CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125390Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

MEMORANDUM

BLA #:	BLA 125390
Drug Name:	Metreleptin
Applicant:	Amylin Pharmaceuticals
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Bradley McEvoy, DrPH
Concurring Reviewers:	Mark Rothmann, PhD, Team Leader Thomas Permutt, PhD, Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Julie Golden, MD, Medical Officer James Smith, MD, Medical Team Leader Jean-Marc Guettier, MD, Acting Medical Division Director
Project Manager:	Patricia Madara

The purpose of this memorandum is to convey my concurrence with the revised indication for MYALEPT (metreleptin). The revised indication, as it appears in the February 10, 2014 draft label, is "an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy."

Furthermore, I believe my concurrence with the revised indication is not in opposition to the recommendations I made in my statistical review of metreleptin that was submitted to DARRTS on November 25, 2013. While I did recommend against the overall approval for metreleptin, this position was made in reference to indication proposed by the sponsor at the time the BLA was submitted (i.e., "Metreleptin for the treatment of metabolic disorders associated with lipodystrophy including diabetes mellitus and/or hypertriglyceridemia in pediatrics and adults with inherited or acquired lipdystrophy"). In my recommendations I did not, however, rule-out the possibility that metreleptin be approved in a subset of the studied population that had a favorable risk-benefit profile. Rather than attempt to define such a subset, I instead advised that the guidance given at the December 11, 2013 advisory committee meeting also consider challenges of being able to reliably identify a subgroup based on post hoc considerations. The revised indication, in my opinion, reflects the input DMEP received at the advisory committee meeting.

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/s/

BRADLEY W MCEVOY
02/21/2014

MARK D ROTHMANN
02/21/2014
I concur

THOMAS J PERMUTT
02/21/2014
I concur

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #:	BLA 125390
Drug Name:	Metreleptin
Indication(s):	Treatment of metabolic disorders associated with lipodystrophy
Applicant:	Amylin Pharmaceuticals
Date(s):	Review Due Date: November 27, 2013 Stamp Date: March 27, 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Bradley McEvoy, DrPH
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Keywords: Single-arm design, rare disease

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1 EXECUTIVE SUMMARY

Amlyin proposes metreleptin, a recombinant analog of human leptin, for the treatment of metabolic disorders associated with lipodystrophy including diabetes mellitus and/or hypertriglyceridemia in pediatrics and adults with inherited or acquired lipdystrophy. The submission is supported by the evaluation of HbA1c and fasting triglyceride in three single-arm studies.

1.1 Conclusions

The single-arm studies that are used to support the submission were found to have (b) (4)

Based on these considerations, I recommend against the overall approval for the proposed indication. At an upcoming Advisory Committee meeting important input will be sought on the efficacy and safety of metreleptin in various lipodystrophy populations. While the discussion may provide guidance on whether the risk-benefit profile to support approval of metreleptin in a subset of the studied population, I would advise that such a regulatory decision strongly consider the challenges of reliably identifying a subgroup based on post hoc considerations. If such a group is identified, I would recommend the sponsor conduct a randomized, placebo-controlled, double-blind trial that adequately restricts background concomitant medication in order to isolate the effect of metreleptin in the group.

1.2 Brief Overview of Clinical Studies

The three studies reviewed for this BLA submission all had an open-label, uncontrolled design. Studies 20010769 (769) and FHA101 (101) are currently ongoing and open-ended, with continuing patient enrollment. Patients that completed the pilot Study 991265 (265) could continue to receive metreleptin and provide follow-up information by enrolling in Study 769.

Study 265 investigated metreleptin in patients with clinically significant lipodystrophy that were >14 years of age, had circulating leptin concentrations < 4.0 ng/mL for females or < 3.0 ng/mL for males, and at least 1 of 3 metabolic abnormalities: diabetes mellitus; fasting insulin concentration > 30µU/mL; or fasting hypertriglyceridemia > 200mg/dL. This study enrolled 12 patients at two centers; the submission only included data on the nine patients enrolled at the National Institutes of Health (NIH). Seven of the nine NIH patients were followed in Study 769.

Study 769 is currently investigating metreleptin in patients with clinically significant lipodystrophy that are > 6 months of age, circulating leptin concentration of <12.0 ng/mL for females ≥ 5 years, <8.0 ng/mL for males ≥ 5 years, and < 6.0 ng/mL for females and males 6 < 5 years, and at least 1 of 3 metabolic abnormalities in Study 265. The inclusion criteria became less restrictive over time, allowing for patients that are younger (original: ≥ 5 years) and have higher circulating leptin concentrations (original: < 6.0 ng/mL for females and < 3.0 ng/mL for males).

As of the current data cutoff 63 patients have enrolled and received metreleptin under this protocol.

Study 101 is currently investigating metreleptin in patients with physician confirmed lipodystrophy ≥ 5 years of age and at least 1 of 2 metabolic abnormalities: diabetes mellitus; or fasting triglyceride concentration > 200mg/dL. As of the current data cutoff 28 patients in three sites have received metreleptin under this protocol.

1.3 Statistical Issues and Findings

The study design and execution of the study protocols raises concern that the changes in metabolic parameters summarized in this review and by the sponsor may not reflect the true effect of metreleptin in the studied population. Confidence in these results is limited by

- The single-arm design in a heterogeneous study.
- Several patients increased use of diabetic and lipid-lowering medications during study follow-up. The accuracy of such usage is further limited by this information not being systematically collected during study follow-up. Furthermore, the guidance in Study 769 that concomitant medication was not to be increased appears to have been deliberately violated in order to maximize lipid and glycemic control with metreleptin.
- Change in metabolic parameters may be partially attributed to the phenomena of regression to the mean.

Other issues encountered during this review include:

- The degree of missing data in Studies 769 and 101.
- Differences between the estimates of mean change and median change.
- The studies had different inclusion criteria, with the later studies (Studies769 and 101) having less dramatic changes in metabolic parameters and a more inclusive lipodystrophy study population.
- A number of patients were assigned a modified baseline date based on non-optimal experiences (e.g., compliance issues and/or an adverse event) when they first initiated treatment with metreleptin.

There were notable differences in patient characteristics across studies. Compared to Studies 769 and 101, Study 265 was more likely to have patients with generalized lipodystrophy (265: 89%; 769: 60%; 101: 18%), diabetes (265: 100%; 769: 81%; 101: 75%), baseline HbA1c > 7% (265: 100%; 769: 65%; 101: 68%), and baseline fasting triglycerides > 500 mg/dL (265: 66%; 769: 31%; 101: 19%). Moreover, only 41% and 11% of patients in Studies 769 and 101, respectively, would have satisfied the Study 265 inclusion criteria based baseline age and leptin concentration.

The summary of baseline, month 12 and change from baseline for HbA1c and fasting triglyceride are shown below by study. The mean reduction in HbA1c at month 12 from baseline was greatest in Study 265 (1.8%), followed by Study 769 (1.3%) and Study 101 (0.9%). For fasting triglyceride there were similar trends, with the median change in Study 265 (-526 mg/dL) being greater than the median change for Study 769 (-76 mg/dL) and Study 101 (-134 mg/dL).

Table 1. Summary of primary endpoints by study

HbA1c (%)				
Study	N*	Baseline mean ± sd	Month 12 mean ± sd	Change from baseline mean (95% CI)
265	9	9.2 ± 1.4	7.4 ± 1.6	-1.8 (-2.7, -0.9)
769	47	8.0 ± 2.2	6.7 ± 1.7	-1.3 (-1.7, -0.8)
101	10	8.4 ± 1.8	7.5 ± 1.7	-0.9 (-2.0, 0.2)
Fasting Triglycerides (%)				
Study	N*	Baseline median (25^{th}, 75^{th})‡	Month 12 median (25^{th}, 75^{th})‡	Change from baseline median (25^{th}, 75^{th})‡
265	8	819 (497, 2050)	433 (125, 720)	-526 (-1622, -311)
769	49	335 (193, 503)	179 (109, 342)	-76 (-303, -1)
101	10	341 (193, 354)	164 (92, 275)	-134 (-324, -10)

‡ percentile; *excludes patients without a baseline or month 12 measurement.

Because findings from Studies 101 and 769 did not replicate the magnitude of changes observed in Study 265, an exploratory investigation was performed in these studies in the subset of patients that would satisfy the Study 265 criteria based on age and baseline leptin. In Study 769 this group was found to yield changes that were reasonably similar to the changes observed in Study 265 at month 12. In Study 101 the impact on HbA1c was evident by the lack of change in the group that did not satisfy the Study 265 criteria.

Subgroup analysis showed the average decrease in HbA1c at month 12 was greater in the group with generalized lipodystrophy compared to the group with the partial lipodystrophy, and in the group with diabetes at baseline compared to the group without diabetes at baseline.

2 INTRODUCTION

2.1 Overview

This document summarizes the design, findings and statistical issues from three single-arm studies used to support use of metreleptin for the treatment of metabolic disorders associated with lipodystrophy.

2.1.1 Class and Indication

Metreleptin is a new molecular entity, a recombinant analog of human leptin. The original indication was changed after the BLA was submitted for review. The original and revised indications are shown below.

Table 2. Original and Revised Indication Language

Indication	Language
Original	Metreleptin for the treatment of metabolic disorders associated with lipodystrophy including diabetes mellitus and/or hypertriglyceridemia in pediatrics and adults with inherited or acquired lipdystrophy.
Revised*	Metreleptin for the treatment of pediatric and adult patients with: • Generalized lipodystrophy • Metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis.

*Submitted October 30, 2013

The sponsor contends that the refined indication will "better identify appropriate patients with lipodystrophy who will benefit from metreleptin treatment". However, it is of concern that the revised indication may not reliably predict these patients since the change in the indication was primarily data driven. This review will therefore evaluate the submission as it relates to the original indication. Subsets of the studied population are also evaluated in this review; these subsets, however, may not correspond to the subsets implied by the sponsor's revised indication.

2.1.2 History of Drug Development

Metreleptin was submitted to IND 50,259 on March 29, 1996 for the treatment of obesity. At the End-Of-Phase 2 (EOP2) meeting held on May 16, 2001, Amgen (the former sponsor) noted the development program for obesity had been discontinued and they were pursuing metreleptin for the treatment of metabolic disorders associated with lipodystrophy. Later that year metreleptin was granted orphan status for treatment of metabolic disorders associated with lipodystrophy. On March 3, 2003, Amylin Pharmaceuticals assumed responsibility of the IND from Amgen.

At the EOP2 meeting there was a discussion regarding the size of the pivotal trial dataset for the lipodystrophy application. In the minutes for that meeting, FDA was in general agreement that the 9 patients with lipodystrophy included in the then ongoing pilot study (Study 265) would be acceptable. After the IND was transferred from Amgen to Amylin, there were subsequent discussions at an October 17, 2007 and July 11, 2012 Type C meeting about the adequacy of the clinical database. On March 27, 2013 the application for metreleptin was submitted for review under BLA 125390. Metreleptin is scheduled to be discussed at a Advisory Committee meeting on December 11, 2013.

2.1.3 Specific Studies Reviewed

Three studies reviewed for this BLA submission all had an open-label, uncontrolled design. Studies 769 and 101 are currently ongoing and open-ended, with continuing patient enrollment. Patients that completed Study 265 could continue to receive metreleptin and provide follow-up information by enrolling in Study 769. Study 769 started April 2001 with data available from this study up until the July 11, 2011 data cutoff. Study 101 started March 2009 with data

available from this study up until the March 7, 2012 data cutoff. Additional trial details are shown below.

Table 3. Overview of studies evaluated in this review

Study	Design Features	Study Population
991265 (265)	Open-label, single-arm.	Males and females >14 years of age regardless of ethnicity with clinically significant LD, circulating leptin concentrations < 4.0 ng/mL (females) or < 3.0 ng/mL (males), and either diabetes mellitus, fasting insulin > 30μU/mL or fasting hypertriglyceridemia > 200mg/dL
20010769 (769)	Ongoing, open-label, single-arm, continuing enrollment.	Males and female > 6 months of age regardless of ethnicity with clinically significant LD, circulating leptin concentration of <12.0 ng/mL (females ≥ 5 years), <8.0 ng/mL (males ≥ 5 years) or < 6.0 ng/mL (females and males 6 mos. to 5 years), and either diabetes mellitus, fasting insulin > 30μU/mL or fasting hypertriglyceridemia* > 200mg/dL
FHA101 (101)	Ongoing, open-label, single-arm, continuing enrollment.	Males and females ≥ 5 years of age with physician confirmed LD, and either diabetes mellitus or fasting triglyceride > 200mg/dL.

LD-lipodystrophy; *postprandially elevated TG > 500 mg/dL when fasting is not clinically indicated (e.g., infants)

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission, organized as an .enx file, was archived at the following link:

http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680dc2c18>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The statistical reviewer was able to replicate key finding for the primary study endpoints presented in the Clinical Efficacy Update (CEU). Below is a listing of data issues that were encountered.

The datasets for Study 265 did not include true baseline data on patients 90105 and 90106. The sponsor was notified of this issue and provided revised datasets. The submission also did not include data on three patients treated under the protocol for Study 265 at the University of Texas, Southwest (UTSW). The exclusion of these patients' was based the sponsor's interpretation of the agreement from the October 2007 Type C meeting.

In Study 769 the visit window definition for select visits overlapped.

In Study 101 select patients were assigned a missing value at their derived study visit (months 6 and 9) even though they had another visit within the visit window with an available measurement. The sponsor was notified of this issue and acknowledged the oversight.

3.2 Evaluation of Efficacy

The design and findings from Studies 265 and 769 are presented separately from Study 101. However, unlike the sponsor that presented findings from Studies 265 and 769 together based on pooling data across studies, this review will evaluate them separately. The primary reason for this is to see whether findings in Study 265 were replicated in Study 769, which is important since 1) Study 769 investigated a more inclusive lipodystrophy population reflective of the proposed indication, and 2) findings from Study 265 were used in part to justify the single-arm design for Study 769.

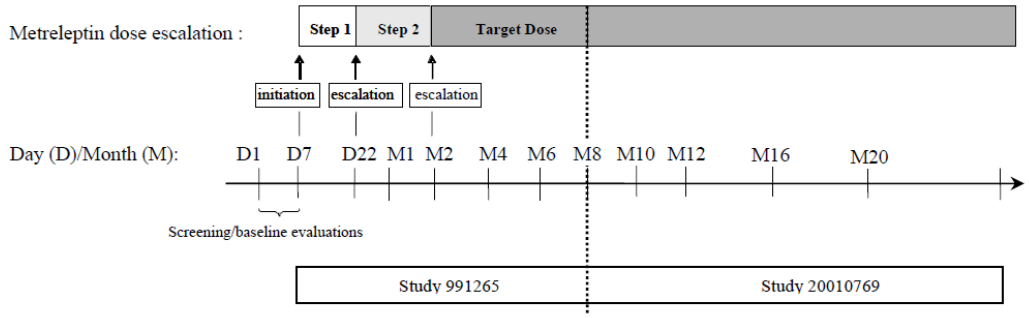
The presentation of results for Study 101 also differs from the sponsor's presentation in the CEU. In particular, analyses in this review include patients with partial lipodystrophy and generalized lipodystrophy. In the CEU analyses were limited to the partial lipodystrophy group.

3.2.1 Studies 991265 and 20010769

3.2.1.1 Study Design and Endpoints

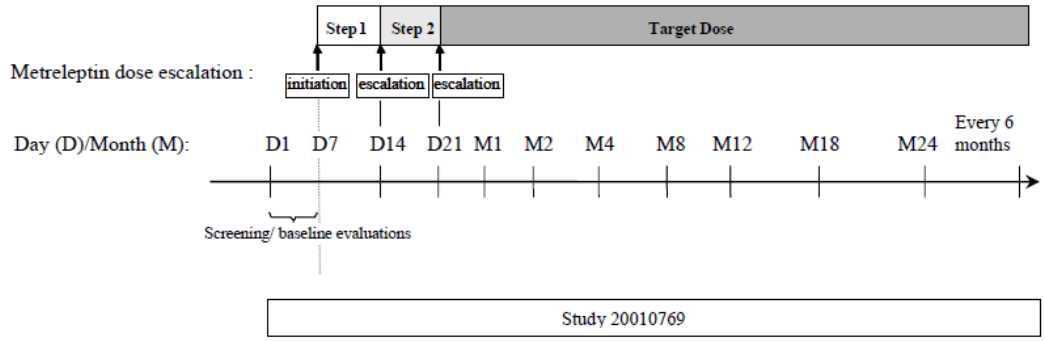
Both studies have an open-label, single arm design, as shown in the two figures below. Study 265 enrolled 12 patients at two centers (NIH and UTSW) with treatment duration amended from 4 months to beyond 8 months (Amendment 2). As noted above, data from 3 patients treated at UTSW was not included in the BLA submission. Of the nine patients enrolled at the NIH in Study 265, seven had continued follow-up in Study 769. Study 769 is currently ongoing and being conducted at a single site study (NIH) with treatment duration amended from 12 months to beyond 12 months (Amendment 1, 2003). As of the current data cutoff 63 patients have enrolled and have received metreleptin under this protocol.

Figure 1. Design of Study 265



Source: Clinical Efficacy Update, Appendix 1, page 1961.

Figure 2. Design of Study 769



Source: Clinical Efficacy Update, Appendix 1, page 1961.

Patients with lipodystrophy were included in either study if they did not have HIV and had one of the following three metabolic anomalies: diabetes mellitus; fasting insulin concentration > 30 µU/mL; or fasting hypertriglyceridemia > 200 mg/dL. Other inclusion criteria differed between the studies. Compared to Study 265, Study 769 allowed for younger patients and higher circulating leptin concentrations. Refer to Table 3 for specific inclusion criteria. The Study 769 inclusion criteria also became less restrictive over time by 1) increasing circulating leptin concentrations from 6.0 ng/mL to 12.0 ng/mL for females and 3.0 ng/mL to 8.0 ng/mL for males, and 2) lowering the age limit from ≥ 5 years to ≥ 6 months.

Both studies allowed metreleptin to be added to existing lipid and glucose lowering therapies, with baseline therapy allowed to be tapered but not increased during the study. Investigator adherence to this design feature is critical to allow changes in study endpoints to be attributed to metreleptin with confidence. However, a notable limitation of this development program is that this information was not systematically collected during study follow-up. Furthermore, it appears the guidance for Study 769 was not adhered to as use of these concomitant medications and metreleptin was done to maximize lipid and glycemic control. This concern is supported by the following statement justifying metreleptin dosing (Amendment A, 2006):

> *These proposed doses are based on the observations of 38 patients that we have treated on leptin therapy for 3 months up to 6 years. Doses have needed to be increased from earlier versions, as target levels for glycemia and lipids levels are trying to be achieved. For example in 6 women with partial lipodystrophy, only 2 were able to achieve target levels for glycemia after 1 year, and 1 patient for both glycemia and lipids.* ***But when the dose of leptin was increased to 0.12 mg/kg/day along with maximizing their existing standard therapies*** *[bold added], all had HbA1c levels less than 8.0% and 5 out of 6 had HbA1c levels less than 7%.*

Target dose in both studies was achieved via an age-sex dependent two-step dose escalation. The timing of the escalations is shown in the Figures above. In Study 769 there were changes in metreleptin administration with patients that enrolled later starting with a higher initial dose, resulting in less dose escalation.

Sample sizes were derived based on being able to detect clinically meaningful differences using information from a cross-section study of patients with generalized lipodystrophy. For Study 265 the target size of 12 patients was based on detecting a 1.5% decrease in HbA1c (standard deviation (SD) of 1.6%) and 660 mg/dL decrease in fasting triglyceride (SD 800 mg/dL) at month 4 with 80% power and 5% type-I error rate (two-sided). An initial sample size of 10 patients for Study 769 was estimated using similar assumptions, except that the timing was for month 12 and the target decrease for HbA1c was 1.0%; the sample size was subsequently increased to 40 patients (Amendment 1, 2003) and later to 75 patients (Amendment B, 2007).

Several issues exist around the primary endpoints. First, while both protocols list HbA1c and fasting triglyceride as primary endpoints, the SAP additionally lists fasting plasma glucose as a primary endpoint. Second, instead of specifying a specific visit to evaluate the efficacy of metreleptin (in either the SAP or the protocols), the SAP states comparisons with baseline will be done at certain milestone visits (months 4, 8, 12). Lastly, visit window definitions are generous and over-lap for the milestone and others visits. Visit windows were defined by the sponsor as follows: ±1 month for the Month 1 and Month 2 visits, ±2 months for the Month 4 and Month 6 visits, ±4 months for the Month 8 through the Month 24 visits, and ±6 months for visits subsequent to Month 24.

To address the above issues, this review will not treat fasting plasma glucose as a primary endpoint and will focus on Month 4 and 12 visits (per consultation with Dr. Julie Golden). More emphasis will be placed on results from Month 12 results due to less missing data. For Month 4 the window will be ± 2 months and ± 4 months for Month 12. The visit (within the respective visit window) that is closest to visit month will be used for the analysis. New visit assignments were done only for Study 769 since Study 265 did not have missing data at month 4 or 12.

Visit windows were derived by the sponsor based on the patient's first metreleptin dose except for four patients that were assigned a modified first dose date due to non-compliance and/or an adverse event experience after initiating metreleptin. For two patients the modified baseline date was approximately three years after their first metreleptin exposure. Refer to the Appendix for the sponsor's narrative and circumstances used to justify the modified baseline date. This review uses information based on the modified baseline date for these patients with the exception of Section 3.2.1.4.5 that presents findings according to their true baseline date.

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Table 4 displays patient disposition according to the protocol of initial enrollment.

None of the 9 patients enrolled in Study 265 withdrew within one year of their first metreleptin dose. Two patients did not enroll in Study 769 after beginning metreleptin treatment under Study 265 (90102, 90103). For patient 90103 the description provided in the sponsor's study report that this patient elected not to enroll in Study 769 is considered inadequate as it ignores important preceding events. A more informative description was provided in the SAP (page 17) "Patient

90103 would have been consented onto Study 20010769 in Jan 2002 (Month 16 visit), but it was decided to not enroll the patient into the study due to a serious adverse event. The patient was withdrawn from Study 991265 in Jun 2002 and never signed the Informed Consent for Study 20010769 because the patient met an exclusion criterion for the latter study." Of the four patients that withdrew in Study 265 (90102, 90105, 90106, 90106), Patient 90106 died after being withdrawn in March 2010 due kidney failure, and Patient 90105 withdrew May 2001 due to psychiatric difficulties and other issues but later enrolled in Study 769.

Study 769 had an overall withdraw rate of approximately 25% (16/63) and a 10% (6/63) withdraw rate within one year of first metreleptin treatment. Five patients that withdrew for reason "Other" was due to enrollment in another program.

Table 4. Patient disposition (Studies 265 and 769)

Category	Study 265	Study 769
Received at least one metreleptin dose (overall population)	12	63
Study site: NIH	9	63
Study site: UTSW	3	0
NIH Site		
Received at least one metreleptin dose (analysis population)	9	63
Treated in 265 prior to enrolling in 769	7	NA
Assigned a modified baseline date	2	2
Withdrew from study (Withdrew within one year of first metreleptin dose)	4 (0)	16 (6)
Ineligibility determined	0 (0)	2 (2)
Adverse event including death	1 (0)	4 (3)
Noncompliance	1 (0)	4 (1)
Other	2 (0)	6 (0)

NA-not applicable

Missing Data

Missing data was more prevalent in Study 769 than in Study 265. In Study 769 missing data was also much more prevalent among patients that enrolled later in the study compared to those that enrolled earlier (Table 5). In Study 265 all patients had a month 4 and month 12 measurement.

Table 5. Missing data on at least one primary endpoint (Study 769)

Patients	First dose date	Month 4	Month 12
90110-90124	11/29/2001-7/19/2003	0/15 (0%)	0/15 (0%)
90125-90139	9/24/2003-5/1/2007	3/15 (20%)	2/15 (13%)
90140-90154	5/22/2007-2/6/2009	9/15 (60%)	6/15 (40%)
90155-90172	2/10/2009-5/11/2011	9/18 (50%)	6/15* (40%)

*Excludes 3 patients not eligible for month 12 visit based on first metreleptin dose

Due to the ongoing nature of Study 769, 60 patients were eligible for a month 12 visit based on the timing of their first metreleptin dose relative to the data cutoff; all 63 patients were eligible for a month 4 visit. A high degree of patients were excluded from the month 4 analysis, 33% for triglycerides and 37% for HbA1c. The number of patients excluded from the month 12 analysis is notably better, 18% for triglycerides and 22% for HbA1c. Note this amount of missing data is different than the amount in the sponsor's CEU due to the over-lapping visit windows. For instance, the sponsor's month 12 HbA1c analysis used data on 41 patients, whereas the analysis presented in this review is based on 47 patients.

Demographic and Baseline Characteristics

Demographic and baseline characteristics are summarized below by study and lipodystrophy type (generalized or partial). While patients in the two studies had similar average age and were mostly Caucasian, differences were observed. Compared to Study 769, Study 265 had more patients with generalized lipodystrophy (89% vs. 60%), diabetes (100% vs. 81%), higher average HbA1c (9.2% vs. 8.1%) and fasting triglycerides (1809 mg/dL vs. 170 mg/dL), and lower average fasting leptin (1.8 ng/dL vs. 2.7 ng/dL). In addition, all patients in Study 265 were female compared to 81% in Study 769.

Differences in patient characteristics by lipodystrophy type were also observed; the following observations are from Study 769 since Study 265 had one patient with partial lipodystrophy. Compared to the partial lipodystrophy group, the generalized lipodystrophy group were more likely to be male (30% vs. 0%), younger (18 years vs. 33 years), non-Caucasian (58% vs. 9%), have lower average fasting leptin levels (1.3 ng/dL vs. 5.0 ng/dL) and higher average HbA1c levels (8.4% vs. 7.6%).

Table 6. Demographic and baseline characteristics by study (Studies 265 and 769) and lipodystrophy type

	Study 265			Study 769		
		Lipodystrophy type			Lipodystrophy type	
	Overall N=9	Generalized N=8	Partial N=1	Overall N=63	Generalized N=40	Partial N=23
Gender						
Male	0	0	0	12	12	0
Female	9	8	1	51	28	23
Age (years)						
≤ 17 years	5	5	0	34	30	4
Mean (SD)	25 (12)	23 (10)	42 (-)	24 (17)	18 (15)	33 (16)
Min, Max	13, 42	13, 42	-	1, 68	1, 68	2, 64
BMI (kg/m^2)						
Mean (SD)	21 (4)	20 (3)	15 (-)	22 (4)	21 (3)	24 (5)
Min, Max	15, 25	15, 24	-	14, 32	14, 27	14, 32
Race						
Caucasian	6	5	1	38	17	21
Black	2	2	0	7	7	0
Asian	0	0	0	3	2	1
Hispanic	0	0	0	10	10	0
Other	1	1	0	5	4	1
LD Type						
Acquired generalized	3	3	-	13	13	-
Congenital generalized	5	5	-	27	27	-
Acquired partial	0	-	0	4	-	4
Familial partial	1	-	1	19	-	19
Diabetes						
Yes	9	8	1	51	30	21
No	0	0	0	12	10	2
Fasting Leptin (ng/mL)	N=8	N=7	N=1	N=60	N=37	N=23
Mean (SD)	1.8 (1.1)	1.7 (1.1)	2.5 (-)	2.7 (2.8)	1.3 (1.1)	5.0 (3.1)
Min, Max	0.5, 3.7	0.5, 3.7	-	0.3, 14.1	0.3, 5.2	1.0, 14.1
HbA1c (%)				N=62	N=39	N=23
> 7.0%	9	8	1	40	28	12
Mean (SD)	9.2 (1.4)	9.1 (1.5)	9.5 (-)	8.1 (2.2)	8.4 (2.2)	7.6 (2.2)
Min, Max	7.6, 11.6	7.6, 11.6	-	4.5, 13.7	4.5, 13.7	4.6, 13.3
Fasting TG (mg/dL)	N=8	N=7	N=1			
> 500 mg/dL	6	5	1	19	12	7
Mean (SD)	1809 (2419)	1953 (2576)	802 (-)	944 (2038)	667 (871)	1425 (3158)
Min, Max	322, 7420	322,7240	-	49, 12697	49, 3631	101, 12697
Fasting Glucose (mg/dL)						
Mean (SD)	221 (122)	210 (125)	315 (-)	170 (82)	179 (78)	156 (89)
Min, Max	98, 478	98, 478	-	49, 394	71, 394	49, 367

Concomitant Medications

Antidiabetic and lipid lowering concomitant medication use for patients who reached month 12 are summarized below for the two studies. Several patients either stopped or decreased use of these medications during study follow-up. However, several patients also increased or initiated use of these medications, which lessens confidence in being able to attribute changes in metabolic parameters to exclusively to metreleptin. That said, to assess the potential influence of concomitant medication use (which was not collected systematically) requires concurrent

evaluation of the changes in metabolic parameters. Refer to the clinical review by Dr. Julie Golden for additional patient-level evaluation.

The problem of attributing changes in metabolic parameters to metreleptin in the presence of concomitant medication use is highlighted by the profile for patient 90162 below. At baseline she had an HbA1c of 7.8% and was not taking any antidiabetic medication. By month 8 she started metformin (500mg BID), and had a lower HbA1c value of 5.6% at month 12.

Protocol 991265 and 20010769 — Supporting Data Summary 1.3.6.2 — (Page 1 of 1)
Diabetes Management Medication Change at Month 12
Population: Intent-to-Treat Subjects Taking Anti-Diabetes Medications at Baseline Who Reached Month 12 (N=55)

Baseline Meds Category[1]	Stopped	Decreased	Unchanged	Increased	Insulin Added	Oral Added	Indeterminate
Insulin Alone (N=8)	4 (50.0%)	2 (25.0%)	1 (12.5%)				1 (12.5%)
1 Oral Agent Only (N=15)	2 (13.3%)	1 (6.7%)	9 (60.0%)	1 (6.7%)	1 (6.7%)		1 (6.7%)
2 or More Oral Agents Only (N=12)	3 (25.0%)	2 (16.7%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	1 (8.3%)
(Insulin + Oral Agent) Only (N=18)	6 (33.3%)	7 (38.9%)	1 (5.6%)	3 (16.7%)			1 (5.6%)
No Meds (N=2)						2 (100.0%)	

[1] Status of insulin treatment at baseline, changes are determined by insulin dose only.

Cross-reference: Appendix: 3.7.2, 3.7.3 and 3.7.4.
Program: S:\biostats - READ ONLY\AC164594SLD\IIT265\ClinicalUpdate\Pgm\TFL\t-dm-chg.sas — Version: 30JAN2013:13:18:25

Protocol 991265 and 20010769 — Supporting Data Summary 1.3.7.2 — (Page 1 of 1)
Lipid Lowering Medication Change at Month 12
Population: Intent-to-Treat Subjects Taking Lipid Lowering Medications at Baseline Who Reached Month 12 (N=31)

Baseline Meds Category[1]	Stopped	Decreased	Unchanged	Increased	Fibrate Added	Non-Fibrate Added	Indeterminate
Fibrate Alone (N=15)	2 (13.3%)	3 (20.0%)	10 (66.7%)				
Any Fibrate (N=21)	2 (9.5%)	5 (23.8%)	14 (66.7%)				
Non-Fibrate (N=8)		1 (12.5%)	4 (50.0%)	1 (12.5%)	2 (25.0%)		
No Meds (N=2)					2 (100.0%)		

[1] Status of fibrate treatment at baseline, changes are determined by fibrate dose only. Only subjects received fibrate treatment either at baseline or month 12 are included.

Cross-reference: Appendix: 3.7.2 and 3.7.5.
Program: S:\biostats - READ ONLY\AC164594SLD\IIT265\ClinicalUpdate\Pgm\TFL\t-ll-chg.sas — Version: 30JAN2013:13:20:39

90162 / AGL / 11-year-old Caucasian Female / Baseline Medication Category: No Meds				
	Baseline	**Month 4**	**Month 8**	**Month 12**
HbA1c (%)	7.8	7.2	NA	5.6
Triglycerides (mg/dL)	337	198	NA	107
Concomitant Medications (TDD)				
Metformin (mg)	0	0	1000	1000
Anti-diabetic Added at 12 months:	Addition of metformin prior to M8, continuing past M12.			

[1] TDD = Total Daily Dose.

Cross-Reference: NIH Appendices 3.7.3, 3.7.4, 3.8.2, 3.9.2

3.2.1.3 Statistical Methodologies

The analysis set used in this and in the sponsor's review include all patients who received at least one dose of metreleptin. The sponsor's referral to this analysis population as an intent-to-treat

(ITT) population, however, is inappropriate as this convention is defined only in the context of a randomized control trial.

Due to formal hypotheses tests not being performed per the SAP, descriptive statistics are used to summarize visits and to compare the change in baseline levels at month 4 and month 12; 95% confidence intervals (CI) for the mean change from baseline are also presented. Other descriptive statistics presented are the number of patients with non-missing values, standard deviation (SD), median, and 25^{th} and 75^{th} percentile. The median will be the primary summary method for the triglyceride endpoint to minimize the influence of extreme values. Additional discussion on the use of median versus mean is provided below. Importantly, the lack of formal testing coupled with the single-arm design makes the evaluation of study results rely on clinical judgment and information external to the study.

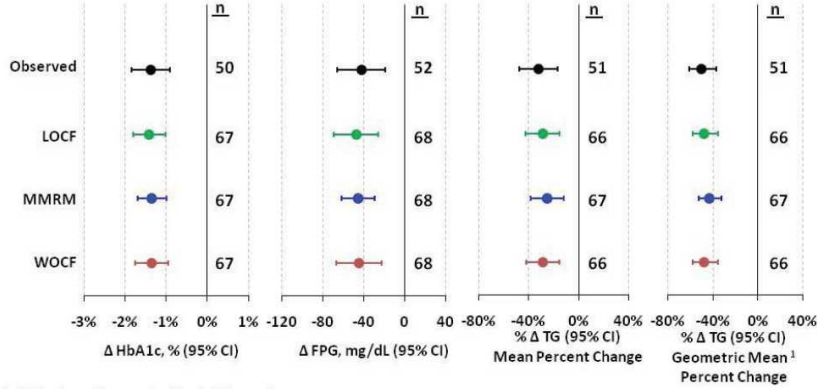
Patients with missing values (at baseline or at follow-up) were excluded in the calculation of descriptive summaries and CIs. Extrapolating findings from the group with data to the full sample requires the strong assumption that the missing data is missing completely at random (i.e., the complete cases are a random sample of all the cases). Comparison of results across visits is also problematic since the patients included in the analysis for one visit may not necessarily be included in the analysis for another visit. Alternative statistical models for missing data were not investigated. Without a control arm any approach would require making assumptions that would be difficult to justify empirically or clinically. However, in Section 3.2.1.4.6 an exploratory response analysis is presented which treats patients with missing data as a non-response, leading to conservative estimates of the true response rate. The response criteria developed in consultation with Dr. Julie Golden is as follows. An HbA1c response is a patient with baseline HbA1c > 7% that either had a 2.0% decrease in HbA1c at month 12 or HbA1c $\leq$ 7% at month 12. A triglycerides response is a patient with baseline levels > 500 mg/dL that had a 12 month value $\leq$ 500 mg/dL.

The informative and alternative "tipping-point" strategy to investigate the impact of missing data could not be performed due to the absence of formal study hypotheses. That is, a judgment on whether responses in patients that were not included in the analysis could be such that the analysis based on patients with available data would transition from "win" to "lose" cannot be done since there is no "win" criteria.

The sponsor in their Advisory Committee briefing document presented findings for missing data imputation algorithms/models to address missing data at month 12 using pooled data from Studies 265 and 769. While this review did not highlight findings from these approaches for reasons described above, they nonetheless raise an important point. From the sponsor's investigation, displayed below, they concluded that 1) there was no meaningful difference in results between the missing data approaches and the findings from the observed data, and 2) the magnitude of change for these endpoints was substantial. While the former conclusion is reasonable, whether one interprets the change as substantial, however, is sensitive to the metric used to summarize central tendency. To illustrate this the Table below shows mean change and median change with accompany 95% CI for HbA1c at month 12 for Study 769 using observed data and two separate missing data imputation approaches. While for a given metric (median or mean) the magnitude of change based on the observed data is reasonably similar to the change

from the different imputation approaches, there are differences across metrics for a given missing data approach. This difference results from the asymmetry of the change scores resulting from a sizable number of patients not having dramatic changes scores (See Figure 3). The mean and median both provide distinctive yet useful information to evaluate metreleptin. However, in this setting where there is concern about regression to the mean and the potential impact of concomitant medication use, the conservativeness of the median is particularly informative.

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



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

Table 7. HbA1c (%) missing data sensitivity analysis (Study 769)

Missing data Approach	N	Mean Change 95% CI	Median Change 95% CI*
Observed Data	47	-1.3 (-1.7, -0.8)	-0.6 (-1.5, -0.4)
LOCF	59	-1.3 (-1.7, -0.8)	-0.6 (-1.5, -0.3)
BOCF	59	-1.0 (-1.4, -0.6)	-0.4 (-0.7, 0.0)

BOCF-baseline observation carried forward;

*CI calculated using percentile bootstrap method from 1000 resampled datasets

3.2.1.4 Results and Conclusions

3.2.1.4.1 Month 12

HbA1c

Both studies overall showed a lower HbA1c at month 12 compared to baseline (Table 8), with the average decrease 1.3% (95% CI = -1.7, -0.8) for Study 769 not being as dramatic as the 1.8% (95% CI=-2.7, -0.9) decrease for Study 265. One can postulate that the change not being as dramatic in Study 769 may be attributable to 1) the type of lipodystrophy patients studied in Study 265 may have differentially benefited from metreleptin than the more inclusive population in Study 769, or 2) the effect in Study 265 is a random high. The former point may be supported by Figure 3, which shows patients in Study 769 had baseline HbA1c levels that were not investigated in Study 265 and these patients did have responses consistent with the higher levels. Another possible explanation is the apparent lack of benefit in the partial lipodystrophy group compared to the generalized group. This grouping, however, does not appear to sufficiently discriminate who appears to benefit from metreleptin on this endpoint since several patients with generalized lipodystrophy had normal HbA1c levels at baseline and did not have a favorable response on this endpoint (Figure 3).

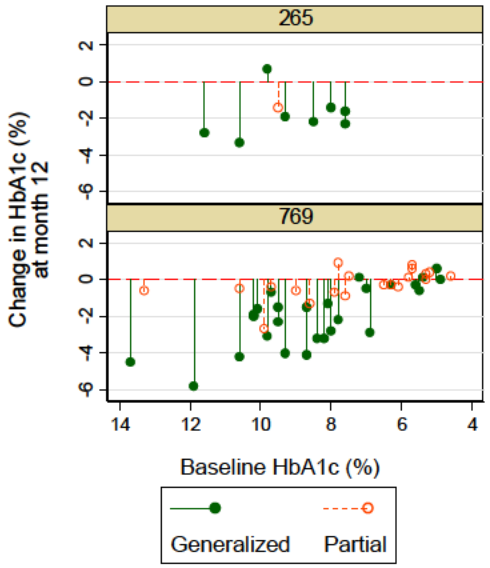
The high concentration of patients in Study 769 with normal baseline HbA1c levels also presents challenges summarizing changes overall and relative to Study 265. The median change reveals a decrease of 0.6% that is not as impressive as the 1.3% decrease estimated by the mean. Furthermore, notice that within the lipodystrophy groups the median and means are similar. For Study 265 this was not a concern as the median change -1.9% was similar to the mean change -1.8%.

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	7.4 ± 1.6	-1.8 (-2.7, -0.9)
			9.3 (8.0, 9.8)	7.3 (6.3, 8.1)	-1.9 (-2.3, -1.4)
	Generalized	8	9.1 ± 1.5	7.3 ± 1.7	-1.9 (-2.9, -0.8)
			8.9 (7.8, 10.2)	6.9 (6.2, 8.1)	-2.0 (-2.5, -1.5)
	Partial	1	9.5 ± NA	8.1 ± NA	-1.4 (-, -)
			9.5 (-,-)	8.1 (-,-)	-1.4 (-, -)
769	Overall	47	8.0 ± 2.2	6.7 ± 1.7	-1.3 (-1.7, -0.8)
			7.9 (5.8, 9.7)	6.4 (5.5, 7.7)	-0.6 (-2.3, -0.0)
	Generalized	27	8.4 ± 2.2	6.4 ± 1.4	-2.0 (-2.6, -1.3)
			8.4 (6.9, 9.8)	6.1 (5.2, 7.3)	-1.9 (-3.2, -0.5)
	Partial	20	7.4 ± 2.2	7.2 ± 1.9	-0.3 (-0.6, 0.1)
			7.0 (5.7, 8.8)	6.6 (5.8, 8.1)	-0.3 (-0.6, 0.2)

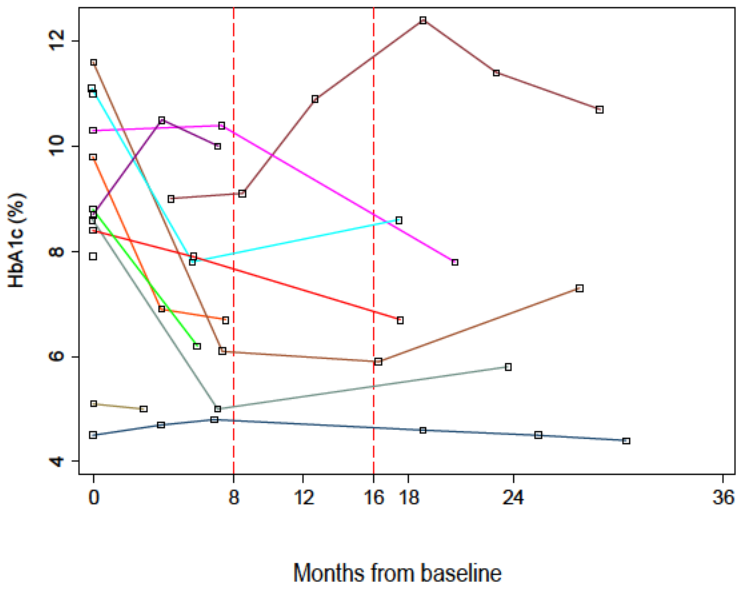
‡percentile; NA-not applicable.

Figure 3. Dropline plot of baseline HbA1c and change in HbA1c at month 12 by study (Studies 265 and 769)



Response profiles for the group in Study 769 that were eligible but were not included in the month 12 analysis are shown below. There is not an obvious pattern in the response to support interpolations within the 12 window with a high degree of certainty. That said, it is informative that the responses for most of these patients just outside of the lower limit of the 12 month window tended to be lower than the baseline levels.

Figure 4. HbA1c response profile for patients not included in the 12 month analysis (Study 769)



Fasting Triglycerides

Both studies showed lower fasting triglycerides at month 12 compared to baseline (Table 9), with the median change -76 mg/dL in Study 769 not as dramatic as the -526 mg/dL in Study 265. Similar to the HbA1c endpoint, the greater degree of change in Study 265 may in part be related to the higher baseline levels (which may be the consequence of the study population). However, the lipodystrophy subtype grouping (generalized vs. partial) does not appear to sufficiently discriminate who appears to benefit from metreleptin. Several patients in Study 769 with generalized lipodystrophy had triglyceride levels below 500 mg/dL at baseline and did not have a favorable response on this endpoint (Figure 5).

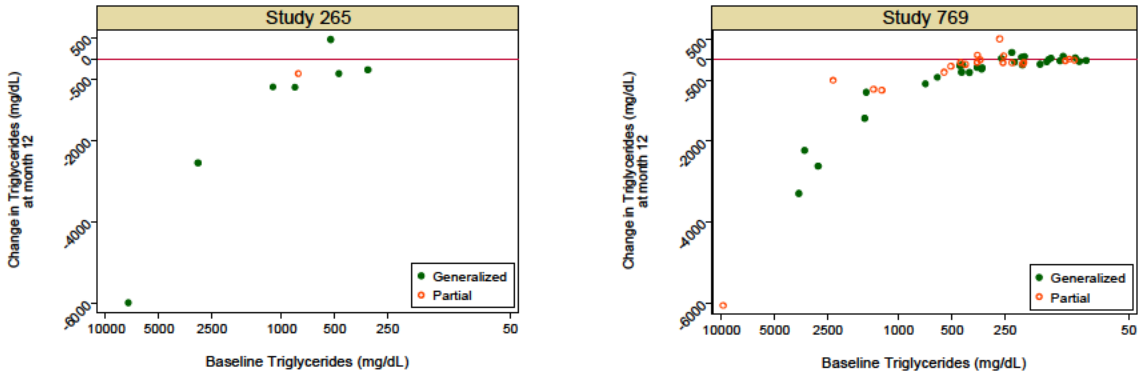
The skewed nature of the change values is particularly evident in Study 769 where the mean change does not lie between the 25th and 75th percentiles.

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 (25th, 75th)‡	Month 12 mean ± se median (25th, 75th)‡	Change from baseline mean (95% CI) median (25th, 75th)‡
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)

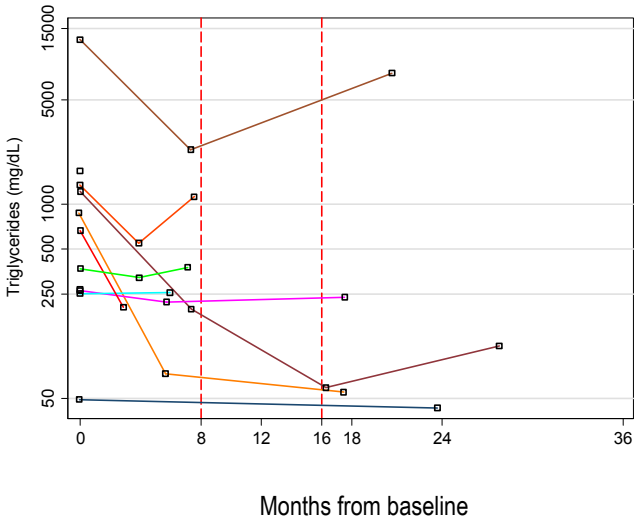
‡percentile

Figure 5. Scatterplot of baseline fasting triglycerides and change in fasting triglycerides at month 12 by study (Studies 265 and 769)



There is not an obvious pattern in response profiles about the 12 month window for patients not included in the analysis (Figure 6) to support interpolation within the 12 window with a high degree of certainty.

Figure 6. Fasting triglyceride response profile for patients not included in the 12 month analysis (Study 769)



3.2.1.4.2 Study 265 inclusion criteria applied to Study 769

Because the overall findings for Study 769 above did not replicate changes observed in Study 265, this section investigates whether the Study 265 findings are qualitatively replicated among the subgroup in Study 769 at month 12 that would have satisfied the Study 265 inclusion criteria (based on age and leptin levels). A total of 26 patients satisfied the Study 265 criteria based on age and leptin levels, with 18 having measurements at baseline and month 12. An additional two patients could not be classified due to missing leptin concentrations.

Compared to the group that did not satisfy the Study 265 inclusion criteria (Table 10), the group that did had notably greater average decreases from baseline in HbA1c (2.2% vs. 0.7%) and greater median change for fasting triglyceride (-369 mg/dL vs. -46 mg/dL). Furthermore, these decreases for the group that satisfied the Study 265 criteria in Study 769 are reasonably similar to the changes for Study 265 presented above.

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

Satisfied 265 Inc. cirtiera	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})‡
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

3.2.1.4.3 Initial Study 769 inclusion criteria

In light of the findings in the previous section, an important question centers on the impact of making the Study 769 inclusion criteria less restrictive. A total of 45 patients in Study 769 would have satisfied the initial Study 769 study inclusion criteria based on age and leptin concentrations.

Compared to the group that did not satisfy the initial inclusion criteria, the group that did had greater average decreases from baseline in HbA1c (1.6% vs. 0.4%) and median change for fasting triglyceride (-129 mg/dL vs. 67 mg/dL). While these differences suggest a difference between these groups, it also reveals that the patients that did satisfy the initial Study 769 criteria *but did not* satisfy the Study 265 inclusion criteria had marginally favorable responses since the changes were smaller in magnitude compared to the group that satisfied the 265 criteria.

Table 11. Month 12 result for groups defined by initial Study 769 inclusion criteria (Study 769)

Satisfied initial 769 inc. criteria	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})‡
HbA1c (%)				
Yes	34	8.2 ± 2.3	6.6 (1.7	-1.6 (-2.2, -1.0)
		8.1 (6.3, 9.7)	6.3 (5.6, 7.3)	-1.3 (-2.9, 0.1)
No*	13	7.4 ± 2.1	7.0 (1.7	-0.4 (-0.8, -0.1)
		6.5 (5.6, 9.5)	6.5 (5.5, 8.4)	-0.4 (-0.7, -0.0)
Fasting Triglycerides (mg/dL)				
Yes	36	952 ± 1762	367 ± 655	-585 (-995, -175)
		378 (143, 651)	168 (105, 312)	-129 (-466, -33)
No*	13	339 ± 360	341 ± 218	2 (-173, 177)
		228 (198, 343)	295 (209, 407)	67 (-74, 102)

*Includes patients with missing baseline leptin levels

3.2.1.4.4 Month 4

Descriptive summaries below show a decrease from baseline in HbA1c and triglycerides at month 4 that are not too different from the changes and trends observed at month 12.

Table 12. Baseline and month 4 results by study (Studies 265 and 769)

Study	N	Baseline mean ± sd median (25^{th}, 75^{th})‡	Month 4 mean ± sd median (25^{th}, 75^{th})‡	Change from baseline mean (95% CI) median (25^{th}, 75^{th})‡
HbA1c (%)				
265	9	9.2 ± 1.4	7.4 ± 1.7	-1.7 (-2.5, -1.0)
		9.3 (8.0, 9.8)	7.0 (6.5, 7.9)	-1.8 (-2.6, -1.4)
769	40	8.2 ± 2.1	7.1 ± 1.9	-1.1 (-1.6, -0.6)
		8.4 (6.6, 9.7)	7.3 (5.5, 8.1)	-0.6 (-1.6, -0.2)
Fasting Triglycerides (mg/dL)				
265	8	1809 ± 2419	1146 ± 1955	-663 (-2609, 1283)
		819 (497, 2050)	310 (137, 1187)	-398 (-653, -167)
769	42	708 ± 876	327 ± 378	-381 (-606, -157)
		369 (196, 702)	216 (129, 322)	-94 (-313, -22)

3.2.1.4.5 True baseline information

This section investigates the impact of assigning a modified baseline for four patients. Similar findings were observed for the analyses using these patients' true baseline information at month 12 shown below (Table 12) and their modified baseline date (Tables 7 and 8). Similar trends were also observed at month 4 (results not shown).

Table 13. Baseline and month 12 results by study (Studies 265 and 769)

Study	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})‡
HbA1c (%)				
265	9	9.2 ± 1.4	7.2 ± 1.3	-2.0 (-2.5, -1.5)
		9.3 (8.0, 9.8)	7.3 (6.6, 8.2)	-2.0 (-2.3, -1.5)
769	46	8.0 ± 2.2	6.8 ± 1.7	-1.2 (-1.7, -0.7)
		7.9 (5.8, 9.7)	6.5 (5.6, 7.7)	-0.6 (-2.2, -0.0)
Fasting Triglycerides (mg/dL)				
265	8	1826 ± 2417	500 ± 475	-1326 (-3026, 374)
		767 (497, 2169)	391 (136, 721)	-384 (-1558.0, -284)
769	48	798 ± 1555	365 ± 575	-433 (-750, -117)
		302 (176, 527)	194 (108, 345)	-70 (-304, 6)

3.2.1.4.6 Proportion of Responses

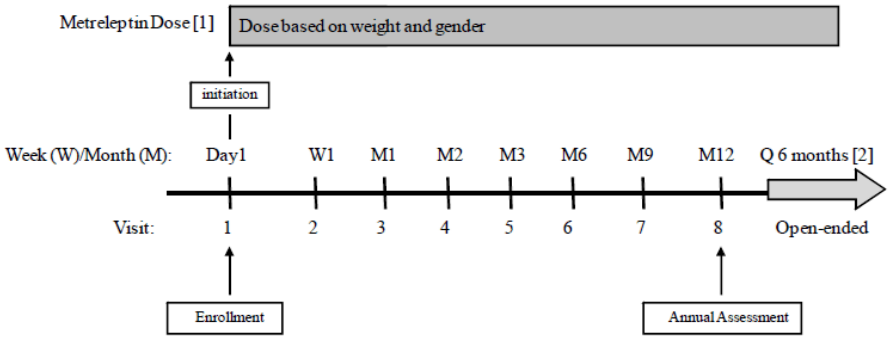
Unlike the analyses presented above, the response analysis incorporates information on patients with missing data by treating them as non-responses. For HbA1c the 67% (6/9) response rate in Study 265 was greater than the 36% (14/39) in Study 769. While the proportion of response in fasting triglyceride was also greater in Study 265 (67%, 4/6) than in Study 769 (42%, 8/19), the comparison is limited by the few patients with fasting triglycerides levels > 500 mg/dL at baseline.

3.2.2 Study FHA101

3.2.2.1 Study Design and Endpoints

Study 101 is an open-label, multi-center, single-arm design as shown in Figure 7. As of the March 7, 2012 data cutoff, 28 patients in three sites have received metreleptin under this protocol. Males and females ≥ 5 years with physician confirmed lipodystrophy without HIV were eligible for study inclusion if that had either diabetes mellitus or fasting triglyceride concentration > 200mg/dL. Unlike Studies 265 and 769, Study 101 did not include inclusion/exclusion criteria related to baseline leptin concentrations. Follow-up visits were scheduled monthly for the first 3 months of metreleptin treatment, and every 3 months thereafter for the first year. After one year of metreleptin treatment, patients were to return to the treatment site every 6 months or as directed by the investigator.

Figure 7. FHA101 study design



A significant protocol limitation is the absence of instructions not to increase antidiabetic or lipid during follow-up, as done Studies 265 and 769. The only recommendation provided was these concomitant medications may require adjustment as insulin resistance and hypertriglyceridemia improve. The extent of concomitant medication use cannot be evaluated accurately as this information was not systematically collected during study follow-up.

Daily recommended dose was gender-weight dependent. Based on clinical response (e.g., inadequate metabolic control or excessive weight loss or tolerability issues), metreleptin dose could be adjusted. After patients reached a stable dose and achieved desired improvements in metabolic parameters, patients could to transition from BID to QD dosing regimen without altering total daily dose.

Sample size justification provided in the protocol was the following. “Since no statistical inferences are planned, the study will not be powered and no formal sample size will be stipulated. Approximately 10-30 subjects are expected to enroll into this treatment protocol in 2008.”

Efficacy endpoints listed in the protocol were HbA1c, fasting plasma glucose, fasting triglycerides, and Tanner stagging. In this review HbA1c and triglycerides will be treated as primary endpoints. Neither the SAP nor the protocol listed a specific visit or visits to assess change in the study endpoints from the baseline. While the CEU presents summaries for baseline and Months 3, 6, 9 and 12, this review will focus on Months 3 and 12. Visit windows for this study do not over-lap. The sponsor defined window for month 3 is between months 2.5 and 4.5 and ± 1.5 months for month 12. Visit windows were derived based on patients first metreleptin; no patients were assigned a modified first dose date.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Table 14 summarizes patient disposition for 28 patients that received metreleptin as of the current data cut-off. The one-year and overall withdrawal rate is 21% (6/28) and 30% (8/28), respectively. Reasons for consent withdraw were desire to get pregnant (648004), reason unspecified (648007), and travel burden coupled with lack of efficacy (648013). Of the three patients that withdrew due to an adverse event, two had a fatal outcome (648008, 649001) and the other was due to non-serious muscle spasms (648021).

Table 14. Patient disposition (Study 101)

Category	N
Received at least one metreleptin dose (analysis population)	28
Withdrew from study (Withdrew within one year of first metreleptin dose)	8 (6)
Consent withdrawn	3 (1)
Adverse event including death	3 (3)
Investigator decision	1 (1)
Lost-to-follow-up	1 (1)

Missing Data

Seven patients had insufficient time in study to have a month 12 visit; only 10 of the 21 patients eligible for a month 12 visit had a month 12 measurement. The amount of missing data at month 3 was notably better, with 23 of the 28 eligible patients having a month 3 measurement.

Demographic and Baseline Characteristics

The greater percentage of patients in this study (Table 15) were female and Caucasians, were more likely to have partial lipodystrophy than generalized lipodystrophy, were more likely to be older than 18 years of age, and have a baseline HbA1c > 7.0% and fasting triglycerides below 500 mg/dL.

While the Study enrolled fewer patients with generalized lipodystrophy, this group appears different than the partial lipodystrophy group. At baseline the generalized lipodystrophy group tended to be younger (26 years vs. 47 years), have lower BMI (19 kg/m^2 vs. 31 kg/m^2) and fasting leptin (0.7 ng/dL vs. 15 ng/dL), and higher HbA1c (8.6% vs. 7.9%) and triglycerides (3248 mg/dL vs. 402 mg/dL).

Table 15. Demographic and baseline characteristics overall and by lipodystrophy type (Study 101)

		Lipodystrophy type	
	Overall N=28	**Generalized N=5**	**Partial N=23**
Gender			
Male	2	1	1
Female	26	4	22
Age (years)			
≤ 17 years	3	3	0
Mean (SD)	44 (17)	26 (24)	47 (12)
Min, Max	9, 67	9, 67	23, 67
BMI (kg/m^2)			
Mean (SD)	29 (7)	19 (3)	31 (6)
Min, Max	14, 41	14, 23	19, 41
Race			
Caucasian	21	4	17
Black	3	1	2
Asian	0	0	0
Hispanic	1	0	1
Other	3	0	3
LD Type			
Acquired generalized	4	4	-
Congenital generalized	1	1	-
Acquired partial	2	-	2
Familial partial	21	-	21
Diabetes			
Yes	21	3	18
No	7	2	5
Fasting Leptin (ng/mL)	N=22	N=3	N=19
Mean (SD)	12.8 (10.7)	0.7 (-)	15 (10.3)
Min, Max	0.7, 42.9	0.7, 0.7	1.4, 42.9
HbA1c (%)			
> 7.0%	19	4	15
Mean (SD)	8.0 (1.6)	8.6 (1.9)	7.9 (1.5)
Min, Max	5.5, 11.1	5.5, 10.2	5.6, 11.1
Fasting TG (mg/dL)	27	N=4	N=23
> 500 mg/dL	5	2	3
Mean (SD)	824 (2040)	3248 (4974)	402 (537)
Min, Max	66, 10623	170, 10623	66, 2540
Fasting Glucose (mg/dL)	27	N=4	N=23
Mean (SD)	159 (83)	267 (127)	141 (59)
Min, Max	36, 420	110, 420	36, 258

Concomitant Medication Use

Antidiabetic and lipid lowering concomitant medication use for patients that reached month 12 is shown below. While several patients either stopped or decreased use of these medications, several patients also increased or initiated use of these medications which limits confidence in being able to attribute changes that are observed exclusively to metreleptin.

FHA101 2012 Data Cut — Supporting Data Summary 1.3.4.2 — (Page 1 of 1)
Lipid Lowering Medication Change at Month 12
Population: Intent-to-Treat Subjects Taking Lipid Lowering Medications at Baseline Who Reached Month 12 (N = 13)

Baseline Meds Category[1]	Stopped	Decreased	Unchanged	Increased	Fibrate Added	Non-Fibrate Added	Indeterminate
Fibrate Alone (N=2)			1 (50.0%)	1 (50.0%)			
Any Fibrate (N=3)			2 (66.7%)	1 (33.3%)			
Non-Fibrate (N=10)	2 (20.0%)	1 (10.0%)	7 (70.0%)				
No Meds (N=0)							

[1] Subjects with fibrates at baseline. Changes are determined by fibrate dose only.

Cross Reference: Appendix 3.8.2
Program: S:\biostats - READ ONLY\AC164594SLD\FHA101\2012DataCut\Pgm\TFL\t-ll-chg.sas — Version: 29JAN2013:11:17:51

FHA101 2012 Data Cut — Supporting Data Summary 1.3.3.2 — (Page 1 of 1)
Diabetes Management Medication at Month 12
Population: Intent-to-Treat Subjects Taking Anti-Diabetes Medications at Baseline Who Reached Month 12 (N = 10)

Baseline Meds Category[1]	Stopped	Decreased	Unchanged	Increased	Insulin Added	Oral Added	Indeterminate
Insulin Alone (N=0)							
1 Oral Agent Only (N=2)	1 (50.0%)			1 (50.0%)			
2 or More Oral Agents Only (N=2)		1 (50.0%)		1 (50.0%)			
(Insulin + Oral Agent) Only (N=6)		5 (83.3%)		1 (16.7%)			
No Meds (N=0)							

[1] Subjects with insulin at baseline. Changes are determined by insulin dose only.

Cross Reference: Appendix 3.8.2
Program: S:\biostats - READ ONLY\AC164594SLD\FHA101\2012DataCut\Pgm\TFL\t-dm-chg.sas — Version: 29JAN2013:11:16:55

3.2.2.3 Statistical Methodologies

The statistical approach used for this study, including analysis population, analysis method, and handling of missing data is identical to the statistical approach used for Studies 265 and 769. Hence, the statistical issues described for those studies apply to Study 101.

3.2.2.4 Results and Conclusions

3.2.2.4.1 Month 12 Visit

Findings for HbA1c and fasting triglycerides are summarized below. From baseline to month 12 HbA1c decreased on average 0.9% (95% CI = -2.0, 0.2) and the median change in fasting triglycerides was -134 mg/dL. The interpretation of triglyceride levels should be done with particular caution given the high variability in values. It is also difficult compare findings between lipodystrophy groups given the few patients in the generalized lipodystrophy group.

Table 16. Baseline and month 12 results overall and by lipodystrophy type (Study 101)

Population	N	Baseline mean ± sd median (25th, 75th)‡	Month 12 mean ± sd median (25th, 75th)‡	Change from baseline mean (95% CI) median (25th, 75th)‡
HbA1c (%)				
Overall	10	8.4 ± 1.8 8.3 (7.0, 9.1)	7.5 ± 1.7 7.0 (6.8, 7.8)	-0.9 (-2.0, 0.2) -0.5 (-1.3, 0.2)
Generalized	2	7.3 ± 2.5 7.3 (5.5, 9.1)	6.3 ± 2.2 6.3 (4.7, 7.8)	-1.0 (-4.2, 2.1) -1.0 (-1.3, -0.8)
Partial	8	8.7 ± 1.7) 8.3 (7.5, 10.1)	7.8 ± 1.6) 7.0 (6.9, 8.3)	-0.9 (-2.3, 0.6) -0.1 (-1.5, 0.3)
Fasting Triglycerides (mg/dL)				
Overall	10	1369 ± 3259 341 (193, 354)	192 ± 133 164 (92, 275)	-1177 (-3521, 1168) -134 (-324, -10)
Generalized	2	5489 ± 7261 5489 (354, 10623)	85 ± 78 85 (30, 140)	-5404 (-69945, 59138) -5404 (-10483, -324)
Partial	8	339 ± 255 322.5 (194, 348)	219.0 ± 134 228 (108, 278)	-120 (-319, 79) -81 (-173, 33)

3.2.2.4.2 Study 265 inclusion criteria applied to Study 101

This section presents results according to whether patients would have satisfied the Study 265 inclusion criteria (Table 17). Only one of the three patients that satisfied the Study 265 inclusion criteria had a month 12 measurement. While it is difficult to draw conclusion for the group that did satisfy the 265 inclusion criteria, removing this patient from the analysis led to a notable change in the mean change from baseline for HbA1c (0.9% to 0.5%). For the triglyceride endpoint this patient did not have a notable impact.

Table 17. Month 12 result for groups defined by Study 265 inclusion criteria (Study 101)

Month	Satisfied 265 Inc. criteria	N	Baseline mean ± sd median (25th, 75th)‡	Follow-up visit mean ± sd median (25th, 75th)‡	Change from baseline mean (95% CI) median (25th, 75th)‡
HbA1c (%)					
12	Yes	1	11.1 ± NA 11.1 (-,-)	6.4 ± NA 6.4 (-,-)	-4.7 (-,-) -4.7 (-,-)
	No	9*	8.1 ± 1.6 8.1 (7.0, 9.1)	7.6 ± 1.8 7.1 (7.0, 7.8)	-0.5 (-1.1, 0.2) -0.1 (-1.1, 0.2)
Fasting Triglycerides (mg/dL)					
12	Yes	1	193 ± NA 193 (-,-)	92 ± NA 92 (-,-)	-101 (-,-) -101 (-,-)
	No	9*	1499 ± 3429 341 (304, 354)	203 ± 136 188 (124, 275)	-1296 (-3950, 1358) -166 (-324, -10)

*Includes patients with missing baseline leptin levels

3.2.2.4.3 Month 3 Visit

From baseline to month 3 the average HbA1c decreased a marginal 0.4% (95% CI = -1.1, 0.2). The greater change by month 12 (0.9%) presented above, however, has to be interpreted cautiously as the baseline mean for the month12 analysis was greater than the baseline mean for the month 3 analysis, 8.4% vs. 7.9%. Similar trends were observed for fasting triglycerides.

Table 18. Baseline and month 3 results (Study 101)

Month	N	Baseline mean ± sd median (25^{th}, 75^{th})‡	Month 3 mean ± sd median (25^{th}, 75^{th})‡	Change from baseline mean (95% CI) median (25^{th}, 75^{th})‡
HbA1c (%)				
3	23	7.9 ± 1.6	7.5 ± 1.7	-0.4 (-1.1, 0.2)
		8.1 (6.8, 9.0)	7.4 (6.3, 8.6)	-0.0 (-0.7, 0.2)
Fasting Triglycerides (mg/dL)				
3	22	844 ± 2225	304 ± 241	-540 (-1452, 371)
		254 (170, 354)	253 (105, 434)	-29 (-139, 18)

3.2.2.4.4 Response Analysis

Responder results are not presented for triglycerides due to the limited number of patients with baseline with levels exceeding 500 mg/dL. For HbA1c the response rate was 19% (3/16).

3.3 Evaluation of Safety

An evaluation of safety is included in the FDA clinical review by Dr. Julie Golden.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses presented below are based on pooling month 12 data from the three studies. Because the individual studies differ in important ways, including inclusion criteria and window definitions, results must be interpreted with extreme caution.

4.1 Gender, Race, Age, and Geographic Region

The average change in HbA1c at month 12 was fairly similar in males compared to females, in the younger age group compared to the older age group, and in Caucasians and non-Caucasians. Similar observations were observed for average change in fasting triglycerides.

Table 19. Pooled Month 12 results for demographic subgroups

Group	Level	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})‡
HbA1c (%)					
Sex	Female	56	8.2 ± 2.1 8.1 (6.7, 9.7)	7.0 ± 1.7 6.7 (5.7, 7.8)	-1.3 (-1.7, -0.8) -0.7 (-2.3, 0.0)
	Male	10	7.9 ± 2.1 8.7 (5.5, 9.5)	6.5 ± 1.4 6.4 (5.3, 8.0)	-1.4 (-2.3, -0.5) -1.4 (-2.0, -0.6)
Age	≥ 17 years	36	8.4 ± 1.8 8.3 (7.3, 9.5)	7.4 ± 1.7 7.0 (6.3, 8.1)	-1.1 (-1.6, -0.6) -0.6 (-1.8, 0.0)
	< 17 years	30	7.9 ± 2.4 7.9 (5.5, 9.8)	6.4 ± 1.6 5.8 (5.3, 7.3)	-1.5 (-2.1, -0.9) -1.4 (-2.9, -0.0)
Race	Caucasian	44	8.1 ± 2.2 8.0 (6.4, 9.5)	7.1 ± 1.8 7.0 (5.7, 8.1)	-1.1 (-1.5, -0.7) -0.7 (-1.9, -0.0)
	Non-Caucasian	22	8.3 ± 2.0 8.6 (6.5, 9.8)	6.6 ± 1.5 6.3 (5.5, 7.2)	-1.7 (-2.5, -0.8) -1.5 (-3.1, -0.0)
Fasting Triglycerides (mg/dL)					
Sex	Female	56	1146 ± 2138 358 (213, 878)	390 ± 560 234 (118, 416)	-756 (-1250, -263) -137 (-619, -9)
	Male	11	241 ± 129 201 (137, 354)	161 ± 101 153 (55, 268)	-80 (-156, -4) -52 (-137, 12)
Age	≥ 17 years	35	909.3 ± 1690 359 (220, 836)	407 ± 643 268 (124, 378)	-502 (-896, -109) -137 (-593, -26)
	< 17 years	32	1094 ± 2282 295 (143.0, 478)	293 ± 337 161 (99, 307)	-801.3 (-1581, -21) -110.0 (-315, 24)
Race	Caucasian	44	908 ± 1853 339 (195, 474)	387 ± 619 183 (101, 367)	-521 (-926, -116) -98 (-304, -15)
	Non-Caucasian	23	1170 ± 2241 449 (199, 919)	287 ± 230 209 (140, 339)	-883 (-1862, 96) -137 (-700, 53)

4.2 Other Special/Subgroup Populations

Factors considered for the subgroup analyses in this section include:

- Baseline insulin use (Yes, No)
- Baseline lipid medication (Yes, No)
- Diabetes at baseline (Yes, No)
- Baseline HbA1c (≤ 7.0%, > 7.0%)
- Baseline triglycerides (≤ 500 mg/dL, > 500 mg/dL)

Note that subgroup analyses by study were presented above for lipodystrophy type (generalized vs. partial) and Study 265 inclusion criteria. Findings from these groups will not be discussed in this section.

The average decrease in HbA1c at month 12 was greater in the group with diabetes at baseline compared to the group without diabetes at baseline, and in the group with high baseline HbA1c compared to the group with low baseline HbA1c. The average change was fairly similar in the groups defined by insulin use at baseline, lipid lowering medication use at baseline, and high triglyceride levels.

With the exception of groups defined by baseline triglycerides levels and diabetes status, there does not appear to be any notable differences between groups on triglyceride levels.

Table 20. Pooled Month 12 results by metabolic subgroups

Group	Level	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})‡
HbA1c (%)					
Baseline Insulin Use	Yes	29	9.3 ± 1.8 9.3 (8.0, 10.1)	7.6 ± 1.9 7.3 (6.5, 8.5)	-1.6 (-2.2, -1.0) -1.5 (-2.3, -0.5)
	No	37	7.4 ± 1.9 7.5 (5.6, 8.6)	6.4 ± 1.2 6.0 (5.5, 7.2)	-1.0 (-1.5, -0.5) -0.4 (-1.6, 0.1)
Baseline Lipid Meds.	Yes	37	8.3 ± 1.8 8.2 (7.0, 9.5)	7.2 ± 1.3 7.1 (6.3, 8.0)	-1.1 (-1.6, -0.6) -0.7 (-2.0, 0.1)
	No	29	8.1 ± 2.5 7.9 (6.3, 9.8)	6.6 ± 2.0 6.0 (5.3, 7.2)	-1.5 (-2.1, -0.9) -0.9 (-2.8, -0.3)
Diabetic	Yes	58	8.6 ± 1.9 8.5 (7.5, 9.8)	7.1 ± 1.7 7.0 (6.0, 8.1)	-1.4 (-1.9, -1.0) -1.3 (-2.3, -0.3)
	No	8	5.3 ± 0.5 5.4 (5.0, 5.5)	5.3 ± 0.4 5.3 (4.9, 5.5)	-0.0 (-0.3, 0.3) -0.0 (-0.3, 0.2)
HbA1c > 7.0%	Yes	45	9.3 ± 1.5 9.1 (8.1, 10.1)	7.5 ± 1.7 7.3 (6.4, 8.4)	-1.8 (-2.3, -1.3) -1.6 (-2.8, -0.7)
	No	21	5.8 ± 0.7 5.7 (5.3, 6.3)	5.7 ± 0.8 5.6 (5.3, 6.2)	-0.1 (-0.5, 0.2) -0.0 (-0.3, 0.3)
TG >500 mg/dL	Yes	21	9.4 ± 2.0 9.5 (8.5, 9.9)	7.8 ± 1.8 7.4 (6.5, 8.9)	-1.6 (-2.5, -0.8) -1.4 (-2.8, -0.4)
	No	45	7.6 ± 1.9 7.6 (5.8, 9.0)	6.5 ± 1.5 6.4 (5.3, 7.2)	-1.1 (-1.5, -0.7) -0.7 (-2.0, 0.0)
Fasting Triglycerides (mg/dL)					
Baseline Insulin Use	Yes	29	1553 ± 2592 449 (341, 1510)	411 ± 674 267 (136, 342)	-1142 (-2001, -283) -303 (-794, -61)
	No	38	574 ± 1222 258 (141, 433)	308 ± 364 165 (103, 378)	-266 (-589, 57) -70 (-193, 14)
Baseline Lipid Meds.	Yes	38	1168 ± 2099 396 (199, 919)	330 ± 353 268 (124, 378)	-837 (-1495, -179) -129 (-644, -26)
	No	29	775 ± 1828 322 (145, 416)	382 ± 686 168 (107, 342)	-393 (-846, 60) -74 (-305, 12)
Diabetic	Yes	58	1124 ± 2103 359 (220, 836)	367 ± 552 201.5 (107, 355)	-758 (-1232, -283) -147 (-593, -46)
	No	9	183 ± 79 141 (122, 228)	263 ± 218 177 (142, 273)	80 (-69, 229) 40 (12, 92)
HbA1c > 7.0%	Yes	45	1265 ± 2350 396 (201, 836)	360 ± 580 179 (107, 342)	-905 (-1511, -300) -166 (-644, -52)
	No	22	450 ± 548 302 (141, 359)	338 ± 377 238 (142, 407)	-113 (-284, 59) -15 (-184, 80)
TG >500 mg/dL	Yes	21	2622 ± 2979 1377 (802, 2984)	682 ± 823 424 (215, 716)	-1943 (-3141, -745) -726 (-2543, -499)
	No	46	255 ± 117 241 (145, 354)	203 ± 146 153 (99, 295)	-53 (-98, -7) -57 (-121, 34)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Notable issues encountered in this review include:

- The single-arm design in a heterogeneous study.
- Several patients increased use of diabetic and lipid-lowering medications during study follow-up. The accuracy of such usage is further limited by this information not being systematically collected during study follow-up. Furthermore, the guidance in Study 769 that concomitant medication was not to be increased appears to have been deliberately violated in order to maximize lipid and glycemic control with metreleptin.
- Change in metabolic parameters may be partially attributed to the phenomena of regression to the mean.
- The degree of missing data in Studies 769 and 101.
- Differences between the estimates of mean change and median change.
- The studies had different inclusion criteria, with the later studies (Studies769 and 101) having less dramatic changes in metabolic parameters and a more inclusive lipodystrophy study population.
- A number of patients were assigned a modified baseline date based on non-optimal experiences (e.g., compliance issues and/or an adverse event) when they first initiated treatment with metreleptin.

5.2 Collective Evidence

This review investigated non-interventional data on 100 patients treated with metreleptin in three studies with different manifestations of lipodystrophy. Descriptive summaries of change from baseline for HbA1c and fasting triglyceride in the more inclusive studies 769 and 101 (which is reflective of the proposed indication) were found not to be as dramatic as the changes observed in the first study of metreleptin in patients with lipodystrophy (Study 265). A post hoc investigation of the group in Studies 769 and 101 that satisfied the Study 265 inclusion criteria based on age and fasting leptin levels found changes that were similar to changes observed in Study 265. Responses varied across various subgroups, with the magnitude of change of HbA1c and fasting triglyceride being more favorable for groups with greater degrees of metabolic abnormalities or leptin deficiency.

5.3 Conclusions and Recommendations

The statistical reviewer does not support the overall approval of metreleptin for the treatment of metabolic disorders associated with lipodystrophy including diabetes mellitus and/or hypertriglyceridemia in pediatrics and adults with inherited or acquired lipdystrophy. This conclusion is supported by (b) (4) Based on these considerations, I recommend against the

overall approval for the proposed indication. At an upcoming Advisory Committee meeting important input will be sought on the efficacy and safety of metreleptin in various lipodystrophy populations. While the discussion may provide guidance on whether the risk-benefit profile to support approval of metreleptin in a subset of the studied population, I would advise that such a regulatory decision strongly consider the challenges of reliably identifying a subgroup based on post hoc considerations. If such a group is identified, I would recommend the sponsor conduct a randomized, placebo-controlled, double-blind trial that adequately restricts background concomitant medication in order to isolate the effect of metreleptin in the group..

APPENDICES

Table 21. Patients assigned a modified baseline

Study-Patient	True baseline date	Modified baseline date	Reason for modified date
265-90105	9/27/2000	10/29/2003	Adverse event and compliance issues
265-90106	9/08/2000	11/15/2000	Adverse event
769-90110	11/29/2001	7/22/2004	Adverse event and compliance issues
769-90128	7/21/2004	11/21/2004	Compliance issues

Below are the narratives detailing events/circumstances that led the sponsor to assign a modified baseline date (SAP, page 15-16):

- Patient 90105 has the following study medication dosing log: the patient initiated metreleptin treatment on 27 Sep 2000 but stopped treatment after experiencing an adverse reaction after the second dose. The patient reinitiated treatment on 12 Nov 2000 and was on metreleptin for about 6 months (Nov 2000 to May 2001), then was off drug for about 6 months, resumed medication for about 13 months (Nov 2001 to Dec 2002), then off drug again for about 3 months, resumed medication for about 1 month (Mar 2003 to Apr 2003), then was off drug again for 6 months, resumed medication on 29 Oct 2003, and was on treatment as of the 2009 data cutoff. Per the investigator, the patient was compliant after Nov 2003. Thus 29 Oct 2003 will be used as the modified first dose date. Only clinical laboratory and vital sign data collected at baseline and since 29 Oct 2003 will be used for summaries and analyses. Data from other visits will be listed only.

- Patient 90106 initiated metreleptin treatment on 08 Sept 2000 but experienced an adverse event on the second day of treatment, and metreleptin was discontinued. She re-initiated metreleptin on 19 Sep 2000 but again discontinued 1 day later after she experienced another adverse event. Metreleptin was restarted on 15 Nov 2000 and continued until 29 May 2002 with unclear dosing regimen and compliance between 17 Jan 2002 and 29 May 2002. The patient restarted the medication on Aug 2008 and was on treatment as of the 2009 data cutoff. Thus 15 Nov 2000 will be used as the modified first dose date. The modified last dose date is set to be 29 May 2002. Only clinical laboratory and vital sign data collected at baseline and between 15 Nov 2000 and 29 May 2002 will be used for summaries and analyses. Data from other visits will be listed only.

- Patient 90110 initiated metreleptin treatment on 29 Nov 2001 but experienced an adverse event after about 1 month, and metreleptin was discontinued on 07Jan 2002. She resumed medication for about 4 months (Feb 2002 to Jun 2002), but discontinued 12 Jun 2002 after another adverse event. She was off drug for about 2 years. The patient restarted medication on 22 Jul 2004 and was on treatment as of the data cutoff. Thus 22 Jul 2004 will be used as the modified first dose date. Only clinical laboratory and vital sign data collected at baseline and since 22 Jul 2004 will be used for summaries and analyses. Data from other visits will be listed only.

- Patient 90128 was on metreleptin treatment from 21 Jul 2004 to 25 Jul 2004 and stopped the medication due to noncompliance. The patient resumed metreleptin on 21 Nov 2004 but was extremely non-compliant after Jun 2006 and was withdrawn from the study on 20 Feb 2009 due to noncompliance. Thus 21 Nov 2004 will be used as the modified first dose date. The patient had clinical laboratory data as of Apr 2008, but since the patient was noted by the investigator to be extremely non-compliant after Jun 2006, the modified last dose date is set to be 26 Jun 2006 (as clinical laboratory data are available at this visit date). Only clinical laboratory and vital sign data collected at baseline and between 21 Nov 2004 and 26 Jun 2006 will be used for summaries and analyses. Data from other visits will be listed only.

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/s/

BRADLEY W MCEVOY
11/22/2013

MARK D ROTHMANN
11/22/2013
I concur

THOMAS J PERMUTT
11/25/2013
I concur.

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.	125390
SERIAL NO.	
CONSULT REQUESTED BY OBP	August 21, 2013
DRUG NAME	Myalept (metreleptin)
DOSAGE FORM	
INDICATION	Therapeutic protein
SPONSOR	Amylin Pharmaceuticals (a subsidiary of BMS)
REVIEW FINISHED	October 8, 2013
STATISTICAL REVIEWER	Meiyu Shen, Ph.D.
BIOLOGICAL REVIEWER	Cecelia Tami, Ph.D.
STATISTICAL CONSULT REQUESTED BY	Pat Madara

_____

Meiyu Shen, Mathematical Statistician, PhD

Concur: _____
Yi Tsong Ph.D.
Acting Division Director, DBVI

Distribution: BLA 125390
DB VI/Yi Tsong, Ph.D.
OBP/Pat Madara
OBP/Cecelia Tami, Ph.D.

TABLE OF CONTENTS

STATISTICAL FINDINGS

1.1 Conclusions and recommendations

The (b) (4) shelf life of metreleptin drug product is not supported by the available stability data submitted by the sponsor.

1.2 Background

The Office of Biotechnology Products requested the CMC statistical team to determine the adequacy of the sponsor's statistical approach of analyzing the kinetics of degradation of metreleptin drug product for supporting the proposed expiration dating.

1.3 Purpose of this statistical consult

The purpose of this statistical consult is to evaluate shelf life of metreleptin drug product by analyses of stability data including purity by RP-HPLC and individual specified impurities by RP-HPLC at (b) (4)

1.4 Data

The data cut-off for statistical analysis of stability data was 31 January 2013. Stability results collected after this pull date were not included in this analysis. The following attributes were considered:

• Purity by RP-HPLC
• Individual specified impurities by RP-HPLC

Kinetic analysis results for the remaining attributes tested are not included here because either the data are not amenable to statistical analysis (e.g. appearance), or inspection of the data indicates no trend at the recommended storage condition of (b) (4) or the body of data collected to date is not sufficient for an analysis.

At (b) (4) the sponsor submitted

- one primary stability lot (Lot 592053F) with 50-month data, one primary stability lot (Lot 941353F) with 24-month data,
- one validation lot (Lot 090653F) with 12-month data, one validation (Lot 171003F) with 3-month data,
- three supporting lots (442253F, 560753F, and 671203F) with at least 36-month data.

At (b) (4), the sponsor submitted

- one primary stability lot (Lot 592053F) with 8.5-month data, one primary stability lot (Lot 941353F) with 6.5-month data,
- one validation lot (Lot 090653F) with 6-month data, one validation lot (Lot 171003F) with 3-month data,
- two supporting lots (Lots 442253F and 560753F) with at least 6-month data.

Three lots for supporting stability can not be used for analyses because these lots are manufactured using drug substance previously generated at Amgen although using the proposed commercial manufacturer and process.

Table 1 lists the summary of Metreleptin drug product lots used in the sponsor's stability analyses.

Table 1 Summary of Metreleptin Drug Product Lots

Lot Number	Scale	Commercial process	Primary stability or validation	Time Points Completed (Months)	
				(b) (4)	
592053F	(b) (4)		Primary	50	8.5
941353F			Primary	24	6.5
090653F			Validation	12	6
171003F			Validation	3	3

1.5 Sponsor's statistical method and results

The sponsor conducted analyses of covariance for (b) (4) purity and impurity stability data from Lots 592053F, 941353F, 090653F and 3 supporting lots regardless of how many month data are available for each lot. In the sponsor's linear model (derived from zero order kinetics), the time was a continuous variable and lots was a categorical variable. The pooling test was used here to pool slope and intercept across the lots.

The sponsor fitted zero-order kinetic model to the purity and impurity data.
Attribute Value = $I_0 + k_0 t$.

Similarly, the sponsor conducted analyses of covariance for (b) (4) purity and impurity stability data from Lots 592053F, 941353F, 090653F and 2 supporting lots.

The sponsor's analyses for (b) (4) purity were listed in Table 2.

Table 2 Sponsor's Analyses for Degradation Kinetics of Metreleptin Drug Product Percent Purity Results by RP-HPLC for Samples Stored at (b) (4)

Lot Number	(b) (4)
592053F	
941353F	
090653F	
171003F	
442253F	
560753F	
671203F	

The sponsor also analyzed the impurity data regarding (b) (4)

The sponsor concluded that none of the attributes are shelf life limiting (b) (4) at the recommended storage condition. All data for all lots studied (primary and supporting stability results) were well within the proposed criteria for all attributes when stored at 2-8°C (b) (4) months or longer.

1.6 Reviewer's comments on the sponsor's statistical method

The sponsor's stability data can not be used for supporting the shelf-life estimation because

1. two "primary stability" lots (Lots 592053F and 941353F) (b) (4) ;
2. three supporting stability lots were manufactured (b) (4)
3. two validation lots were manufactured (b) (4)

In other words, there is no stability data available for lots manufactured at the commercial scale from the proposed commercial process at the commercial site. Hence, the validity of the sponsor's analyses is questionable.

Furthermore, as shown in Table 2, there are many positive slopes for purity in the analyses of covariance. Positive slope means that the purity increases with the longer time on shelf. For Lot 941353F, purity will increase by 1.235% by the end of 6.5 months when stored at (b) (4) Increase of purity means loss of other components over the time, which can not be explained by measurement errors.

1.7 Reviewer's conclusions

The sponsor's request of (b) (4) for shelf life can not be supported by the sponsor's current available stability data.

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/s/

MEIYU SHEN
10/10/2013

YI TSONG
10/15/2013

STATISTICS FILING CHECKLIST FOR BLA 125390
Myalept (metreleptin for injection)

Filing meeting: April 30, 2013
Statistical reviewer: Bradley McEvoy

BLA Number: 125390 **Applicant: Amylin** **Stamp Date: March 27, 2013**

Drug Name: Myalept **NDA/BLA Type: BLA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___YES _____

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Single arm
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No interim analysis
Appropriate references for novel statistical methodology (if present) are included.			X	Standard method
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			

Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

1. Drug information

- Proposed trade name: Myalept
- Generic name: Metreleptin for injection
- Proposed indication: Treatment of diabetes and/or hypertriglyceridemia in patients with lipodystrophy
- Route of administration: Subcutaneous injection
- Applicant: Amylin Pharmacueticals
- Stamp date: March 27, 2013
- PDUFA date: November 27, 2013

2. Clinical studies

All 3 studies were uncontrolled and open-labeled. Patients in the pilot Study 991265 were allowed to roll over and be followed in Study 20010769. Data from Studies 991265 and 2001769 are pooled by the sponsor.

Study	Number of subjects	Follow-up	Main inclusion criteria
991265	9	Original: 4 mos. Amend 1: 8 mos. Amend 2: > 8 mos.	Patients >14 years of age with clinically significant LD, circulating leptin concentrations < 4.0 ng/mL (females) or < 3.0 ng/mL (males), and at least 1 of 3 metabolic abnormalities.
20010769	63*	Open-ended, ongoing	Patients > 6 months of age with clinically significant LD, circulating leptin concentration of <12.0 ng/mL (females ≥ 5 years), <8.0 ng/mL (males ≥ 5 years) or < 6.0 ng/mL (females and males 6 mos. to 5 years), and at least 1 of 3 metabolic abnormalities.
FHA101	28*	Open-ended, ongoing	Patients ≥ 5 years of age with physician confirmed LD, and at least 1 of 2 metabolic abnormalities.

*Based on current data cut-off

3. Efficacy endpoints

Primary efficacy endpoints:

- HbA1c
- Fasting plasma glucose (in SAP but not protocol for 991265 and 2001769)
- Fasting triglyceride

4. Statistical methods

- Mean change from baseline by visit
- Missing data was not imputed.

5. Data quality

Datasets were provided as SAS transport files. I was able replicate the sponsor's descriptive summaries for HbA1c from FHA101 and the pooled studies 991265/2001769. No analysis program submitted.

Comments for 74-day letter: No comments

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/s/

BRADLEY W MCEVOY
05/09/2013

JON T SAHLROOT
05/09/2013