expanded access protocols (FHA101). As such, changes were made over time to the patient population enrolled, dosing, etc., as investigators made note of responses to treatment. As pointed out by Dr. Golden under Section 6.1.1 of her review, the statistical analysis plan (SAP) was written by the sponsor in 2010, well after these trials were initiated and underway. Hence, all of the efficacy analyses are considered post-hoc and much of the results provided in Drs. McEvoy's and Golden's reviews represent their best attempt at capturing completeness of data.

My memo will summarize the high-level efficacy results in the overall lipodystrophy population and further hone in on the generalized versus partial lipodystrophy patient populations from Studies 265 and 769. Presentation of data from relevant sub-analyses that have shaped the labeling negotiations for this application will also be presented. For a thorough appreciation of the FDA's critical review of efficacy (and safety), the reader is referred to the reviews authored by Drs. Golden and McEvoy.

Studies 265 and 769

The following table summarizes the design of pivotal studies, 265 and 769.

Table 7.1 Design of Studies 265 and 769

	Study 265	Study 769
Design	Open-label, uncontrolled	Open-label, uncontrolled
Status	Completed, patients were given opportunity to continue in Study 769	Ongoing
Inclusion Criteria Age Leptin levels Metabolic abnormalities	 14 yrs < 4 ng/mL (females); < 3 ng/mL(males) At least 1 of the 3: Diabetes mellitus Fasting insulin > 30 ug/mL Fasting TG > 200 mg/dL	 6 mos (originally ≥ 5 yrs) <12 ng/mL (females ≥5 yrs); < 8 (males ≥5 yrs); < 6 ng/mL (age < 5 yrs) At least 1 of the 3: Diabetes mellitus Fasting insulin > 30 ug/mL Fasting TG > 200 mg/dL
Study Site	NIH/UTSW*	NIH
Number of patients	9/3*	63

*due to previous agreement with FDA, data from 2 patients enrolled at Univ of Texas, Southwestern, were not submitted with BLA

Note the differences in inclusion criteria between the two studies. Study 265 was the first study investigating the effects of metreleptin in patients with lipodystrophy and initially targeted a more restrictive population. Early promising results in Study 265 may have contributed to the liberalization of certain eligibility criteria to allow a broader patient population studied in Study 769. A strength of Study 265 over Study 769 was completeness of data collection. For example, there were no withdrawals of patients originally enrolled in Study 265 within one year of first metreleptin dose whereas 10% of patients enrolled directly into Study 769 withdrew within this same timeframe. In addition, there were no missing data at Months 4 or 12 in Study 265, whereas Study 769 had more missing data at these timepoints, particularly for patients who enrolled at a later date in this study (Table 5 from Dr. McEvoy's review). As many as 60% of patients receiving their first dose of metreleptin between May 2007 and May 2011 in Study 769 had missing data on at least one primary endpoint at Month 4 and as many as 40% had missing data at Month 12. Despite this strength, Study 265 was a much smaller database and therefore Study 769 remains an important trial for determining effectiveness of metreleptin.

The characteristics and demographics of these two studies differ in many ways. Table 7.2 summarizes these differences between the two study populations.

Table 7.2. Demographics and baseline characteristics in Studies 265 and 769 (adapted from Table 6 of Dr. McEvoy's review)

	Study 265 N=9		**Study 769 N=63**	
	Generalized N=8 (89%)	**Partial N=1 (11%)**	**Generalized N=40 (65%)**	**Partial N=23 (35%)**
Gender Male Female	 0 8	 0 1	 12 28	 0 23
Age (yrs) </= 17 Mean (SD)	 5 23 (10)	 0 42	 30 18 (15)	 4 33 (16)
LD type AGL CGL APL FPL	 3 5 0 0	 0 0 0 1	 13 27 0 0	 0 0 4 19
Diabetes present, n(%)	8 (100%)	1 (100%)	30 (75%)	21 (91%)
Mean fasting leptin, ng/mL (SD)	1.7 (1.1) data missing in 1	2.5	1.3 (1.1) data missing in 3	5 (3.1) data missing in 2
HbA1c, mean (SD)	9.1 (1.5)	9.5	8.4 (2.2) data missing in 1	7.6 (2.2)
Fasting TG, mg/dL Mean (SD)	 1953 (2576)	 802	 667 (871)	 1425 (3158)

Fasting glucose, mg/dL Mean (SD)	210 (125)	315	179 (78)	156 (89)

All but one patient in Study 265 had generalized LD whereas approximately one-third of the patients in Study 769 had partial LD. Reflecting this difference, there were greater metabolic abnormalities in patients enrolled in Study 265 with all having a diagnosis of diabetes and a higher mean fasting TG level in the overall population (1809 mg/dL) compared to the overall population in Study 769 (944 mg/dL). The overall mean fasting leptin level was lower in Study 265 (1.8 ng/mL) than in Study 769 (2.7 ng/mL), likely reflecting allowance of patients with higher leptin levels into the latter study.

The FDA statistical review focused on HbA1c and fasting triglycerides (Tgs) as the primary measures of efficacy. Dr. Golden's review also summarizes other efficacy endpoints. This memo summarizes results for HbA1c and fasting Tgs. In addition, since the proposed label includes (b) (4) I will also reference the consult from FDA's Division of Gastroenterology and Inborn Errors Products (DGIEP).

HbA1c

The following table from Dr. McEvoy's review summarizes the HbA1c findings at Month 12 in Studies 265 and 769. In both studies there is an observed reduction from Baseline in mean and median HbA1c values for the overall cohort of patients with available data (Study 769 had missing data in 16 patients at Month 12). The reduction in HbA1c is greater in the generalized LD population than partial LD population in both studies.

Table 8. Baseline and month 12 HbA1c results by study (Studies 265 and 769) and lipodystrophy type

Study	Population	N	Baseline mean ± sd median (25^{th}, 75^{th})‡	Month 12 mean ± sd median (25^{th}, 75^{th})‡	Change from baseline mean (95% CI) median (25^{th}, 75^{th})‡
265	Overall	9	9.2 ± 1.4 9.3 (8.0, 9.8)	7.4 ± 1.6 7.3 (6.3, 8.1)	-1.8 (-2.7, -0.9) -1.9 (-2.3, -1.4)
	Generalized	8	9.1 ± 1.5 8.9 (7.8, 10.2)	7.3 ± 1.7 6.9 (6.2, 8.1)	-1.9 (-2.9, -0.8) -2.0 (-2.5, -1.5)
	Partial	1	9.5 ± NA 9.5 (-,-)	8.1 ± NA 8.1 (-,-)	-1.4 (-, -) -1.4 (-, -)
769	Overall	47	8.0 ± 2.2 7.9 (5.8, 9.7)	6.7 ± 1.7 6.4 (5.5, 7.7)	-1.3 (-1.7, -0.8) -0.6 (-2.3, -0.0)
	Generalized	27	8.4 ± 2.2 8.4 (6.9, 9.8)	6.4 ± 1.4 6.1 (5.2, 7.3)	-2.0 (-2.6, -1.3) -1.9 (-3.2, -0.5)
	Partial	20	7.4 ± 2.2 7.0 (5.7, 8.8)	7.2 ± 1.9 6.6 (5.8, 8.1)	-0.3 (-0.6, 0.1) -0.3 (-0.6, 0.2)

‡percentile; NA-not applicable.

Fasting Triglycerides

The following table from Dr. McEvoy's review summarizes the findings on fasting Tgs at Month 12 in Studies 265 and 769. In both studies there is an observed reduction from Baseline in mean and median Tg values for the overall cohort of patients with available data (Studies 265 and 769 had missing data in 1 and 14 patients, respectively, at Month 12). A

differential effect of treatment by LD population is more difficult to discern on this efficacy measure but this may also be due to the variability in Tg levels.

Table 9. Baseline and month 12 fasting triglycerides (mg/dL) results by study (Studies 265 and 769) and lipodystrophy type

Study	Population	N	Baseline mean ± se median (25^{th}, 75^{th})‡	Month 12 mean ± se median (25^{th}, 75^{th})‡	Change from baseline mean (95% CI) median (25^{th}, 75^{th})‡
265	Overall	8	1809 ± 2419 819 (497, 2050)	507 ± 482 433 (125, 720)	-1302 (-3037, 432) -526 (-1622, -311)
	Generalized	7	1953 ± 2576 836 (471, 2984)	516 ± 520 424 (113, 996)	-1437 (-3475, 600) -692 (-2543, -263)
	Partial	1	802 ± NA 802 (802-, 802)	443± NA 443 (443, 443)	-359 (-, -) -359 (-, -)
769	Overall	49	790 ± 1540 335 (193, 503)	360 ± 570 179 (109, 342)	-429 (-739, -120) -76 (-303, -1)
	Generalized	29	667 ± 979 261 (145, 449)	229 ± 223 168 (103, 273)	-439 (-766, -111) -118 (-305, 12)
	Partial	20	967 ± 2127 350 (212, 526)	551 ± 826 321 (143, 483)	-416 (-1050, 219) -70 (-227, -4)

‡percentile

Even though there was a reduction from baseline in both mean and median HbA1c and fasting Tgs levels in the overall, generalized, and partial LD populations, Drs. Golden and McEvoy repeatedly remind us that the absence of a control group and the concomitant use of therapies to treat these metabolic disturbances confound the results and make it difficult to attribute all changes to metreleptin treatment.

In her review, Dr. Golden does an in-depth review of patient-level data to help us tease out the impact of concomitant medications and allow for some degree of confidence in concluding that metreleptin is having a favorable effect on the metabolic derangement of lipodystrophy. However, her review also provides examples where additional therapies cannot be dismissed, making it difficult to discriminate between the contribution of metreleptin versus these therapies to any clinical improvement observed. I provide two such examples from her advisory committee presentation.

Case 1 NIH Patient 90156, 22 yo female with CGL

	Baseline	Month 4	Month 8	Month 12
HbA1c (%)	11.9	6.1	ND	6.1
TG (mg/dL)	3631	220	ND	339
Insulin	150 U TID	0	0	0
Metformin	500 mg BID	0	0	0

In Case 1, the patient's Baseline HbA1c and Tgs are clearly elevated. Both these parameters decline with metreleptin treatment. It should be noted that this patient was also receiving

metformin and very high doses of insulin at Baseline and was able to discontinue both anti-diabetic therapies while maintaining the improved glycemic control. The discontinuation of both these anti-diabetic therapies and marked reduction in HbA1c provide reasonable support that metreleptin is improving the insulin resistance in this patient.

Case 2 NIH Patient 90162, 11 yo female with AGL

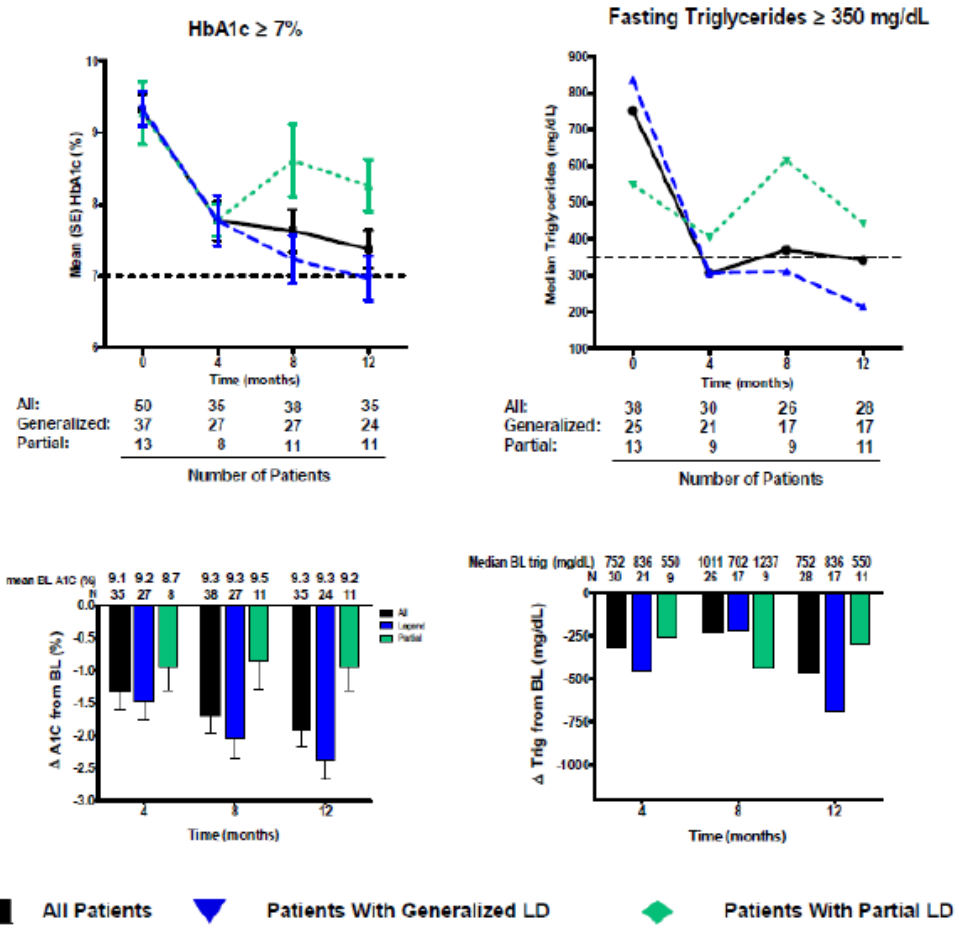
	Baseline	Month 4	Month 8	Month 12
HbA1c (%)	7.8	7.2	NA	5.6
TG (mg/dL)	337	198	NA	107
Metformin	-	-	500 mg BID	500 mg BID

In contrast, Case 2 also had a notable 2.2% reduction in HbA1c by Month 12. However, Dr. Golden was able to identify the initiation of metformin 500 mg bid at Month 8 in this patient. Such therapy could be attributed to the improved glycemic control and dampen a conclusion that all improvement is due to metreleptin alone. Other examples of concomitant medication use confounding data interpretation are presented in Dr. Golden's review, underscoring the difficulty in evaluating the true effect of metreleptin in many of these cases.

Generalized versus Partial Lipodystrophy

The FDA review team noted differences in efficacy results between the generalized and partial LD patient populations. The following Figure 21 from Dr. Golden's review nicely summarizes the differences in response to metreleptin on both HbA1c and Tgs by LD type.

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



Dr. Golden points out that even in the subgroup of partial LD patients with HbA1c ≥ 7% and Tgs ≥ 350 mg/dL, the response to metreleptin is less than that observed in patients with generalized LD. This difference in response might be the result of differences in leptin levels. Study 265 inclusion criteria restricted enrollment to a population with low leptin levels (among other eligibility criteria) whereas Study 769 allowed more patients with higher leptin levels. Dr. McEvoy performed some exploratory analyses of Study 769 applying the eligibility criteria from Study 265 (i.e., leptin levels < 4 for females, <3 for males and age >/= 14 years). He was able to identify 18 patients enrolled in Study 769 who could have also been enrolled as part of Study 265 who also had efficacy measures at Month 12. Table 10 below from his review summarizes this exploratory analysis. The 18 patients meeting the more restrictive eligibility criteria had a greater response to metreleptin, which was also similar to the response observed in the 9 patients enrolled in Study 265.

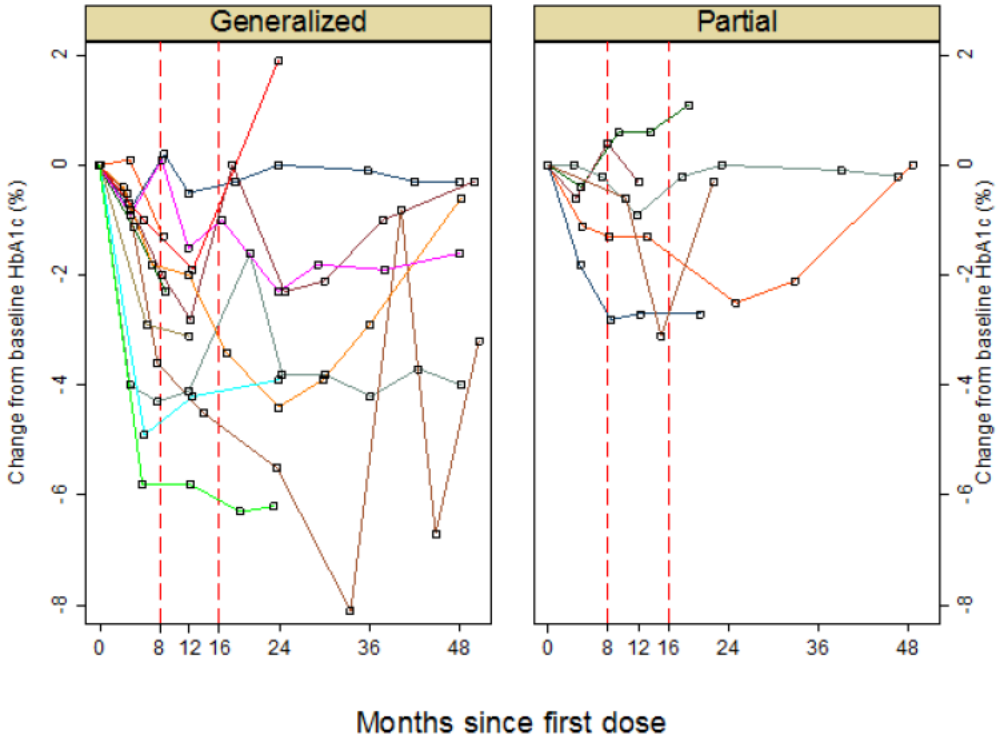
Table 10. Month 12 result for groups defined by Study 265 inclusion criteria (Study 769)

Satisfied 265 Inc. cirtiera	N	Baseline mean ± sd median (25th, 75th)‡	Month 12 mean ± sd median (25th, 75th)‡	Change from baseline mean (95% CI) median (25th, 75th)‡
HbA1c (%)				
Yes	18	9.3 ± 2.2	7.1 ± 1.8	-2.2 (-3.0, -1.3)
		9.1 (8.0, 10.2)	6.8 (6.3, 7.3)	-1.9 (-3.1, -0.9)
No	29*	7.1 ± 1.8	6.5 ± 1.6	-0.7 (-1.2, -0.2)
		6.9 (5.5, 8.4)	5.7 (5.3, 7.7)	-0.3 (-0.7, 0.1)
Fasting Triglycerides (mg/dL)				
Yes	18	1500 ± 2317	555 ± 893	-945 (-1713, -176)
		525 (255, 1543)	174 (109, 494)	-369 (-743, -76)
No	31*	377 ± 522	247 ± 176	-130 (-315, 55)
		228 (145, 359)	209 (107, 342)	-46 (-118, 40)

*Includes patients with missing baseline leptin levels

Recall that these 18 patients were identified based, in part, on having leptin levels low enough that would have qualified them for the more-restrictive Study 265. When these 18 patients were characterized further by LD subtype and baseline leptin level, 12 were generalized LD patients with a mean baseline leptin level of 1.3 ng/mL and 6 were partial LD patients with a mean baseline leptin level of 3.1 ng/mL (data not presented in primary reviews but provided at my request to Dr. McEvoy). Similar to the Figure 21 from Dr. Golden's review, the partial LD patients had a more attenuated reduction in HbA1c than the generalized LD population as depicted in this figure provided by Dr. McEvoy.

Figure 7.1 HbA1c Reduction in 18 patients from Study 769 meeting Eligibility Criteria of Study 265



Liver Parameters

As already described in the reviews of Drs. Golden and Weintraub (FDA GI consultant), patients with lipodystrophy have ectopic accumulation of fat in muscle and liver tissue. For the latter, some patients may present with hepatomegaly and steatosis, clinical presentations often described in non-alcoholic fatty liver disease (NAFLD) but not specific to lipodystrophy. The clinical course of NAFLD is variable, but some patients may progress to steatohepatitis (NASH) with increased risk for developing cirrhosis. Cirrhosis may occur in patients with generalized lipodystrophy and while hepatic complications are recognized as part of all the lipodystrophic syndromes, these complications may also be the result of other hepatic disorders (e.g., autoimmune hepatitis in those with acquired LDs).

The applicant has proposed language in labeling (b) (4) Upon review of the proposed label, DMEP had concerns that the statements were implied claims of metreleptin's efficacy on (b) (4) DGIEP was consulted as expertise lies within this division

[1] Revised indication submitted by applicant included the following: "Myalept (metreleptin for injection) is……indicated for the treatment of pediatric and adult patients with…. metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis."

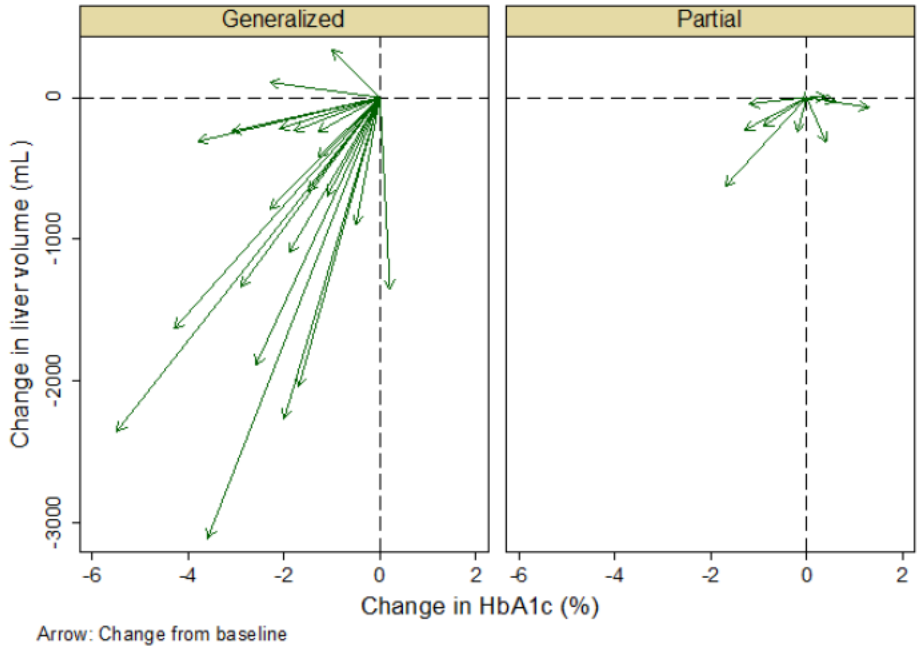
for the review of therapies being developed to treat liver diseases. The following 4 questions were posed to DGIEP:

1. Please provide your opinion on the clinical importance of changes in the available hepatic parameters in patients with lipodystrophy treated with metreleptin: ALT/AST, liver volume, biopsy results.
2. Given the heterogeneity of lipodystrophy, can we predict who is likely to develop complications of NAFLD? Is it possible to predict who might benefit from treatment?
3. Are there safety concerns with treating patients who have other liver diseases, such as autoimmune hepatitis with metreleptin?
4. If metreleptin is ultimately approved for the treatment of metabolic disorders (i.e., diabetes mellitus, severe hypertriglyceridemia) associated with lipodystrophy, how would you describe the changes in hepatic parameters in labeling (if at all)?

Please see the consult authored by Dr. Lauren Weintraub for responses. Overall, DGIEP noted the difficulties in making conclusions on the effect of metreleptin on liver parameters due to the uncontrolled trials, missing data, data captured in a non-random fashion, non-specificity of some of the biomarkers, and presence of other liver processes.

During the open public hearing at the advisory committee meeting, several patients, likely with generalized LD, provided passionate testimonials on the improvement in their hepatomegaly as a result of metreleptin treatment. Dr. Weintraub noted the improvements in liver volume in the subset of patients with pre- and post-treatment MRIs (See Table 4 from her consult) that was limited to the 23 generalized LD patients (~ -26 to -28% change from baseline) whereas the 10 partial LD patients had no (one patient with APL) to modest reduction (-7%) in liver volumes. The applicant would like to attribute these changes to improvements in NAFLD; however, Dr. Weintraub argues that these changes are more likely due to improvements in glycogenosis through improvements in insulin resistance. To further explore this relationship, Dr. McEvoy provided the following plot of change in liver volume and its relationship to change in HbA1c in both the generalized and partial LD patients.

Figure 7.2 Relationship between Change in Liver Volume and Change in HbA1c in Generalized and Partial LD patients with pre- and post- MRI evaluations.



Hence, while there is evidence that some patients with hepatomegaly had reduced liver volume while on metreleptin treatment, there is a notable difference in magnitude of liver volume reduction between the two LD populations with marked reductions observed in the generalized LD patients and not in partial LD patients. In addition, improved liver size correlates with improvements in glycemic control, not necessarily evidence of any effect of treatment on NAFLD or NASH.

DGIEP does not recommend inclusion of any language in labeling (b) (4) I concur with this recommendation (b) (4) I would note that exclusion of such information from the label is unlikely to prevent lipodystrophic patients with hepatomegaly from receiving this product as they would likely be prescribed metreleptin for other accompanying metabolic disturbances (e.g., dysglycemia and/or severe hypertriglyceridemia).

Conclusions on Efficacy

The Division has concluded that while reductions in the efficacy endpoints, HbA1c and fasting Tgs, were observed in the generalized and partial LD populations, (b) (4) therefore, the Division recommends limiting the indication to this population (b) (4)

8. Safety

The same limitations of open-label, single-arm trials and study conduct in interpreting trial results apply to the safety assessment. However, unlike the efficacy review which was limited to studies specific to patients with lipodystrophy, Dr. Golden has also reviewed metreleptin safety as evaluated for other indications, including pooled controlled trials evaluating treatment of obesity.

Knowledge of endogenous leptin activity and the potential impact of its activation of the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway on the immune system led the FDA review to hone in on several adverse events of special interest including immunogenicity, malignancies, and autoimmunity. The pharmacologic effect of metreleptin also raised concerns for risks of hypoglycemia and pancreatitis, which were also covered in Dr. Golden's review.

Immunogenicity

By virtue of being a therapeutic protein, assessment for immunogenicity has been a focus throughout this program, including review by staff in the Division of Therapeutic Proteins. Please see the very detailed review authored by Dr. Laura Salazar-Fontana from DTP for their assessments of immunogenicity.

Metreleptin is highly immunogenic with >90% of patients developing anti-drug antibodies. There is evidence that some of these patients developed neutralizing antibodies but the frequency of this occurring is not known due to the reliability of the assays used and the testing performed. Dr. Golden describes 1 patient with generalized lipodystrophy and 3 patients evaluated in the obesity program who had documented high titers for neutralizing antibodies associated with adverse events, raising concern that their presence may adversely impair endogenous leptin activity resulting in impaired immune response and subsequent risk for infections or loss of efficacy. With regard to loss of endogenous leptin activity, it is particularly concerning should metreleptin be used off-label in the non-leptin deficient patients with general obesity. As noted above, 3 cases were reported in the obesity program evaluating use of metreleptin-pramlintide wherein marked weight gain was observed in the setting of high titer neutralizing antibodies. These reports suggest that development of neutralizing antibodies to leptin may result in a leptin-deficient like state.

Malignancies

Three cases of T-cell lymphoma were observed in the NIH trials in patients with acquired generalized LD. Two of these cases had baseline hematologic disease or were on cell growth promoters (erythropoietin or G-CSF), but the third patient had no known hematologic disorder. Hematologic malignancies, including T-cell lymphoma, associated with lipodystrophy in patients not receiving metreleptin have been described in the literature. The design and scope of this clinical database is inadequate for us to attribute cancer risk to metreleptin therapy. Nevertheless, this theoretical risk remains a concern with the long-term use of this product, particularly in patients with acquired forms of lipodystrophy who have an increased risk for malignancies.

Autoimmunity

Urticaria and injection site reactions were reported with use of metreleptin. A few cases of autoimmune hepatitis and one patient with membranoproliferative glomerulonephritis developing renal failure were also observed; however, autoimmune disorders are common in patients with acquired lipodystrophy, so it remains unclear if metreleptin played a causal role, including exacerbation, in these autoimmune disorders.

Hypoglycemia (See Section 7.3.5 of Dr. Golden's Review)

Hypoglycemia, mostly mild or moderate in intensity, was reported in 8/72 (11.1%) of patients receiving concomitant insulin therapy in Studies 265 and 769 and in 7/28 (25%) of patients in the expanded access trial, FHA 101, including one patient who had a severe event requiring external assistance. Most of the patients in FHA 101 reporting hypoglycemia were also receiving concomitant insulin or a sulfonylurea.

Labeling will include this risk under Warnings and Precautions with recommendations for dosage adjustments in insulin or insulin secretagogues to reduce this risk. Recommendations for close monitoring of blood glucose levels are also being put forward.

Pancreatitis

The applicant has proposed language on the potential risk for pancreatitis with discontinuation of metreleptin therapy citing rebound hypertriglyceridemia as a potential etiology. Dr. Golden has summarized the cases of pancreatitis in the program (Table 51 from her review) noting that all cases occurred in patients with a history of pancreatitis. She could not identify compelling evidence that non-compliance to metreleptin therapy resulted in pancreatitis and recommends against labeling (b) (4)

Conclusions on Safety

The most concerning safety findings of metreleptin therapy are development of anti-drug antibodies, particularly neutralizing antibodies, and the risk for lymphoma. Although serious, the review team felt that the benefits of metreleptin in patients with generalized lipodystrophy outweighed these risks; however, (b) (4) The team was also concerned about the potential for off-label use of the product in other forms of lipodystrophy and in the treatment of obesity in the general population. For the latter, the reviewers felt strongly that there should be a contraindication in the treatment of general obesity as clinical data for such programs reviewed under the specific INDs have not shown efficacy to justify risks. Further supportive of the contraindication is the identification of three cases of high-titer neutralizing antibodies developing in patients receiving metreleptin alone or in combination with pramlintide who had marked weight gain, which might be evidence of inducing a leptin-deficient-like state.

These concerns have formed the basis for a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). Metreleptin will be marketed through a restricted distribution program because of the risks associated with developing neutralizing antibodies and the risk for lymphoma.

9. Advisory Committee Meeting

This application was discussed at a public advisory committee on December 11, 2013. The members were asked to discuss four points: the patient population in which substantial evidence for efficacy has been demonstrated; whether there was evidence that metreleptin produced clinically meaningful effects on treating hepatic steatosis; safety issues; and whether any additional pre-marketing studies were needed for any of the lipodystrophy populations.

The two voting questions were for whether the benefits of metreleptin exceeded the risks for each of the two populations of lipodystrophy patients (generalized and partial). The votes are summarized as follows:

- For generalized lipodystrophy, 11 members voted 'yes' and 1 voted 'no' that the benefits exceeded the risks

- For partial lipodystrophy, 2 members voted 'yes" and 10 voted 'no' that the benefits exceeded the risks

These votes reflect the overall recommendation also being made by the review division. It should also be noted that members' explanations/rationale for their vote similarly expressed concerns about confounders and difficulties in being able to identify the partial LD patients from a general obese population to ensure a favorable benefit-risk profile of metreleptin therapy.

The majority of the panel did not believe the evidence supported a separate indication for treating hepatic steatosis. One hepatologist (Dr. Lavine) felt that the generalized population likely had what would be called NASH and that metreleptin therapy would likely have a positive effect on this, if present. He added that since the panel was leaning towards limiting the indication to just the generalized population, "there's no reason to make this a separate indication."

10. Pediatrics

Patients under the age of 18 were enrolled in the two pivotal NIH trials, the youngest patient being one year of age. The majority of these patients had generalized lipodystrophy (n=35) whereas only 4 patients under the age of 18 had partial lipodystrophy. Dr. Golden has summarized the efficacy and safety in the pediatric population. There is no basis to withhold approval in the pediatric population with generalized lipodystrophy although the label must warn against use of the diluent containing the preservative benzyl alcohol in neonates and infants. The product will also be available with sterile, preservative-free water as a diluent for reconstitution. Labeling will include relevant instructions for use and discard.

Since this application received orphan designation, it is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

Please see memos of Drs. Colman and Golden. No further pending regulatory issues precluding approval.

12. Labeling

See accompanying agreed-upon labeling. The originally proposed indication by the company was modified to the following:

MYALEPT is a leptin analog indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

This is accompanied by a Limitations of Use section as follows:

- 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 without concurrent evidence of generalized lipodystrophy

In addition, the BLA will be approved with a REMS with ETASU with a boxed warning to describe the risks of developing anti-metreleptin Abs, risks of developing lymphoma, and to inform prescribers that the product is available only through a restricted program.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Approval is recommended for only the patient population with generalized lipodystrophy. Despite the study design challenges, I believe there was sufficient evidence that metreleptin contributed significantly to the improvements of glycemic parameters and hypertriglyceridemia. Analyses performed by lipodystrophy type showed a greater treatment effect in the generalized LD population versus the partial LD population. Although use of concomitant therapies clouded the assessment of efficacy in both populations, there were notable examples of patients with generalized LD who had significant reductions in HbA1c and discontinuation of their anti-diabetic therapies, lending support to a conclusion that

metreleptin favorably impacted insulin resistance in these patients. In the partial LD population, numerous analyses revealed a more modest treatment effect.

Although the applicant has argued that there are no approved therapies for either of these populations, I do not believe the clinical program adequately characterized benefits-risks of metreleptin therapy in the partial LD population. The potential for long-term safety of immunogenicity and cancer risks requires a more robust assessment of efficacy to justify taking on these risks. Furthermore, the clinical presentation of patients with partial LD is more heterogeneous and, in some cases, difficult to distinguish from the general obese population.

Until additional studies of metreleptin are conducted in the partial LD population wherein protocols ensure an adequate evaluation of its safety and efficacy in these patients, I believe the most favorable benefit-risk calculus for metreleptin at this juncture is to allow approval for use in only adults and pediatric patients with generalized lipodystrophy.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

This BLA will be approved with a REMS with ETASU. The goal of the REMS is to mitigate the risks of serious adverse sequelae due to the development of anti-drug antibodies with neutralizing activity (i.e., loss of endogenous leptin activity and its consequences, as well as loss of efficacy) and the risk of lymphoma by educating prescribers about these risks and by limiting the population exposed to patients for whom the benefits are believed to outweigh the risks.

To limit access to the indicated population, there will be prescriber certification, pharmacy certification, and documentation of safe use conditions, which includes prescriber attestation that each patient has a diagnosis consistent with the approved indication.

Please see DRISK review by Dr. Suzanne Berkman-Robottom for a thorough discussion of the REMS with ETASU program.

- Recommendation for other Postmarketing Requirements and Commitments

This BLA will be approved with 7 post-marketing requirements and 8 post-marketing commitments. These are listed in the approval letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
02/24/2014