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RESEARCH**

APPLICATION NUMBER:

125390Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template-PMR #1-Product Exposure Registry

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # 125390
 Product Name: Myalept (metreleptin)

PMR#1 Description: A long-term prospective observational study (product exposure registry) of patients treated with Myalept (metreleptin), regardless of indication, to evaluate serious risks related to the use of Myalept (metreleptin), by indication, including: fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, serious infections resulting in hospitalization or death, new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, lymphoma, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes, and all deaths (including causes of death). After agreement with FDA on a targeted sample size, the registry will include patients prescribed Myalept (metreleptin) and will continue for 10 years from the date of last patient’s enrollment, or September 2029, whichever is later.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2014</u>
	Study/Trial Completion:	<u>09/30/2029</u>
	Final Report Submission:	<u>03/31/2030</u>
	Other: Interim reports	09/31/2015
		09/31/2016
		09/31/2017
		09/31/2018
		09/31/2019
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		09/31/2021
		09/31/2022
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		09/31/2025
		09/31/2026
		09/31/2027
		09/31/2028
		<u>09/31/2029</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety

- Small subpopulation affected
- Theoretical concern
- Other

Generalized lipodystrophy is a rare disorder characterized by the loss of body fat. As the hormone leptin is primarily produced by fat tissue, patients with generalized lipodystrophy are leptin deficient. As a consequence of a lack of adequate storage depots for body fat (and resultant ectopic deposition of fat in tissues such as muscle and liver), as well as leptin deficiency, patients with generalized lipodystrophy often develop life-threatening co-morbidities such as insulin-dependent diabetes mellitus and acute pancreatitis from extreme hypertriglyceridemia. Myalept (metreleptin) was granted orphan drug designation for the treatment of lipodystrophy. Known and potential safety concerns include serious adverse sequelae due to the development of neutralizing antibodies [loss of endogenous leptin activity (e.g., severe infections), worsening of metabolic disease, T-cell lymphoma/ other malignancies, autoimmune disorders (e.g., autoimmune hepatitis, membranoproliferative glomerulonephritis), hypersensitivity reactions, pancreatitis, hepatic adverse events, and hypoglycemia. Given the small population affected by this disorder (less than ~1 in a million) and limitations in the conduct of the clinical trials, a post-marketing registry is required to generate additional person-years to assess risks related to the long-term use of the drug.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The paucity of long-term safety data on Myalept (metreleptin) remains a concern. Because of the rarity of lipodystrophy, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Myalept (metreleptin) is limited. In addition, the obesity development program was discontinued. Myalept (metreleptin) pre-clinical and clinical development programs revealed known and potential serious risks associated with its use including serious adverse sequelae due to the development of neutralizing antibodies [loss of endogenous leptin activity (e.g., severe infections) and loss of efficacy (e.g., increases in triglycerides, worsening diabetes mellitus)], autoimmune disorders (e.g., autoimmune hepatitis, membranoproliferative glomerulonephritis), hypersensitivity reactions, pancreatitis, hepatic adverse events, and hypoglycemia. The goal of the enhanced pharmacovigilance study is to gather additional data to better assess risks related to the long-term use of the drug. The goal of the registry is to generate additional person-years of exposure to assess these and other serious risks related to Myalept (metreleptin) use. The registry will include a sample of patients prescribed Myalept (metreleptin) and continue for 10 years from the date of last patient enrollment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- X FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- X Assess a known serious risk related to the use of the drug?
- X Assess signals of serious risk related to the use of the drug?
- X Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

X Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The registry will include a sample of patients prescribed Myalept (metreleptin) and followed for 10 years to describe the following:

- a. Patient age, sex, and race
- b. Country of treatment
- c. Type of generalized lipodystrophy (congenital or acquired)
- d. History of autoimmune disease
- e. History of pancreatitis
- f. Other medical history
- g. Concomitant medications, including start and stop dates
- h. Use of dietary and vitamin supplements
- i. Metreleptin dose, duration of use, start date, discontinuation date, reasons for discontinuation, person-years of exposure
- j. HbA1C
- k. Serum lipid levels
- l. Antibody titer and neutralizing antibodies if applicable

Data to be provided should include incidence rates for the following outcomes of interest:

- Malignancies, including hematologic and solid tumors
- Serious infections resulting in hospitalization or death
- Serious hypersensitivity reactions
- Fatal, hemorrhagic or necrotizing pancreatitis
- Hepatic adverse events including hepatic transaminase elevations with and without bilirubin elevations, cirrhosis and hepatic failure
- Autoimmune disorders including autoimmune hepatitis, lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, glomerulonephritis
- Serious /severe hypoglycemic events

Required

- Observational pharmacoepidemiologic study
- X Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

X Other

A long-term, prospective, observational study (product exposure registry) of patients treated with Myalept (metreleptin), regardless of indication, to evaluate potential serious risks related to the use of Myalept (metreleptin), by indication, including: fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, serious infections resulting in hospitalization or death, new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes, and all deaths (including causes of death). After agreement on a targeted sample size, the registry will include patients prescribed Myalept (metreleptin) and will continue for 10 years from the date of the last patient's enrollment. The sponsor will submit annual updates regarding patient enrollment and study progress and interim analyses of study results at 3 and 7 years.

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template-PMR #2-Neutralizing antibody ligand binding assay

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # 125390
Product Name: Myalept (metreleptin)

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

PMR#2 Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 03/31/2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus (often requiring hundreds of units of insulin daily), pancreatitis, and premature death. Metreleptin is highly immunogenic. The majority of patients with generalized lipodystrophy evaluated in the trials developed anti-metreleptin antibodies (84%). Anti-metreleptin antibodies with neutralizing activity associated with adverse events consistent with loss of endogenous leptin activity and/or loss of MYALEPT efficacy was observed in 6% (2/33) of the patients with generalized lipodystrophy tested; however, the incompleteness of the current immunogenicity database precludes understanding of the magnitude and persistence of the observed anti-leptin antibody responses. One of the 2 patients was a 19 year-old female with CGL, who appeared to have loss of metabolic control in association with the neutralizing antibodies, and was additionally reported to have multiple hospitalizations for sepsis. The second patient, an 18-year-old female with CGL, developed neutralizing antibodies associated with loss of efficacy; she also had an adverse event of sepsis, although the temporal relationship with that event is less clear. Because of the role that leptin plays in the functioning of the immune system, it is theoretically possible that neutralizing antibodies to leptin could have implications for immune functioning (i.e., immunodeficiency), even in patients with very low endogenous leptin. A number of adverse events (excessive weight gain, glucose intolerance, diabetes mellitus) associated with the development of antibodies with neutralizing activity in patients treated with metreleptin in a development program for the treatment of obesity. As (1) this is a rare life threatening disease, (2) the majority of lipodystrophy patients did not show clinical sequelae because of neutralizing antibody responses, and (3) distribution of this drug will be limited to generalized lipodystrophy patients, this study can be a post-marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The neutralizing cell based assay lacks sensitivity due to a high degree of matrix interference derived from the presence of endogenous serum leptin. Since the only difference between metreleptin and the native protein resides in the presence of one additional amino acid residue, cells cannot discriminate between the stimulatory dose of metreleptin added to the assay cultures and the amount present in serum. This interferes with the detection of samples with low concentration of neutralizing antibodies. A ligand binding assay would have reduced matrix interference and increased sensitivity that would allow for identification of samples with low levels of neutralizing antibodies that are not detected in the current bioassay.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- X FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- X Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

X Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be conducted in generalized lipodystrophy patients enrolled in on-going clinical trials, samples collected in previous trials, and a new safety trial proposed in a separate PMR.

Required

Observational pharmacoepidemiologic study

Registry studies

X Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Continuation of Question 4

X Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Stored and banked serum samples from patients that have received metreleptin treatment under the clinical development program should also be tested and analyzed together

Meta-analysis or pooled analysis of previous studies/clinical trials

X Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

X Other

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

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template-PMR #3 Neutralizing antibody retest-NIH study

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125390
Product Name: Myalept (metreleptin)

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

PMR#1 Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 08/31/2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus (often requiring hundreds of units of insulin daily), pancreatitis, and premature death. Adipose tissue is the main source of leptin in humans, although other cells such as cells of the immune system also produce leptin. The development of neutralizing antibodies was linked to loss of efficacy and/or loss of endogenous leptin activity in five patients receiving metreleptin treatment. Three of those patients are in the obese population in which metreleptin will be contraindicated. Peak neutralizing antibody responses were reported at the time when the following adverse events were observed: severe infections, worsening glycemic control, hypertriglyceridemia, and excessive weight gain. As (1) this is a rare life threatening disease, (2) the majority of lipodystrophy patients did not show clinical sequelae because of neutralizing antibody responses, and (3) distribution of this drug will be limited to generalized lipodystrophy patients, this can be a post-marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The bioassay used to determine the presence of anti-leptin antibodies with neutralizing activity in samples collected from patients enrolled in pivotal studies NIH 991265/20010769 and FHA 101 lacked sensitivity due to a high degree of matrix interference. Thus, there is a concern over underreporting the number neutralizing antibody positive patients enrolled under these two studies. Given the concern over loss of efficacy to metreleptin treatment and the potential loss of endogenous leptin function, testing of banked clinical samples with a ligand binding assay with reduced matrix interference and increased sensitivity would allow identification of samples with low levels of neutralizing antibodies that were not detected with the current bioassay.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be conducted in banked samples from lipodystrophy patients enrolled in previous clinical trials.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- X Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Stored and banked serum samples from patients that have received metreleptin treatment under the clinical development program should also be tested and analyzed together

- Meta-analysis or pooled analysis of previous studies/clinical trials
 - X Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

X Other

To test all banked clinical samples from pivotal clinical studies NIH 991265/20010769 and study FHA101 for the presence of neutralizing antibodies against leptin using the ligand binding assay developed and validated under PMR #2 described above, and to correlate neutralizing antibodies with clinical events.

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template-PMR #4 - Immunogenicity clinical study

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # 125390

Product Name: Myalept (metreleptin)

PMR #4 Description:

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

PMR Schedule Milestones:	Final Protocol Submission:	<u>12/31/2014</u>
	Study/Trial Completion:	<u>12/31/2021</u>
	Final Report Submission:	<u>12/31/2022</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus (often requiring hundreds of units of insulin daily), pancreatitis, and premature death. Adipose tissue is the main source of leptin in humans, although other cells such as cells of the immune system also produce leptin. The development of neutralizing antibodies was linked to loss of efficacy and/or loss of endogenous leptin activity in five patients receiving metreleptin treatment. Three of those patients are in the obese population in which metreleptin will be contraindicated. Peak neutralizing antibody responses were reported at the time when the following adverse events were observed: severe infections, worsening glycemic control, hypertriglyceridemia, and excessive weight gain. As (1) this is a rare life threatening disease, (2) the majority of lipodystrophy patients did not show clinical sequelae because of neutralizing antibody responses, and (3) distribution of this drug will be limited to generalized lipodystrophy patients, this can be a post-marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The lack of systematic sample collection in Studies NIH 991265 and NIH 20010769 prevents accurate evaluation of antibody response, magnitude, and persistence with metreleptin treatment. Given the concern over loss of efficacy to metreleptin treatment and the potential loss of endogenous leptin function, this new study will provide missing information on the natural history of anti-metreleptin antibodies in patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

X Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be conducted in serum samples collected from patients receiving metreleptin treatment through prescriptions of the marketed product and currently enrolled under ongoing clinical trials.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- X Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Stored and banked serum samples from patients that have received metreleptin treatment under the clinical development program should also be tested and analyzed together

- Meta-analysis or pooled analysis of previous studies/clinical trials
- X Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

X Other

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

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template: PMR #5-Enhanced Pharmacovigilance

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA #	125390																														
Product Name:	Myalept (metreleptin)																														
PMR #5 Description:	An assessment and analysis of spontaneous reports of serious risks related to the use of Myalept (metreleptin) including: fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, serious infections resulting in hospitalization or death, new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes, and all deaths (including causes of death) in patients treated with Myalept (metreleptin) regardless of indication for 10 years from the date of approval.																														
PMR/PMC Schedule Milestones:	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%;">Final Protocol Submission:</td> <td style="text-align: right; border-bottom: 1px solid black;">05/31/2014</td> </tr> <tr> <td>Study/Trial Completion:</td> <td style="text-align: right; border-bottom: 1px solid black;">05/31/2024</td> </tr> <tr> <td>Final Report Submission:</td> <td style="text-align: right; border-bottom: 1px solid black;">07/31/2024</td> </tr> <tr> <td>Other: Interim Reports:</td> <td style="text-align: right;">3/31/2015</td> </tr> <tr> <td></td> <td style="text-align: right;">9/30/2015</td> </tr> <tr> <td></td> <td style="text-align: right;">3/31/2016</td> </tr> <tr> <td></td> <td style="text-align: right;">9/30/2016</td> </tr> <tr> <td></td> <td style="text-align: right;">3/31/2017</td> </tr> <tr> <td></td> <td style="text-align: right;">9/30/2017</td> </tr> <tr> <td></td> <td style="text-align: right;">3/31/2018</td> </tr> <tr> <td></td> <td style="text-align: right;">3/31/2019</td> </tr> <tr> <td></td> <td style="text-align: right;">3/31/2020</td> </tr> <tr> <td></td> <td style="text-align: right;">3/31/2021</td> </tr> <tr> <td></td> <td style="text-align: right;">3/31/2022</td> </tr> <tr> <td></td> <td style="text-align: right; border-bottom: 1px solid black;">3/31/2023</td> </tr> </table>	Final Protocol Submission:	05/31/2014	Study/Trial Completion:	05/31/2024	Final Report Submission:	07/31/2024	Other: Interim Reports:	3/31/2015		9/30/2015		3/31/2016		9/30/2016		3/31/2017		9/30/2017		3/31/2018		3/31/2019		3/31/2020		3/31/2021		3/31/2022		3/31/2023
Final Protocol Submission:	05/31/2014																														
Study/Trial Completion:	05/31/2024																														
Final Report Submission:	07/31/2024																														
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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Generalized lipodystrophy is a rare disorder characterized by the loss of body fat. As the hormone leptin is primarily produced by fat tissue, patients with generalized lipodystrophy are leptin deficient. As a consequence of a lack of adequate storage depots for body fat (and resultant ectopic deposition of fat in tissues such as muscle and liver), as well as leptin deficiency, patients with generalized lipodystrophy often develop life-threatening co-morbidities such as insulin-dependent diabetes mellitus and acute pancreatitis from extreme hypertriglyceridemia. Myalept (metreleptin) was granted orphan drug designation for the treatment of lipodystrophy. Known and potential safety concerns include serious adverse sequelae due to the development of neutralizing antibodies [loss of endogenous leptin activity (e.g., severe infections), worsening of metabolic disease], T-cell lymphoma / other malignancies, autoimmune disorders (e.g., autoimmune hepatitis, membranoproliferative glomerulonephritis), hypersensitivity reactions, pancreatitis, hepatic adverse events, and hypoglycemia. Given the small population affected by this disorder (less than ~1 in a million) and limitations in the conduct of the clinical trials, enhanced pharmacovigilance is required to generate additional data to better assess risks related to the long-term use of the drug in this patient population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The paucity of long-term safety data on Myalept (metreleptin) remains a concern. Because of the rarity of lipodystrophy, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Myalept (metreleptin) is limited. In addition, the obesity development program was discontinued. Myalept (metreleptin) pre-clinical and clinical development programs revealed known and potential serious risks associated with its use including serious adverse sequelae due to the development of neutralizing antibodies [loss of endogenous leptin activity (e.g., severe infections) and loss of efficacy (e.g., increases in triglycerides, worsening diabetes mellitus)], autoimmune disorders (e.g., autoimmune hepatitis, membranoproliferative glomerulonephritis), hypersensitivity reactions, pancreatitis, hepatic adverse events, and hypoglycemia. The goal of the enhanced pharmacovigilance study is to gather additional data to better assess risks related to the long-term use of the drug. The study will continue for a period of 10 years from the date of approval.

Although the AEs of concern will be monitored in the registry PMR, since registry participation is voluntary, enrollment may be poor and there is no assurance that it will always provide results that are generalizable to the entire patient population. Enhanced pharmacovigilance (ePV) is designed to provide more detailed information for better description of the clinical phenotypes or clinical characterization of the cases; it is especially important for rare outcomes because it covers reports from all sources. Additionally, ePV studies could provide a good numerator for describing reporting rates in the context of drug exposure data should reliable measures of exposure be available. Therefore ePV would complement the registry study to assess risks related to long term use of Myalept (metreleptin) in this patient population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

X Assess a known serious risk related to the use of the drug?

X Assess signals of serious risk related to the use of the drug?

X Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

X Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The enhanced pharmacovigilance program will include the following:

a) Active query of reporters to obtain additional clinical information related to reports of serious infections resulting in hospitalization or death, new diagnoses of autoimmune disorders (for instance autoimmune hepatitis, lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, glomerulonephritis), autoimmune disease exacerbation, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes, fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, and all deaths (including causes of death) regardless of indication for 10 years from the date of last patient's enrollment in patients treated with Myalept (metreleptin). The sponsor should actively query reporters for the following information:

(i) For reports of malignancy: patient age, gender, and race (if available), cancer site, timing and duration of Myalept (metreleptin) exposure in relation to diagnosis, concomitant medications administered/pathology reports/supportive procedures and other risk factors for the specific cancer, preferably source documents, malignancy stage and findings that support the stage (if applicable).

(ii) For reports of infections, immune-mediated reactions (such as SLE, rheumatoid arthritis, glomerulonephritis, vasculitis, autoimmune hepatitis etc.) and serious hypersensitivity reactions: nature of the event, supporting laboratory data, timing and duration of Myalept (metreleptin) exposure, and other risk factors

(iii) For reports of pancreatitis /hepatic abnormalities: liver/pancreas-related laboratory (including viral serology for hepatic events), imaging (e.g. CT, ultrasound, MRCP or ERCP); biopsy and pathology results, duration of Myalept (metreleptin) exposure, preferably source documents, and other risk factors for pancreatic/hepatic abnormalities

(iv) For reports of pregnancy, the sponsor should actively query reporters for comorbid conditions, concomitant medication use, other relevant exposures (smoking, alcohol), duration of Myalept (metreleptin), action taken with Myalept (metreleptin) and the week of gestation at which the action was taken, and the outcome of the pregnancy.

b) Expedited reporting to FDA of all initial and follow-up reports of all adverse events listed above. Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period. The annual summary and analysis will also include pertinent findings from ongoing or newly analyzed clinical trials and findings from the published medical literature

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - X Other (provide explanation)
Enhanced pharmacovigilance program
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

X Other

The Sponsor agrees to provide the requested assessments and analyses within the Periodic Benefit Risk Evaluation Report (PBRER), Section 16- SIGNAL AND RISK EVALUATION based on the International Birth Date 24-March-2013 (Japan).

The Sponsor agrees to provide PBRERs every 6 months for the first three (3) years following FDA approval and then annually thereafter.

The Sponsor agrees to report adverse events of special interest as listed in the PMR regardless of expectedness following 15-day expedited reporting timeline.

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
 - X Are the objectives clear from the description of the PMR/PMC?
 - X Has the applicant adequately justified the choice of schedule milestone dates?
 - X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

X *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template: PMR #6 - HCP method validation

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

BLA # 125390
Product Name: Myalept (metreleptin)

PMR#6 Description: To determine the approximate percent of potential impurities derived from the *E. coli* cell line used to manufacture metreleptin that are detected by the ELISA to assess for host cell proteins (HCP) in metreleptin drug substance using a sensitive and discriminating assay such as 2D gel electrophoresis to detect impurities that can lead to increased immunogenicity. If the currently validated assay does not detect a majority of proteins distributed evenly throughout a 2D gel electrophoresis or equivalent method, then a new assay to detect HCP will be developed, validated, and implemented. If the current assay provides adequate HCP detection then a protocol for qualification of new HCP kits will be developed, validated, and implemented. The revised specifications together with supporting information will be submitted to your BLA in accordance with 21 CFR 601.12.

PMR#1 Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 05/31/2014
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- X Unmet need
- X Life-threatening condition
- X Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- X Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. Adipose tissue is the main source of leptin in humans, although other cells, such as cells of the immune system, also produce leptin. The development of neutralizing antibodies was linked to loss of efficacy and/or loss of endogenous leptin activity in at least five patients receiving metreleptin treatment. Three of those patients are in the obese population in which metreleptin will be contraindicated. Peak neutralizing antibody responses were reported at the time when the following adverse events were observed: worsening glycemic control, hypertriglyceridemia, and / or excessive weight gain. Host cell proteins can act as adjuvants to increase the immunogenicity of co-administered proteins. As (1) the manufacturing process for this product is well controlled, (2) this is a rare life threatening disease, (3) the majority of lipodystrophy patients did not show clinical sequelae because of neutralizing antibody responses, and (4) distribution of this drug will be limited to generalized lipodystrophy patients, this can be a post-marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The current commercial ELISA uses an anti-HCP antibody that claims detection of 74% of the antigen pool from the substrate strain of *E. coli* used in the manufacture of metreleptin drug substance (DS) but no data to support this level of coverage by the antiserum has been provided. Moreover, during the prior approval inspection, data were reviewed that indicated the ELISA does not provide adequate coverage of the *E. coli* antigen pool for the specific cell line used to manufacture metreleptin. The sponsor did not perform adequate qualification of the commercial anti-HCP antiserum using a sensitive and discriminating method (e.g. 2Dimensional gels) to provide meaningful evaluation of the percentage of host cell proteins the assay is able to identify. The aim of this PMR is to prevent the release of DS lots with potentially high *E. Coli* derived proteins. Although the sponsor has a consistent manufacturing process and the current ELISA to detect HCP is adequate to detect HCP under routine conditions of operation, it is not clear that the assay can detect changes to HCP content when there are planned or unplanned manufacturing deviations. As this is a rare life threatening disease, the manufacturing process is well controlled, and an HCP assay is being used, this can be done as a post-marketing requirement.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

X Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

X Other (provide explanation)

This PMR is for evaluation of a method used to detect impurities that can lead to increased immunogenicity.

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

X Other

The Sponsor agrees to implement a protocol for qualification of new HCP kits. This protocol will include comparative testing by the validated HCP ELISA. This protocol will also include a determination of the approximate percent of potential protein impurities derived from the E. coli cell line used to manufacture metreleptin that are detected by the ELISA to assess for host cell proteins (HCP) in metreleptin drug substance using a sensitive and discriminating characterization method such as 2D gel.

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template: PMR # 7- BWFI-DP-In use stability

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

BLA # 125390
Product Name: Myalept (metreleptin)

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

PMR/PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 11/30/2014
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. Adipose tissue is the main source of leptin in humans, although other cells, such as cells of the immune system, also produce leptin. The development of neutralizing antibodies was linked to loss of efficacy and/or loss of endogenous leptin activity in five patients receiving metreleptin treatment. Three of those patients are in the obese population in which metreleptin will be contraindicated.

Metreleptin can be reconstituted in WFI for a single use or in WFI containing 0.9% benzyl alcohol (BFWI) to allow for multiple doses over a period of up to 3 days. Reconstitution with BFWI results in a consistent increase in oligomer content that may contribute to the development of anti drug antibodies. However, BFWI has been the sole diluent for metreleptin since 2007 to allow for multi-dose use of metreleptin in clinical trials. As such, the safety and efficacy profile of metreleptin reconstituted in BFWI is well characterized. Therefore, additional data confirming the in use stability of metreleptin after reconstitution in BFWI can be provided as a post marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

When metreleptin is reconstituted in BWFI, a (b) (4) is observed. The data provided in the submission to support the 3 day in-use stability of Myalept after reconstitution with BWFI derives from studies using only one lot of metreleptin (Lot 941352F) that show a further increase of approximately (b) (4) for 3 days . Because the presence of protein aggregates poses a safety concern (potential immunogenicity) the Sponsor is asked to provide data derived from additional drug product lots to confirm the proposed 3 days in use stability of metreleptin reconstituted BWFI.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor agrees to confirm the in-use stability of metreleptin drug product (DP) reconstituted in bacteriostatic water for injection containing 0.9% benzyl alcohol (BWFI) with data derived from three additional DP lots.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

XOther

The Sponsor agrees to confirm in-use stability of metreleptin drug product (DP) reconstituted in bacteriostatic water for injection containing 0.9% benzyl alcohol (BFWI) with data derived from three lots (the three drug product process validation lots).

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

XThis PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC) - PMC#1-WCB method

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125390
Product Name: Myalept (metreleptin)

PMC #1 Description: To develop, validate, and implement a suitable assay for the assessment of the genetic stability of metreleptin Working Cell Bank (WCB).

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 04/30/2015
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. As this is a rare life threatening disease, the manufacturing process for metreleptin is well controlled, and a method is already in place to control for WCB genetic stability, this can be a post-marketing requirement.

2. Describe the particular review issue and the goal of the study.

A high variability in the number of retained plasmid copy numbers in metreleptin WCB was observed during the review of this application. This variability was attributed to inadequacies in the method used for testing (Quantitative Fluorescence Polymerase Chain reaction, QF-PCR). Thus, a suitable method should be developed, validated, and implemented to provide more accurate data on WCB stability when the sponsor is qualifying new WCBs.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
 Assay
 Sterility
 Potency
 Product delivery
 Drug substance characterization
 Intermediates characterization
 Impurity characterization
 Reformulation
 Manufacturing process issues
 Other

Describe the agreed-upon study:

The sponsor will develop, validate, and implement a new assay for assessing the genetic stability of WCBs.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
 Are the objectives clear from the description of the PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

XThis PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC) - PMC#2 - qPCR Ecoli DNA detection

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125390
Product Name: Myalept (metreleptin)

PMC #2 Description: To develop, validate, and implement the quantitative Polymerase Chain Reaction (qPCR) method to detect *E.coli* DNA impurities in drug substance lots. Information demonstrating successful additional validation of the current method may be provided in lieu of developing, validating, and implementing a new method. The revised specification together with the validation information will be submitted to your BLA in accordance with 21 CFR 601.12.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 02/28/2015
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism complications include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. The qPCR method used to specifically detect *E. coli* DNA impurities was not adequately validated. Therefore, this method needs additional validation. As generalized lipodystrophy is a rare life threatening disease, the manufacturing process is well controlled, and a method is in place to assess for *E. coli* DNA, this can be a post-marketing commitment.

2. Describe the particular review issue and the goal of the study.

The assay validation exercise was not performed as needed to ensure that the assay method performs as expected. Deficiencies in the method validation exercise are noted below:



To avoid this artifact, each PCR run should include a validated *E.coli* DNA standard curve in order to extrapolate the sample/control Ct values to determine the DNA content of the individual reactions.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

This PMC is to develop, validate and implement a new method to detect host cell DNA or provide information showing that the current method was successfully validated.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?

- X Has the applicant adequately justified the choice of schedule milestone dates?
 - X Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- X *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)-PMC#3-DP specification limits

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125390
Product Name: Myalept (metreleptin)

PMC #3 Description: To revise Myalept drug product (DP) release and stability specifications acceptance limits for: purity and impurities by reverse phase-high performance liquid chromatography RP-HPLC, metreleptin content by ultra-violet (UV) Spectrophotometry and potency using water for injection (WFI) as diluent and total oligomer content after reconstitution with bacteriostatic WFI containing 0.9% benzyl alcohol (BWFI). Data collected from 20 production scale Myalept DP lots and knowledge about the clinical importance of product quality attributes will be used to justify the revised acceptance criteria. The revised specifications together with supporting information will be submitted to your BLA in accordance with 21 CFR 601.12.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 06/30/2019
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. This is a rare life threatening disease, the manufacturing process is well controlled and release specifications acceptance criteria are already in place. Data from more lots that are not available at the time of approval are needed, and this can be done as a post-marketing commitment.

2. Describe the particular review issue and the goal of the study.

] A limited number of DP lots manufactured with the proposed commercial process were available at the time of submission to support the selected acceptance criteria for DP release and stability testing. Therefore, the Sponsor is asked to revise the proposed specifications after enough drug product lots are manufactured with the approved commercial process to allow for acceptance criteria to be set based on clinical and manufacturing experience. Revision of the specifications will ensure that the manufacturing process is controlled and consistently delivers a product of the expected quality. The existence of sufficient clinical experience using drug product derived from comparable manufacturing processes, allows approval.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The Sponsor agrees to revise metreleptin drug product (DP) release and stability specifications acceptance limits for: purity and impurities by reverse phase-high performance liquid chromatography (RP-HPLC), metreleptin content by ultra-violet (UV) spectrophotometry, potency using water for injection (WFI) as diluent, and total oligomer content after reconstitution with bacteriostatic WFI containing 0.9% benzyl alcohol (BWFI). The data provided to the BLA for these attributes includes a minimum of 12 clinical lots and includes 2 production scale Myalept DP lots (2 process validation lots). The Sponsor agrees to revise these specifications when data has been collected from twenty (20) production scale Myalept DP lots.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC): PMC#4- DP-SVP's

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA #	125390
Product Name:	Myalept (metreleptin)
PMC #4 Description:	To characterize subvisible particles (SVPs) in the (b) (4) size range in metreleptin drug product for release, stability, and under forced or stressed degradation conditions. Results of these studies will be used to assess the risk of SVPs to patients and propose an appropriate strategy for controlling SVP.
PMC Schedule Milestones:	Final Protocol Submission: _____ Study/Trial Completion: _____ Final Report Submission: <u>06/30/2017</u> Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. The development of neutralizing antibodies was linked to loss of efficacy and/or loss of endogenous leptin activity in five patients receiving metreleptin treatment. SVPs are considered a potential critical quality attribute (CQA) given their theoretical impact on the immunogenicity of therapeutic proteins. Therefore, SVPs should be characterized on release and stability and an appropriate control strategy should be developed based on the results of the characterization studies. Specifications are in place to monitor SVPs smaller than (b) (4). Since the risk of SVP in the (b) (4) range is theoretical, this is a rare life threatening disease, and the majority of lipodystrophy patients did not show clinical sequelae because of neutralizing antibody responses, this can be a post-marketing commitment.

2. Describe the particular review issue and the goal of the study.

The applicant has not developed a method or provided any information on the presence of SVPs in metreleptin DP at release or under stability conditions. The studies would allow the sponsor to assess the risk of SVP to patient safety and determine an appropriate regulatory strategy for controlling this CQA.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The Sponsor agrees to characterize subvisible particles (SVPs) in the (b) (4) size range in metreleptin drug product for release, stability, and under forced or stressed degradation conditions.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)-PMC#5- Two tiered RM protocol

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125390
Product Name: Myalept (metreleptin)

PMC #5 Description: To develop a two-tiered reference material (RM) system comprised of a primary and working RMs that are representative of clinical trial and production material. The working RM will be used for testing of production lots and will be calibrated against the primary reference material.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 03/31/2015
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. As this is a rare life threatening disease, the manufacturing process is well controlled, and an appropriate working RM is currently available, this can be a post-marketing commitment.

2. Describe the particular review issue and the goal of the study.

Development of a two-tiered RM system with a primary RM used to calibrate the working RM and working RMs used in the testing of production lots helps prevent drift in product quality over time because all working RMs are calibrated against the same RM rather than the previous working RM. The establishment of a two tiered RM system is advocated in ICH Q6B "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological products". This PMC provides for the development of a two tiered reference material system as described in ICH Q6b "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological products". The sponsor currently has a single reference material, which is not consistent with guidance.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The Sponsor agrees to develop a two-tiered reference material (RM) system comprised of a primary and working RMs that are representative of clinical trial and production material. The working RM will be used for testing of production lots and will be calibrated against the primary

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)-PMC#6-Extractables and Leachables

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125390
Product Name: Myalept (metreleptin)

PMC #6 Description: To assess the impact of drug product container closure extractables and leachables on product quality, by (1) determining the extractable substances of both the stopper and vials containing reconstituted drug product (b) (4) and (2) providing detailed data (number of tested vials, method description) on leachable studies to support the summary results in Table 4a-1, submitted on November 7, 2013, as part of your response to the FDA information requests (IR) sent on October 8, 2013. The drug product should be reconstituted in the presence and absence of benzyl alcohol to conduct these studies.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 05/31/2018
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Metreleptin is a replacement therapy for treating the complications of generalized lipodystrophy. Generalized lipodystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have dysregulated metabolism; complications may include insulin resistance and very high serum triglycerides. This can lead to difficult to control diabetes mellitus, pancreatitis, and premature death. Compounds can leach from primary container closures and impact drug product quality. The leachables and extractables assessments and data provided by the sponsor were inadequate because they were incomplete. As lipodystrophy is a rare life threatening disease, the manufacturing process is well controlled, and stability data provided to date indicate that the product is stable in the primary container closure, this study can be performed as a post marketing commitment.

2. Describe the particular review issue and the goal of the study.

Extractable studies on the reconstituted drug product are needed to assess (1) additional potential leachables that were not detected in the studies performed by the rubber stopper manufacturer on this container closure part, and (2) interference of the drug product on the sensitivity of the analytical method. Drug Product vials were reconstituted with BWFI (b) (4) the presence of leachables. However the detailed data (number of vials, method description) that support the summarized results included in table 4a-1 of the sponsor's response to the FDA Information Request letter dated October 8, 2013. A study of extractable substances from the reconstituted drug product (b) (4) (in the presence and absence of benzyl alcohol) should be provided together with the above requested data on leachables as part of a post-marketing commitment.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

This study is to perform extractables testing using the (b) (4) that is used for drug product and using drug product. This is FDA's standard expectation for extractables testing because it provides the most relevant information. Further, the sponsor provided results from assessments, in which (b) (4) were used that were performed by container closure manufacturers. However they did not provide the details of the assessments so we could not fully review them. The sponsor is asked to provide that information.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

APPEARS THIS WAY ON ORIGINAL



PMR/PMC Development Template: Product Quality (CMC)-PMC #7*-Minimum leak size

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125390
Product Name: Myalept (Metreleptin)

PMC #7 Description: To perform studies to determine the minimum leak size detectable by the dye and microbial ingress container closure integrity test methods. The final report will be submitted to the BLA in accordance with 21 CFR 601.12.

PMC Schedule Milestones: Final Protocol Submission: N/A
Study/Trial Completion: N/A
Final Report Submission: 12/31/2014
Other: N/A

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

As detailed below in item 2, the Sponsor is being requested to perform studies to determine the minimum detectable leak size (perforation diameter) using the dye and microbial ingress test for the Myalept container closure system. This value was not established during the validation studies submitted with the original BLA. In Amendment 125390/0.56, the Sponsor stated that completion of the requested studies within the review period was not possible, and that they were willing to conduct them as a PMC. A commitment was submitted 1/21/2014 in Amendment 125390/0.60.

2. Describe the particular review issue and the goal of the study.

During performance of the dye and microbial ingress validation studies for container-closure integrity, the Sponsor did not determine the minimum detectable leak size. Without knowledge of method sensitivity, the validity of the container integrity studies cannot be properly assessed. The goal of the requested studies will be to determine the minimum leak size detectable by the dye and microbial ingress methods. The dye and microbial ingress methods are described in protocol TM-0362.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor agrees to perform supplemental studies to determine the minimum container closure leak size detectable by the dye and microbial ingress assays. These studies will be performed by breaching the Metreleptin drug product stopper with controlled (b) (4) to a (b) (4), and determining leakage by the dye ingress assay described in TM-0372. In addition, the sponsor will develop and validate a microbial ingress method using controlled (b) (4), and determine leakage by microbial ingress. The final report will be submitted to the BLA in accordance with 21 CFR 601.12.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

[Microbiology Quality PMCs Continued Next Page]

PMR/PMC Development Template: Product Quality (CMC)-PMC #8- LAL endotoxin assay

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125390
Product Name: Myalept (Metreleptin)
PMC #8 Description: To verify the reliability of the LAL endotoxin assay by conducting endotoxin spiking studies with three undiluted drug product lots. The drug product lots will be spiked with endotoxin levels close to the specification acceptance criterion, and held for up to 8 days before being assayed. The final report will be submitted to the BLA in accordance with 21 CFR 601.12.

PMC Schedule Milestones:

Final Protocol Submission:	N/A
Study/Trial Completion:	N/A
Final Report Submission:	12/31/2014
Other:	N/A

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

As detailed below in item 2, the Sponsor is being requested to perform studies to verify whether endotoxin levels can be reliably determined in Metreleptin drug product by the LAL method. The data provided to date indicate that the Metreleptin formulation does not inhibit the LAL test if the assay is conducted within an 8 day period, but further studies with additional drug product lots and lower endotoxin spike levels are necessary to verify method reliability. In Amendment 125390/0.60 the Sponsor stated that these studies could not be completed until May, 2014, i.e., until 3 months after the PDUFA goal date of 2/24/2014.

2. Describe the particular review issue and the goal of the study.

1] The Metreleptin drug product formulation contains excipients (e.g., polysorbate) that could result in low endotoxin recovery (LER). In Amendment 125390/0.59 the Sponsor provided data suggesting that the LER phenomenon does not occur with Metreleptin DP when measurement is conducted by the LAL method over time points ranging from 0 to 8 days. However, the studies were conducted with only one drug product lot and with one endotoxin spike level ((b) (4)). The goal of the study will be to verify method reliability with 3 additional drug product lots using endotoxin spike concentrations closer to the acceptance criterion of (b) (4) .

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor agrees to perform endotoxin spike recovery experiments with three lots of drug product. The endotoxin spikes will be added at the specification level (b)(4) and at least (b)(4) the specification level. The hold time studies will be between 0 hours and 8 days. The final report will be submitted to the BLA in accordance with 21 CFR 601.12.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

SUCHITRA M BALAKRISHNAN
02/23/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

DATE: January 21, 2013
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Patricia Madara, Regulatory Project Manager, CDER/OND/ODEII/DMEP
SUBJECT: **BLA 125390**
Applicant: BristolMyers Squibb
Device Constituent: vial and syringe
Drug Constituent: Myalept
Intended Treatment: metabolism disorder associated with lipodystrophy including
hypertriglyceridemia and/or diabetes mellitus
CDRH CTS Tracking No. 1400014

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

Submission No.: BLA 125390

Applicant: BristolMyers Squibb

Device Constituent: vial and syringe

Drug Constituent: Myalept

Intended Treatment: metabolism disorder associated with lipodystrophy including hypertriglyceridemia and/or diabetes mellitus

CDRH CTS Tracking No. 1400014

CDRH Human Factors Involvement History

- 12/20/2013: CDRH HF was requested to perform review human factors study results.
- 1/21/2014: CDRH HF provided review comments to CDER.

Overview and Recommendation

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, requested CRH Human Factors consultative review of the human factors study report submitted under BLA 125390 by BristolMyers Squibb for Myalept drug product to be used along with a vial and a syringe. Note that the Sponsor referenced an approved protocol RESPL110098, but this protocol was not reviewed by CDRH HF.

The report indicated that the study was designed to evaluate the Instructions for Use (IFU). The study included two sessions: the first session was to provide training to study participants, and the second session was to evaluate participants using the IFU and the devices. The Sponsor identified four critical use steps because if one of these steps was incomplete, a patient would not be able to successfully administer an accurate dose. These four steps are: (1) fill the 3mL syringe with 2.2 mL diluent, without any air pockets or large bubbles, (2) mix liquid and powder together to yield a clear, colorless solution without clumps, dry powder or foam, (3) draw medicine into syringe to the assigned dose line (0.75mL) without air pockets or large bubbles, (4) deliver dose of medication. The study also simulated the use of a customer call center, where study participants could request for assistance while they performed hands-on tasks. The study results showed that of the 93 participants, 14 participants did not complete the injection, and 2 completed with assistance. The following table provides a breakdown of the study results for the critical steps that were assessed:

Usability Study Element	Total (N=93)		
	Completed w/o assistance N (%)	Completed with assistance N (%)	Incomplete N (%)
Fill the mixing syringe with 2.2 mL of diluent, without any air pockets or large bubbles (step 2i in the IFU)	83 (89%)	1 (1%)	9 (10%)
Mix liquid and powder together (step 3c in the IFU)	91 (98%)	1 (1%)	1 (1%)
Draw medicine into syringe to the assigned dose line, without any air pockets or large bubbles (step 4i in the IFU)	85 (91%)	0	8 (9%)
Deliver dose of medication (step 5c in the IFU)	93 (100%)	0	0

The consultant needs additional information to complete this review. The additional information should address the following concerns:

- The study report did not provide a clear description of the study participants, and how they are representative of the actual users.
- The report stated that the participants were instructed to simulate dose administration using an injection aid once a dose was prepared. The report was not clear on how the dose was prepared, and whether the preparation was performed by study participants.
- The report also stated that the vial was warmed to ambient temperature as directed in the IFU in advance of participant testing. The consultant was unclear whether this represented a critical task or a knowledge based task, and why it was not evaluated in the study.
- The report did not clarify whether the use of the customer call center is representative of actual use.
- The study results appeared to be incomplete because only objective data were provided in the report. The consultant needs to review the subjective data, i.e. interviewed data from test participants on all incomplete injections, and to review the Sponsor's analysis of the data to determine the root cause of these incomplete injections. The report did not describe whether additional device and/or IFU modifications were made to address the incomplete injections.

Please transmit the following deficiencies to the Sponsor:

We have reviewed your Human Factors/Usability report included in Appendix D. We typically do not review a study report that is designed to determine the effectiveness of the Instructions for Use. We expect to review a study report where representative users performing essential and critical tasks associated with the use of the proposed product, and that the IFU is made available to study participants so that they can refer to the IFU as they desire during the course of using the product. In addition, we cannot review your study report without an accompanying use-related risk analysis. To complete our review, please address the following:

1. The study report did not provide a clear description of the study participants, and how they are representative of the actual users. Please provide this information.
2. The report stated that the participants were instructed to simulate dose administration using an injection aid once a dose was prepared. The report was not clear on how the dose was prepared, and whether the preparation was performed by study participants. Please clarify.
3. The report also stated that the vial was warmed to ambient temperature as directed in the IFU in advance of participant testing. The report did not specify whether this represented a critical task or a knowledge based task, and why it was not evaluated in the study. Please clarify.
4. The report did not specify whether the use of the customer call center is representative of actual use. Please clarify.
5. The study results appeared to be incomplete because only objective data were provided for review. Please submit the subjective data, i.e. interviewed data from test participants on all incomplete injections and your analysis of the data to determine the root cause of these incomplete injections. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. The report did not describe whether additional device and/or IFU modifications were made to address the incomplete injections. The report also did not indicate whether the modifications were validated to ensure that the modifications are effective and do not introduce new problems. Please address the concerns.
6. Please submit a use-related risk analysis. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies.

Appendix 1: Device Related Information

The following proprietary information was obtained from the submission.

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/s/

PATRICIA J MADARA

02/21/2014

Added to DARRTS and signed for CDRH reviewer, Quynh Nhu Nguyen



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review Addendum

DATE: February 3, 2014
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Patricia Madara, Regulatory Project Manager, CDER/OND/ODEII/DMEP
SUBJECT: **BLA 125390**
Applicant: BristolMyers Squibb
Device Constituent: vial and syringe
Drug Constituent: Myalept
Intended Treatment: metabolism disorder associated with lipodystrophy including
hypertriglyceridemia and/or diabetes mellitus
CDRH CTS Tracking No. 1400014

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

Submission No.: BLA 125390

Applicant: BristolMyers Squibb

Device Constituent: vial and syringe

Drug Constituent: Myalept

Intended Treatment: metabolism disorder associated with lipodystrophy including hypertriglyceridemia and/or diabetes mellitus

CDRH CTS Tracking No. 1400014

CDRH Human Factors Involvement History

- 12/20/2013: CDRH HF was requested to perform review human factors study results.
- 1/21/2014: CDRH HF provided review comments to CDER.
- 2/3/2014: CDRH HF provided review addendum that contains outstanding deficiencies.

Overview and Recommendation

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, requested CRH Human Factors consultative review of the human factors study report submitted under BLA 125390 by BristolMyers Squibb for Myalept drug product to be used along with a vial and a syringe. Note that the Sponsor referenced an approved protocol RESPL110098, but this protocol was not reviewed by CDRH HF.

CDRH HF provided a consult review to CDER on 1/21/2014. CDRH HF recommended that the following comments be communicated to the Sponsor:

We have reviewed your Human Factors/Usability report included in Appendix D. We typically do not review a study report that is designed to determine the effectiveness of the Instructions for Use. We expect to review a study report where representative users performing essential and critical tasks associated with the use of the proposed product, and that the IFU is made available to study participants so that they can refer to the IFU as they desire during the course of using the product. In addition, we cannot review your study report without an accompanying use-related risk analysis. To complete our review, please address the following:

1. The study report did not provide a clear description of the study participants, and how they are representative of the actual users. Please provide this information.
2. The report stated that the participants were instructed to simulate dose administration using an injection aid once a dose was prepared. The report was not clear on how the dose was prepared, and whether the preparation was performed by study participants. Please clarify.
3. The report also stated that the vial was warmed to ambient temperature as directed in the IFU in advance of participant testing. The report did not specify whether this represented a critical task or a knowledge based task, and why it was not evaluated in the study. Please clarify.
4. The report did not specify whether the use of the customer call center is representative of actual use. Please clarify.
5. The study results appeared to be incomplete because only objective data were provided for review. Please submit the subjective data, i.e. interviewed data from test participants on all incomplete injections and your analysis of the data to determine the root cause of these incomplete injections. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. The report did not describe whether additional device and/or IFU modifications were made to address

the incomplete injections. The report also did not indicate whether the modifications were validated to ensure that the modifications are effective and do not introduce new problems. Please address the concerns.

6. Please submit a use-related risk analysis. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies.

CDER Division of Medication Error and Prevention Analysis (DMEPA) was asked to provide concurrence to the above deficiencies. DMEPA clarified that the report contained specific information that can be used to address some of the above deficiencies. The following section provides DMEPA's comments regarding the above deficiencies (email dated 1/22/2014 from Yelena Maslov):

1. The study report did not provide a clear description of the study participants, and how they are representative of the actual users. Please provide this information. (p.10 of the HF Factors report). Page 11 provides Table with patient demographics

The demographic attributes designed for this Usability study were based on the anticipated demographics of metreleptin users. (p.10 of the HF Factors report). Page 11 provides Table with patient demographics

2. The report stated that the participants were instructed to simulate dose administration using an injection aid once a dose was prepared. The report was not clear on how the dose was prepared, and whether the preparation was performed by study participants. Please clarify.

The way I read the report, I could infer that the participants performed the steps of preparation and simulated injection given the results and critical steps of the report. For example: The participant then used the IFU to prepare a dose for simulated self-administration while the facilitator observed and coached. (p.7). Participants were observed, with no proactive facilitator discussion, for their ability to perform each of the fundamental steps required for accurate dose preparation and administration. The dose selected, 0.75 mL, was intended to require study participants to draw to a less prominent mark on the syringe, thereby allowing a thorough assessment of the IFU content and its ability to provide clear direction on this fundamental step. The 4 (*four*) fundamental steps to prepare and administer an accurate dose included:

- Fill the 3 mL syringe with 2.2 mL of diluent, without any air pockets or large bubbles (Step 2i in the IFU)
- Mix liquid and powder together, to yield a clear, colorless solution without clumps, dry powder or foam (Step 3c in the IFU)
- Draw medicine into syringe to the assigned dose line (0.75 mL), without any air pockets or large bubbles (Step 4i in the IFU)
- Deliver dose of medication (Step 5c in the IFU)

3. The report also stated that the vial was warmed to ambient temperature as directed in the IFU in advance of participant testing. The report did not specify whether this represented a critical task or a knowledge based task, and why it was not evaluated in the study. Please clarify.

I agree with this finding as well.

4. The report did not specify whether the use of the customer call center is representative of actual use. Please clarify.

I also agree, but I think I assumed that the use of customer call center represents the actual use due to the following statement from the HF study: The study facilitator provided a standardized response to

the question using only the IFU in a manner similar to what the Customer Support Center would be expected to provide.

5. The study results appeared to be incomplete because only objective data were provided for review. Please submit the subjective data, i.e. interviewed data from test participants on all incomplete injections and your analysis of the data to determine the root cause of these incomplete injections. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. The report did not describe whether additional device and/or IFU modifications were made to address the incomplete injections. The report also did not indicate whether the modifications were validated to ensure that the modifications are effective and do not introduce new problems. Please address the concerns.

I agree objective data does not appear to be in the report. However, modifications to the IFU are described on pages 14, 15, and 16.

6. Please submit a use-related risk analysis. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies.

I agree. The Applicant did not provide the responses to these questions. In our review, we evaluated these risks based on the clinical information known about the product.

This consultant realized that the report that was provided along with the consult request was incomplete because it did not contain the information that as referenced in the 1/22/2014 email from DMEPA. The complete report was then provided on 1/28/2014. Review of the complete report indicated that some of CDRH HF original deficiencies were resolved. In particular, the report included information about patient demographic and post-study modifications that were made to the IFU. As a result, the consultant finds following deficiencies remain unaddressed, and they should be communicated to the Sponsor:

We have reviewed your Human Factors/Usability report included in Appendix D. We typically do not review a study report that is designed to determine the effectiveness of the Instructions for Use. We expect to review a study report where representative users performing essential and critical tasks associated with the use of the proposed product, and that the IFU is made available to study participants so that they can refer to the IFU as they desire during the course of using the product. In addition, we cannot review your study report without an accompanying use-related risk analysis. To complete our review, please address the following:

1. The report stated that the vial was warmed to ambient temperature as directed in the IFU in advance of participant testing. The report did not specify whether this represented a critical task or a knowledge based task, and why it was not evaluated in the study. Please clarify.
2. The report did not specify whether the use of the customer call center is representative of actual use. Please clarify.
3. The study results appeared to be incomplete because only objective data were provided for review. Please submit the subjective data, i.e. interviewed data from test participants on all incomplete injections and your analysis of the data to determine the root cause of these incomplete injections. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. The report did not describe whether additional device and/or IFU modifications were made to address the incomplete injections.

4. The report identified several post-study modifications made to the IFU on pages 14 and 15. Since these changes were made specifically to address failures and use errors seen with incomplete injections, we ask that you validate these changes in another simulated use study with at least 15 representative users. The study should demonstrate that the changes are effective in addressing those failures and use errors and that they do not introduce any new use-related problems.
5. Please submit a use-related risk analysis associated with the use of the device. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. There is a more recent draft guidance document that includes the current thinking on human factors at CDRH and recommended approaches to human factors evaluation and testing: Applying Human Factors and Usability Engineering to Optimize Medical Device Design: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

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/s/

PATRICIA J MADARA

02/21/2014

Signing for CDRH reviewer Quynh Nhu Nguyen

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY
PRODUCTS MEDICAL OFFICER CONSULTATION

Date: February 20, 2014
To: Julie Golden, M.D., Medical Officer, DMEP
From: Tracy Kruzick, M.D. M.P.H., Medical Reviewer, DPARP
Through: Banu Karimi-Shah, M.D., Medical Team Leader, DPARP
Through: Lydia Gilbert-McClain, M.D., Deputy Division Director, DPARP
Subject: Immunogenicity of Myalept (metreleptin) for diabetes or hyperlipidemia in subjects with lipodystrophy

General Information

BLA/IND#: BLA 125390
Sponsor: Amylin Pharmaceuticals
Drug Product: Myalept (metreleptin)
Request From: Pat Madara, RPM, DMEP
Date of Request: May 14, 2013
Date Received: May 14, 2013
Materials Reviewed: *Clinical Addendum to the Metreleptin BLA STN125390: Immunogenicity of Metreleptin in Lipodystrophy Subjects and Overweight/Obese Subjects (dated 3/27/2013)*

I. Executive Summary

This is a Medical Officer response to a request for consultation from the Division of Metabolism and Endocrinology Products (DMEP) to assist in understanding the potential clinical implications of the immunogenicity of metreleptin. The bio-analytical issues regarding immunogenicity are addressed in the review completed by the Division of Therapeutic Proteins.

Metreleptin is a recombinant analog of human leptin which is a naturally occurring hormone predominantly secreted by adipose tissue that plays a central role in the neurohormonal regulation of energy homeostasis by inhibiting appetite. The Sponsor, Amylin, has submitted a BLA 125390 for the treatment of diabetes mellitus and/or hypertriglyceridemia in subjects with lipodystrophy (not associated with HIV). Per the request of the Agency at a Type C meeting (July 11, 2012), the Sponsor has provided an immunogenicity addendum with data from clinical programs in both lipodystrophy and obesity which is reviewed here. The Sponsor is not pursuing the obesity indication.

Lipodystrophy is characterized by generalized or partial loss of adipose tissue and leptin deficiency. In lipodystrophy subjects, the profound deficiency of adipose tissue leads to accumulation of fat in the bloodstream (with resultant hypertriglyceridemia) and ectopic deposition of fat in non-adipose tissues such as liver and muscle, leading to metabolic abnormalities including insulin resistance and diabetes. By treating leptin deficiency, metreleptin improves several of these metabolic abnormalities including diabetes and hypertriglyceridemia.

In the clinical development program for lipodystrophy, 58/65 subjects (89%) developed antibodies, and 6/65 (9.2%) developed neutralizing activity. Based on this information, it is highly likely that most patients will develop antibodies, and a small portion will develop neutralizing ability. Most subjects in the lipodystrophy program who developed neutralizing antibodies experienced increased leptin levels and no loss of efficacy, similar to those with non-neutralizing antibodies. However, one subject with high neutralizing antibodies developed decreased leptin levels, decreased efficacy, and was hospitalized for sepsis multiple times. Similarly, in development programs for the obesity indication (no longer ongoing), close to 100% of subjects develop antibodies, and three subjects total developed neutralizing antibodies. These subjects experienced severely decreased leptin levels and accompanying loss of efficacy (weight gain), and in one patient, development of type II diabetes occurred, as might be expected with neutralization of leptin activity.

Alteration of leptin levels in and of itself may have clinical relevance. Leptin increases the function of Th1 lymphocytes and decreases the function of T regulatory (Treg) cells. Leptin deficient mice have been found to have an increased susceptibility to infection and a decreased susceptibility to autoimmunity.¹ Decreased leptin levels could lead to an increased risk of infection but a decreased risk of autoimmunity. Elevated leptin levels could cause the opposite to occur: a decreased risk of infection but a higher risk of autoimmunity. In addition, three cases of non-Hodgkin's lymphoma (T-cell) have been diagnosed in subjects with acquired lipodystrophy treated with metreleptin. Treg cells are involved in tumor immune-responses, although they appear to play both a positive or negative role, depending on the type of cancer. Thus, in subjects who have altered amounts of leptin due to metreleptin treatment, there is a potential risk of an alteration in immune regulation and tumor suppression activity.

Thus, this is a highly immunogenic product, with the potential to cause further leptin deficiency as well as an alteration in the susceptibility to infection, autoimmunity, and cancer. Due to the uncontrolled, open-label nature of the submitted studies, and the small number of patients treated within the clinical development program, it is difficult to draw definitive conclusions regarding safety from the clinical trial data. One can conclude that most patients will develop antibodies, but the exact potential for developing neutralizing activity and the long-term sequelae of antibody development are unknown. Ultimately, it is the risk-benefit consideration in the population in which the drug will be indicated which will determine whether the risks associated with immunogenicity are warranted. The following issues are also addressed the specific questions to DPARP in the next section.

II. Questions Submitted to DPARP

1. What is the clinical relevance of antibody formation with metreleptin therapy, and how does it apply to the lipodystrophy indication?

This product has proven to be highly immunogenic. In the clinical development program, 58/65 subjects (89%) developed antibodies, and 6/65 (9%) developed neutralizing activity. Based on this information, it is highly likely that most patients will develop antibodies, and a small portion will develop antibodies with neutralizing ability. The clinical relevance of antibody formation can only be answered in a theoretical fashion based on what is known about leptin in the literature, due to the small, uncontrolled nature of the clinical development program. Of the patients who developed

neutralizing activity, one patient experienced the expected sequelae of decreased efficacy and increased infectious complications (sepsis). Other patients did not experience decreased efficacy. The concern for patients with partial lipodystrophy, who are not completely leptin-deficient, would be the complete loss of leptin activity due to the development of antibodies. For patients who are completely leptin-deficient, this may be less of an issue, but raises the issue of whether the development of neutralizing antibody to metreleptin in the present may jeopardize responsiveness to potential future therapies. However, the clinical relevance of these risks are only hypothetical, as the design of the clinical development program precludes us from answering these questions in the context of the data.

2. What is the immunogenicity risk to a subject without a low-leptin condition – in other words, with normal or above-normal concentrations of endogenous leptin – who may be prescribed metreleptin off-label for another indication?

While it is difficult to quantify the immunogenicity risk to a subject without a low-leptin condition, the terminated obesity program raises concern that neutralizing antibodies could lead to adverse consequences for these patients. In those few subjects who developed neutralizing activity, leptin levels decreased to undetectable levels. The subjects experienced weight gain and also seemed to have higher immune-related adverse events; one patient developed type II diabetes. Once neutralizing antibodies are present, it is unknown how long they would persist. With persistent low leptin levels, these patients may experience an increased risk of infection and malignancy.

3. Given leptin's role in the immune system, are there specific safety concerns (e.g., autoimmunity, malignancy) with the use of metreleptin in subjects with autoimmune diseases (i.e., certain types of acquired lipodystrophy)?

Increased leptin levels have been associated with increased risk of autoimmunity in in vitro and in vivo models. Therefore, exacerbation of underlying autoimmune disease is of concern. In the clinical development program, there were a few adverse events that may have been autoimmune in nature (e.g., hepatitis, membranoproliferative glomerulonephritis). Theoretically, metreleptin might have played a causal role in the development of these autoimmune adverse events.

4. Do you have any recommendations for additional studies or monitoring?

With respect to recommendations for monitoring, we defer to the review of Division of Therapeutic Proteins.

5. We would like your recommendations of potential AC members with the appropriate expertise to address these issues. (We have considered the authors of a recent NEJM paper on JAKs and STATs in immunity, immunodeficiency, and cancer as potential candidates.)

These recommendations were provided during the course of the review.

III. Background

The Sponsor, Amylin, has submitted a rolling BLA 125390 for the treatment of diabetes mellitus and/or hypertriglyceridemia in subjects with lipodystrophy (not associated with HIV). The final portion of the BLA was submitted in March 2013. This is a priority review application and will go to Advisory Committee on December 11, 2013. The metreleptin clinical development program for lipodystrophy consists of 1 completed NIH study (investigator IND 60534) and 2 ongoing studies (investigator IND 60534 and treatment IND 101824). As of January 2013, 125 subjects with different types of lipodystrophy have been treated with metreleptin.

Per the request of the Agency at a Type C meeting (July 11, 2012), the Sponsor has provided immunogenicity data. These are detailed in *Clinical Addendum to the Metreleptin BLA STN125390: Immunogenicity of Metreleptin in Lipodystrophy Subjects and Overweight/Obese Subjects*. The following are provided for review:

- Antibody data from the lipodystrophy program (study FHA101 and the NIH studies 991265/20010769)
- Antibody data from 5 Amgen studies (phase 2) in overweight subjects without lipodystrophy (included as a supplemental Integrated Summary of Safety)
- Antibody data from 3 Amylin studies (phase 2) in overweight subjects without lipodystrophy

Lipodystrophy

Lipodystrophy is characterized by generalized or partial loss of adipose tissue and leptin deficiency. In lipodystrophy subjects, the profound deficiency of adipose tissue leads to accumulation of fat in the bloodstream (with resultant hypertriglyceridemia) and ectopic deposition of fat in non-adipose tissues such as liver and muscle, leading to metabolic abnormalities including insulin resistance and diabetes. By treating leptin deficiency, metreleptin improves several of these metabolic abnormalities including diabetes and hypertriglyceridemia.

The role of leptin in the immune system

Leptin is believed to serve an important role in immune system regulation. Leptin has opposite effects on T regulatory (Treg) cells and Th1 lymphocytes. In mice, leptin deficiencies are characterized by an increased number and activity of Treg cells. Leptin inhibits proliferation of Treg cells, and Treg cells secrete high amounts of leptin and its receptor in an autocrine loop, controlling their own hyporesponsiveness. Conversely, leptin stimulates Th1 lymphocytes to proliferate and release proinflammatory cytokines.

Leptin also appears to promote the phagocytic function of mouse macrophages and monocytes and stimulates their release of proinflammatory cytokines. In addition, leptin stimulates chemotaxis as well as promotes NK cell development and proliferation.

Based on these observations, a logical assumption is that leptin deficiency would cause a subsequent decrease in Th1 lymphocytes, macrophages, and NK cells leading to an increased risk of infection. Simultaneously, leptin deficiency would cause an increased number of Treg cells potentially decreasing the risk for autoimmunity. Indeed in mice, it has indeed been shown that those mice

deficient in leptin have an increased susceptibility to infection and a decreased susceptibility to autoimmunity.¹

Immunogenicity of metreleptin

Below is an overview of the relevant immunogenicity findings of studies in the *Clinical Addendum to the Metreleptin BLA STN125390: Immunogenicity of Metreleptin in Lipodystrophy Subjects and Overweight/Obese Subjects*. Of note, the leptin assay used in these studies does not distinguish between endogenous leptin and metreleptin. In addition, the Sponsor has focused closely on their assessment of neutralizing potential based on an the (b) (4) Amylin in vitro neutralizing activity assay, categorizing neutralizing activity into negative and four positive groups (A-E) based on the ability of the antibodies to neutralize metreleptin after series of dilutions. This consult focuses on neutralizing negative (Category A) versus neutralizing positive (Categories B-E) antibodies rather than on degree of neutralization.

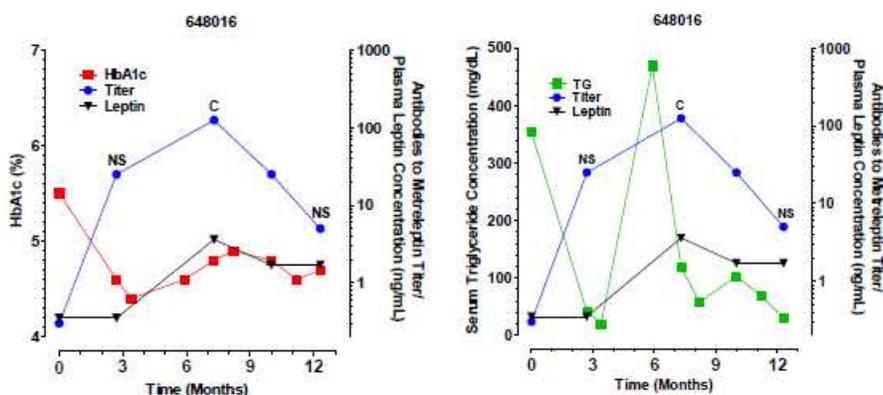
FHA101

The time to peak antibody titer ranged from 3-18 months. 21/22 subjects developed antibodies. The only subject who did not do so was on methotrexate for dermatomyositis. Of the 21 subjects who developed antibodies, 19 had no evidence of neutralizing activity. The other two subjects who did develop neutralizing antibodies are as follows:

- Subject 648016: This subject experienced fecal and urinary incontinence, abnormal liver functions tests, abdominal pain, weight loss, rash, and two events of urticaria, one of which was considered severe.
- Subject 648018: This subject experienced abdominal pain, parasthesia, injection site hematoma, cough, dizziness, fatigue, infectious mononucleosis, and lymphadenopathy.
- Subject 648019: This patient was not described in the *Clinical Addendum* but was reported in the four month safety update. Leptin initially rose then decreased, HgBA1c remained unchanged, and triglycerides increased. Antibody titers alternated between 3125 and 625 every several months.

Subjects 648016 and subject 648018 had antibody titers (125 and 625 ng/mL, respectively), HgbA1c, leptin, and triglycerides as pictured below. Overall, it appears that leptin levels increased with antibody level. Triglycerides ultimately decreased, and HgbA1c stayed at the same level or decreased.

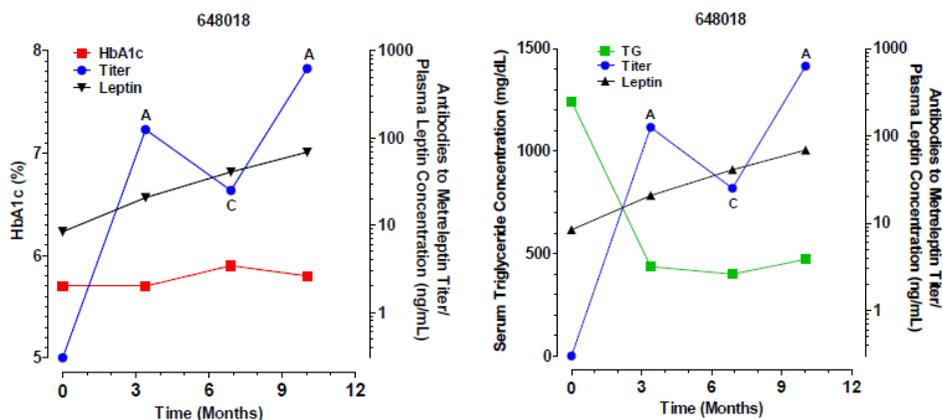
Figure 4. Titer of Binding Antibodies to Metreleptin, Leptin Concentration, and Metabolic Measurements Over Time for Patient 648016 With Category C In Vitro Neutralizing Activity Assay Result at Month 7 (Study FHA101)



TG = triglycerides; NS = non-specific; LLOQ = lower limit of quantification.
 Notes: Time (Month) represents months since the first dose of metreleptin. Time points reflect actual dates of blood sample collection, not analysis visit designations.
 - Antibody data generated using the Amylin methods as described in Sections 4.1.1.1 (binding antibody) and 4.1.1.2 (metreleptin neutralizing activity). C indicates category of in vitro neutralizing activity.
 - Plasma leptin concentration data represent endogenous leptin + circulating metreleptin. Plasma leptin concentration was ~0.7 ng/mL (below LLOQ) at baseline and Month 3.
 Cross-References: FHA101 Appendices 5.3.1, 5.4.1, and 5.6.

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Figure 5. Titer of Binding Antibodies to Metreleptin, Leptin Concentration, and Metabolic Measurements Over Time for Patient 648018 With Category C In Vitro Neutralizing Activity Assay Result at Month 7 (Study FHA101)



TG = triglycerides.
 Notes: Time (Month) represents months since the first dose of metreleptin. Time points reflect actual dates of blood sample collection, not analysis visit designations.
 - Patient 648018 was metreleptin naïve prior to starting Sandoz DS at Month 0.
 - Antibody data generated using the Amylin methods as described in Sections 4.1.1.1 (binding antibody) and 4.1.1.2 (metreleptin neutralizing activity). A, C indicate category of in vitro neutralizing activity.
 - Plasma leptin concentration data represent endogenous leptin + circulating metreleptin.
 Cross-References: FHA101 Appendices 5.3.1, 5.4.1, and 5.6.

Adverse events were found more commonly in those subjects who had antibodies (although this is difficult to assess as only one subject did not develop antibodies) as displayed in the Sponsor chart below.

Table 9. Frequent (Incidence $\geq 5\%$) Treatment-Emergent Adverse Events by Peak Titer of Treatment-Emergent Binding Antibodies to Metreleptin and Preferred Term (Study FHA101, Intent-to-Treat Patients With Antibody Data [N = 22])

Preferred Term [1]	Peak Treatment-Emergent Titer											
	Negative (N = 1)		125 (N = 6)		625 (N = 5)		3125 (N = 5)		15625 (N = 1)		Any Positive (N = 21)	
	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER
Abdominal pain	0 (0.0)	0.00	1 (16.7)	0.11	2 (40.0)	0.39	0 (0.0)	0.00	0 (0.0)	0.00	4 (19.0)	0.14
Anxiety	0 (0.0)	0.00	0 (0.0)	0.00	0 (0.0)	0.00	2 (25.0)	0.15	0 (0.0)	0.00	2 (9.5)	0.07
Back pain	0 (0.0)	0.00	0 (0.0)	0.00	1 (20.0)	0.20	1 (12.5)	0.07	0 (0.0)	0.00	2 (9.5)	0.07
Blood pressure increased	0 (0.0)	0.00	0 (0.0)	0.00	0 (0.0)	0.00	1 (12.5)	0.07	1 (100.0)	0.80	2 (9.5)	0.07
Chest pain	0 (0.0)	0.00	1 (16.7)	0.11	0 (0.0)	0.00	1 (12.5)	0.07	0 (0.0)	0.00	2 (9.5)	0.07
Cough	0 (0.0)	0.00	1 (16.7)	0.11	1 (20.0)	0.20	0 (0.0)	0.00	0 (0.0)	0.00	2 (9.5)	0.07
Dizziness	0 (0.0)	0.00	1 (16.7)	0.11	1 (20.0)	0.20	0 (0.0)	0.00	0 (0.0)	0.00	2 (9.5)	0.07
Fatigue	0 (0.0)	0.00	0 (0.0)	0.00	1 (20.0)	0.20	1 (12.5)	0.07	0 (0.0)	0.00	2 (9.5)	0.07
Headache	0 (0.0)	0.00	1 (16.7)	0.11	0 (0.0)	0.00	1 (12.5)	0.07	0 (0.0)	0.00	2 (9.5)	0.07
Hypoglycaemia	0 (0.0)	0.00	1 (16.7)	0.23	2 (40.0)	1.18	2 (25.0)	0.15	0 (0.0)	0.00	5 (23.8)	0.34
Increased appetite	0 (0.0)	0.00	1 (16.7)	0.11	0 (0.0)	0.00	1 (12.5)	0.07	0 (0.0)	0.00	2 (9.5)	0.07
Injection site haematoma	1 (100.0)	0.34	1 (16.7)	0.11	2 (40.0)	0.39	1 (12.5)	0.07	0 (0.0)	0.00	4 (19.0)	0.14
Injection site urticaria	0 (0.0)	0.00	0 (0.0)	0.00	0 (0.0)	0.00	4 (50.0)	0.30	0 (0.0)	0.00	4 (19.0)	0.14
Lymphadenopathy	1 (100.0)	0.34	1 (16.7)	0.23	1 (20.0)	0.20	1 (12.5)	0.15	0 (0.0)	0.00	3 (14.3)	0.17
Muscle spasms	0 (0.0)	0.00	0 (0.0)	0.00	0 (0.0)	0.00	3 (37.5)	0.30	0 (0.0)	0.00	3 (14.3)	0.14
Musculoskeletal pain	0 (0.0)	0.00	1 (16.7)	0.11	1 (20.0)	0.20	0 (0.0)	0.00	0 (0.0)	0.00	2 (9.5)	0.07
Myalgia	0 (0.0)	0.00	0 (0.0)	0.00	1 (20.0)	0.20	2 (25.0)	0.22	0 (0.0)	0.00	3 (14.3)	0.14
Nausea	0 (0.0)	0.00	3 (50.0)	0.34	2 (40.0)	0.39	3 (37.5)	0.45	0 (0.0)	0.00	9 (42.9)	0.12
Neuropathy peripheral	0 (0.0)	0.00	1 (16.7)	0.11	0 (0.0)	0.00	1 (12.5)	0.07	0 (0.0)	0.00	2 (9.5)	0.07
Sinusitis	0 (0.0)	0.00	0 (0.0)	0.00	0 (0.0)	0.00	3 (37.5)	0.22	0 (0.0)	0.00	3 (14.3)	0.10
Upper respiratory tract infection	1 (100.0)	0.34	0 (0.0)	0.00	0 (0.0)	0.00	3 (37.5)	0.22	0 (0.0)	0.00	4 (19.0)	0.14
Urinary tract infection	0 (0.0)	0.00	1 (16.7)	0.46	1 (20.0)	0.39	4 (50.0)	0.30	0 (0.0)	0.00	6 (28.6)	0.34
Vertigo	0 (0.0)	0.00	1 (16.7)	0.11	0 (0.0)	0.00	0 (0.0)	0.00	0 (0.0)	0.00	2 (9.5)	0.07
Viral infection	0 (0.0)	0.00	0 (0.0)	0.00	0 (0.0)	0.00	2 (25.0)	0.15	0 (0.0)	0.00	2 (9.5)	0.07
Vomiting	0 (0.0)	0.00	1 (16.7)	0.11	1 (20.0)	0.39	1 (12.5)	0.15	0 (0.0)	0.00	3 (14.3)	0.20
Weight decreased	0 (0.0)	0.00	1 (16.7)	0.11	0 (0.0)	0.00	1 (12.5)	0.07	0 (0.0)	0.00	2 (9.5)	0.07

TEAE = treatment-emergent adverse event; AE = adverse event.

Notes: Data reflect a cutoff date of 07 March 2012.

- Per the study protocol, only serious adverse events (SAEs) and AEs considered clinically significant and/or related to study medication were collected.
- TEAEs are defined as those events that occurred or worsened during or after the first dose of metreleptin.
- A frequent TEAE is a TEAE with incidence rate (100*number of subjects with the AE/total number of subjects in the population [22]) $\geq 5\%$.
- Antibody data generated using the Amylin assay method as described in Section 4.1.1.1.
- A treatment-emergent positive titer of antibodies to metreleptin is a positive titer that is observed following a negative or missing titer at baseline or a positive titer that has increased by at least 2 dilutions from a detectable baseline value; otherwise, the titer is treatment-emergent negative.
- No patients had peak treatment-emergent titer of 5 or 25.
- Patient 648017 had a single postbaseline positive sample but the titer could not be determined; this patient is excluded from any individual peak titer category but is included in the Any Positive group.
- n represents the total number of patients experiencing at least one occurrence of a given AE.
- EAER = Exposure Adjusted Event Rate, derived by dividing events by patient years of exposure.

[1] Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0 terms.

Cross-Reference: FHA101 SD5 4.6.5.

In analyzing TEAEs that are potentially immune-related (per MedDRA listing), immune-related AEs occurred in all but two antibody level groups, and for each subject, the TEAE occurred no more than 2.2 months after metreleptin dosing and usually within one month. In most cases, subjects continued treatment for 3 months-2.5 years without recurrence. Injection site reactions appeared at a higher frequency in those with higher antibody titers (see chart provided by Sponsor below). Case narratives of five potential immune-related events were provided by the Sponsor as follows:

- Subject 648016 (negative antibody group): This subject experienced facial swelling that resolved with clindamycin.
- Subject 648019 (positive antibody titers): This subject experienced pruritus 16 days after dosing and injection site urticaria within 30 days of dosing.
- Subject 648004, 648006, 648014 (positive antibody titers): These subjects experienced injection site urticaria up to 22 days after dosing. One subject had injection site inflammation 20 days after dosing.

Table 10. Reported Treatment-Emergent Adverse Events Summarized by Adverse Event Category, Subcategory, Preferred Term, and Peak Titer of Treatment-Emergent Binding Antibodies to Metreleptin (Study FHA101; Intent-to-Treat Patients With Titers of Binding Antibodies to Metreleptin [N = 22])

Adverse Event Category [1] Adverse Event Sub-Category Preferred Term [2]	Peak Treatment-Emergent Titer													
	Negative (N = 1)		125 (N = 6)		625 (N = 5)		3125 (N = 8)		15625 (N = 1)		Any Positive (N = 21)			
	n (%)	Ev EAER	n (%)	Ev EAER	n (%)	Ev EAER	n (%)	Ev EAER	n (%)	Ev EAER	n (%)	Ev EAER		
All TEAEs	1 (100.0)	15 5.10	5 (83.3)	49 5.60	5 (100.0)	28 5.52	8 (100.0)	66 4.93	1 (100.0)	1 0.80	20 (95.2)	148 5.02		
All Potentially Immune-Related TEAEs	1 (100.0)	1 0.34	1 (16.7)	3 0.34	0 (0.0)	0 0.00	5 (62.5)	7 0.52	0 (0.0)	0 0.00	6 (28.6)	10 0.34		
Anaphylaxis, Angioedema, Severe Cutaneous Reaction TEAEs	0 (0.0)	0 0.00	1 (16.7)	3 0.34	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (4.8)	3 0.10		
Rash	0 (0.0)	0 0.00	1 (16.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (4.8)	1 0.03		
Urticaria	0 (0.0)	0 0.00	1 (16.7)	2 0.23	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (4.8)	2 0.07		
Inflammatory Injection Site TEAEs	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	5 (62.5)	6 0.45	0 (0.0)	0 0.00	5 (23.8)	6 0.20		
Injection site inflammation	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (12.5)	2 0.15	0 (0.0)	0 0.00	1 (4.8)	2 0.07		
Injection site urticaria	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	4 (50.0)	4 0.30	0 (0.0)	0 0.00	4 (19.0)	4 0.14		
Other potentially immune-related TEAEs	1 (100.0)	1 0.34	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (12.5)	1 0.07	0 (0.0)	0 0.00	1 (4.8)	1 0.03		
Pruritus	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (12.5)	1 0.07	0 (0.0)	0 0.00	1 (4.8)	1 0.03		
Swelling face	1 (100.0)	1 0.34	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00		
All Other TEAEs	1 (100.0)	14 4.76	5 (83.3)	46 5.25	5 (100.0)	28 5.52	7 (87.5)	59 4.41	1 (100.0)	1 0.80	19 (90.5)	138 4.68		
Mechanical Injection Site TEAEs	1 (100.0)	1 0.34	1 (16.7)	1 0.11	2 (40.0)	2 0.39	1 (12.5)	1 0.07	0 (0.0)	0 0.00	4 (19.0)	4 0.14		
Injection site haematoma	1 (100.0)	1 0.34	1 (16.7)	1 0.11	2 (40.0)	2 0.39	1 (12.5)	1 0.07	0 (0.0)	0 0.00	4 (19.0)	4 0.14		
Nausea	0 (0.0)	0 0.00	3 (50.0)	3 0.34	2 (40.0)	2 0.39	3 (37.5)	6 0.45	0 (0.0)	0 0.00	9 (42.9)	12 0.41		
Other TEAEs	1 (100.0)	13 4.42	4 (66.7)	42 4.80	4 (80.0)	24 4.73	7 (87.5)	52 3.89	1 (100.0)	1 0.80	17 (81.0)	122 4.14		

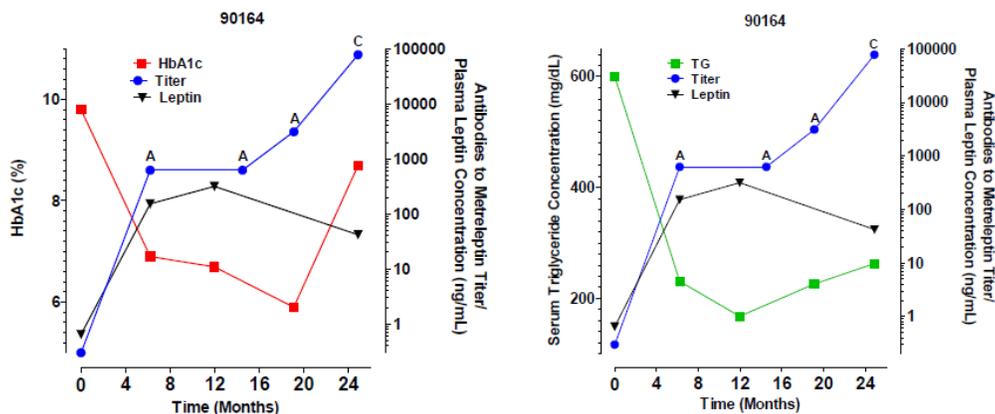
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NIH Studies 991265/20010769

Of the 43 subjects with antibody data, 37 (86%) developed antibodies. The time to peak titer ranged from 1-42 months. Most subjects who developed antibodies to metreleptin continued to maintain antibody titers on treatment. 3/43 subjects (7%, all pediatric) developed neutralizing antibodies and are described below.

Subject 90164: The subject experienced the following after a significant increase in antibody titer from 625 to 78,125: a decrease in plasma leptin after an initial increase (318 ng/mL at month 12 to 42.2 ng/mL at year 2), an increase back to baseline in HgBA1c (9.8% initially to 8.7%), and a slightly increased triglyceride level from baseline (226 mg/dL initially to 263 mg/dL). Only data to year 2 are displayed below.

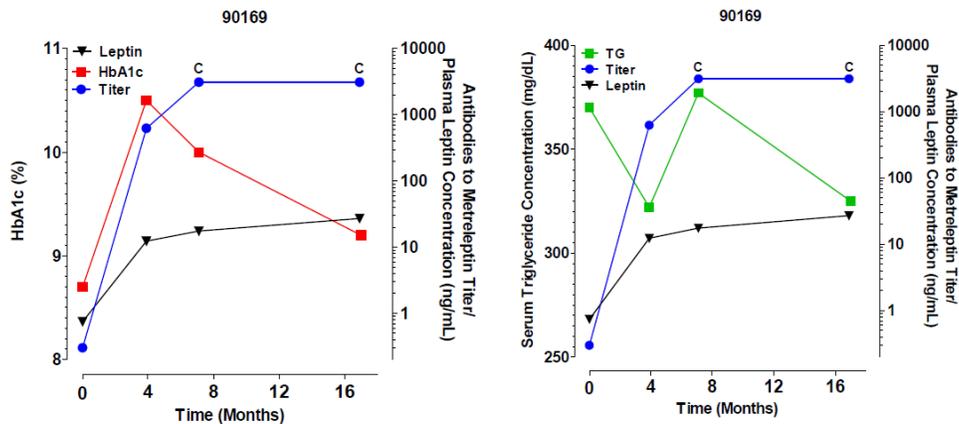
Figure 10. Titer of Binding Antibodies to Metreleptin, Leptin Concentration, and Metabolic Measurements Over Time for Patient 90164 With Category C In Vitro Neutralizing Activity Assay Result at Month 25 (NIH Studies 991265/20010769)



On 8/21/13, the Sponsor reported that the patient had been hospitalized for sepsis in (b) (6) and (b) (6). Antibodies were assessed during the (b) (6) hospitalization and were found to be positive for neutralizing activity; the level (ng/mL) has not yet been reported. No further clinical information was available for review.

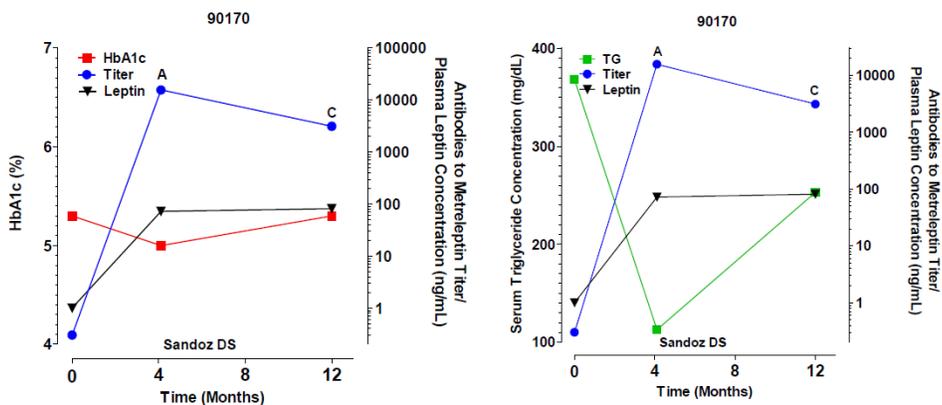
Subject 90169: This subject experienced no AEs. HgbA1c increased and triglycerides decreased, but only slightly. Leptin increased with increasing titers. Titers peaked at 3,125 ng/mL. It was declared that this subject was non-responsive to metreleptin treatment but also that there were concerns with compliance.

Figure 11. Titer of Binding Antibodies to Metreleptin, Leptin Concentration, and Metabolic Measurements Over Time for Patient 90169 With Category C In Vitro Neutralizing Activity Assay Result at Months 7 and 17 (NIH Studies 991265/20010769)



Subject 90170: This subject was diagnosed with anaplastic large cell lymphoma after July 11, 2011 (the cut-off date for reporting). This subject also experienced peripheral edema 345 days after metreleptin. HgbA1c did not change, triglycerides decreased overall, and leptin increased with increasing titers. Titers peaked at 15,625 ng/mL.

Figure 12. Titer of Binding Antibodies to Metreleptin, Leptin Concentration, and Metabolic Measurements Over Time for Patient 90170 With Category C In Vitro Neutralizing Activity Assay Result at Month 12 (NIH Studies 991265/20010769)



There was a trend of those subjects who had positive antibodies experiencing more AEs than those without positive antibodies (of note, the group “≤ 5 peak treatment group” includes those subjects

with no titer as well as those with titers ≤ 5). Once again, this is difficult to assess as most patients developed antibodies.

Table 26. Frequent (Incidence $\geq 5\%$) Treatment-Emergent Adverse Events by Peak Treatment-Emergent Titer of Binding Antibodies to Metreleptin, System Organ Class, and Preferred Term (NIH Studies 991265/20010769, Intent-to-Treat Patients With Titer of Binding Antibodies to Metreleptin [N = 43])

Preferred Term [1]	Peak Treatment-Emergent Titer											
	≤ 5 (N = 12)		25 (N = 8)		125 (N = 11)		625 (N = 6)		3125 (N = 4)		≥ 15625 (N = 2)	
	n (%)	Events (EAER[2])	n (%)	Events (EAER[2])	n (%)	Events (EAER[2])	n (%)	Events (EAER[2])	n (%)	Events (EAER[2])	n (%)	Events (EAER[2])
Alopecia	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	2 (18.2)	3 (0.06)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Arthralgia	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Dizziness	1 (8.3)	1 (0.01)	1 (12.5)	1 (0.04)	1 (9.1)	2 (0.04)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Nausea	2 (16.7)	4 (0.05)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Ovarian cyst	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Paraesthesia	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Upper respiratory tract infection	2 (16.7)	3 (0.04)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Vitamin D deficiency	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Weight decreased	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	3 (27.3)	3 (0.06)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)

There was a trend towards subjects with positive antibodies having more episodes of urticaria and angioedema, although this is difficult to assess as most patients had positive antibodies. Five possible immune events were identified, and four of these subjects continued on metreleptin therapy without further incident. One subject had anaphylaxis that was considered food-related.

Table 27. Treatment-Emergent Adverse Events Summarized by Adverse Event Category, Subcategory, Preferred Term, and Peak Titer of Treatment-Emergent Binding Antibodies to Metreleptin and Preferred Term and (NIH Studies 991265/20010769; Intent-to-Treat Patients With Titer of Binding Antibodies to Metreleptin [N = 43])

Adverse Event Category [1] Adverse Event Sub-Category [1] Preferred Term [2]	Peak Treatment-Emergent Titer											
	≤ 5 (N = 12)		25 (N = 8)		125 (N = 11)		625 (N = 6)		3125 (N = 4)		≥ 15625 (N = 2)	
	n (%)	Events (EAER[3])	n (%)	Events (EAER[3])	n (%)	Events (EAER[3])	n (%)	Events (EAER[3])	n (%)	Events (EAER[3])	n (%)	Events (EAER[3])
All TEAEs	9 (75.0)	62 (0.80)	3 (37.5)	11 (0.43)	8 (72.7)	57 (1.11)	5 (83.3)	19 (0.60)	1 (25.0)	1 (0.10)	1 (50.0)	1 (0.31)
All Potentially Immune-Related TEAEs	2 (16.7)	3 (0.04)	0 (0.0)	0 (0.00)	2 (18.2)	2 (0.04)	2 (33.3)	2 (0.06)	1 (25.0)	1 (0.10)	0 (0.0)	0 (0.00)
Anaphylaxis, Angioedema, Severe Cutaneous Reaction TEAEs	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Anaphylactic reaction	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Urticaria	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Inflammatory Injection Site TEAEs	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	1 (25.0)	1 (0.10)	0 (0.0)	0 (0.00)
Injection site urticaria	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	1 (25.0)	1 (0.10)	0 (0.0)	0 (0.00)
Other Potentially Immune-Related TEAEs	1 (8.3)	2 (0.03)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Arthralgia	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	1 (16.7)	1 (0.03)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Pruritus	1 (8.3)	1 (0.01)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
All Other TEAEs	9 (75.0)	59 (0.76)	3 (37.5)	11 (0.43)	8 (72.7)	55 (1.07)	5 (83.3)	17 (0.54)	0 (0.0)	0 (0.00)	1 (50.0)	1 (0.31)
Mechanical Injection Site TEAEs	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Nausea	2 (16.7)	4 (0.05)	0 (0.0)	0 (0.00)	1 (9.1)	1 (0.02)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.00)
Other TEAEs	9 (75.0)	55 (0.71)	3 (37.5)	11 (0.43)	8 (72.7)	54 (1.05)	5 (83.3)	17 (0.54)	0 (0.0)	0 (0.00)	1 (50.0)	1 (0.31)

Summary of antibody data in lipodystrophy patients

Below is a table summarizing the number of patients in each study with positive antibodies and neutralizing activity.

	Total N	Positive Antibodies	Positive Neutralizing Activity
FHA 101	22	21	3
NIH Studies 991265/20010769	43	37	3
Total from all studies	65	58 (58/65=89%)	6 (6/65=7.7%)

Overall, these patients did not experience a loss of efficacy. Subject 90164 did, however, begin to have decreased leptin levels, increased HgBA1c levels, and increased triglyceride levels at the time of a large increase in antibody titers from 625 to 78,125 ng/mL. Thus, it is possible that with further observance and/or exposure, more patients would develop loss of efficacy as well as worsened leptin deficiency (if the subject was capable of making small amounts of leptin).

Subjects with positive antibodies did seem to have more injection site reactions as would be consistent with anti-drug antibody presence, although this is hard to ascertain as most patients had positive antibodies. In addition, subject 90164 suffered from two episodes of sepsis one year after the study end; she was beginning to experience lowered leptin levels one year prior. As known from mouse models, leptin deficiency is associated with an increased susceptibility to disease so anti-drug antibodies causing a decrease in leptin levels may be causative.

Five Amgen studies in overweight subjects included in the study ISS

Of the 743 subjects, 633 (85.2%) developed antibodies. Most subjects who were positive remained so (456 of 525 available samples). The incidence of TEAEs was higher in the antibody positive group (95.3%) versus the antibody negative group (87.8%). The incidence of immune-related TEAS was higher in the positive antibody group (85.9%) compared to the negative antibody group (67.3%). The events that had higher incidence in the antibody positive versus the antibody negative groups included injection site reactions (erythema, induration, nodules, pruritis, rash, swelling, urticaria, and vesicles), hypersensitivity, and urticaria. Only present in the antibody positive group were eosinophilia, eye swelling/edema, and injection site cellulitis. Seven cases of hypersensitivity occurred; 6 were antibody positive.

Ten other Amgen obesity studies were conducted with metreleptin (not included in the ISS), and the incidence of developing antibodies ranged from 0-100% between the studies. Antibody positive subjects tended to have a higher incidence of injection site erythema and inflammation, headaches, fever, rigors, and diarrhea. Antibody negative subjects had a higher incidence of pruritis.

Amylin pramlintide-metreleptin obesity program

These studies included DFA101 (a proof of concept trial), DFA 102 (a phase 2b dose ranging study), and DFA104 (a phase 2b study of metreleptin and pramlintide). DFA104 was halted after finding neutralizing antibodies in 2 subjects enrolled in the earlier trials. A follow-up study, DFA106 was conducted to evaluate safety.

DFA101

Of 83 ITT subjects, 100% developed antibodies by week 7, and by week 20, all but 1 subject continued to be antibody positive. No subjects reached peak titers after week 4. Those subjects with higher antibody titers had higher leptin levels. Efficacy based on mean change from baseline weight did not decrease with increasing antibody levels; however, as all subjects were antibody positive, there was no negative antibody group to compare if presence versus absence of antibodies altered efficacy.

Potentially immune-mediated TEAEs occurred most often in the highest antibody group. The majority of immune-mediated reactions were injection site reactions. Three subjects experienced hypersensitivity events. One subject had itching/hives/abdominal pain, one subject had swollen face/difficulty breathing, and the third subject narrative is not provided. An additional subject experienced an allergic reaction with the first dose and so did not have antibody testing done (all subjects with hypersensitivity events were withdrawn from the study).

Table 38. Post-Randomization Treatment-Emergent Adverse Events Summarized by Adverse Event Category, Subcategory, Preferred Term, and Peak Titer of Treatment-Emergent Binding Antibodies to Metreleptin (Study DFA101; Population: Intent-to-Treat Subjects [N = 139])

Adverse Event Category [1] Adverse Event Sub-Cat. Preferred Term [2]	Pooled Metreleptin Treatment (N = 83)																	
	Peak Treatment-Emergent Titer																	
	≤5 (N = 4)		25 (N = 8)		125 (N = 11)		625 (N = 27)		3125 (N = 23)		≥15625 (N = 4)							
	n (%)	Ev	EAER	n (%)	Ev	EAER	n (%)	Ev	EAER	n (%)	Ev	EAER	n (%)	Ev	EAER			
All TEAEs	4 (100.0)	8	24.55	4 (50.0)	11	9.05	10 (90.9)	22	7.52	20 (74.1)	50	4.95	18 (78.3)	48	5.96	4 (100.0)	8	5.16
All Potentially Immune-Related TEAEs	0 (0.0)	0	0.00	3 (37.5)	7	5.76	6 (54.5)	11	3.76	13 (48.1)	23	2.27	12 (52.2)	23	2.86	3 (75.0)	4	2.58
Anaphylaxis, Angioedema, Severe Cutaneous Reaction TEAEs	0 (0.0)	0	0.00	1 (12.5)	1	0.82	1 (9.1)	2	0.68	0 (0.0)	0	0.00	2 (8.7)	2	0.25	0 (0.0)	0	0.00
Hypersensitivity	0 (0.0)	0	0.00	1 (12.5)	1	0.82	1 (9.1)	2	0.68	0 (0.0)	0	0.00	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Rash	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Inflammatory Injection Site TEAEs	0 (0.0)	0	0.00	3 (37.5)	6	4.94	6 (54.5)	9	3.08	13 (48.1)	22	2.18	12 (52.2)	20	2.48	3 (75.0)	4	2.58
Injection site erythema	0 (0.0)	0	0.00	2 (25.0)	2	1.65	2 (18.2)	2	0.68	3 (11.1)	3	0.30	3 (13.0)	3	0.37	1 (25.0)	1	0.65
Injection site induration	0 (0.0)	0	0.00	1 (12.5)	1	0.82	2 (18.2)	2	0.68	0 (0.0)	0	0.00	2 (8.7)	2	0.25	0 (0.0)	0	0.00
Injection site inflammation	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Injection site nodule	0 (0.0)	0	0.00	1 (12.5)	2	1.65	0 (0.0)	0	0.00	5 (18.5)	6	0.59	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Injection site oedema	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	1 (25.0)	1	0.65
Injection site pruritus	0 (0.0)	0	0.00	1 (12.5)	1	0.82	2 (18.2)	2	0.68	7 (25.9)	7	0.69	5 (21.7)	5	0.62	0 (0.0)	0	0.00
Injection site rash	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	2 (7.4)	2	0.20	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Injection site swelling	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Injection site urticaria	0 (0.0)	0	0.00	0 (0.0)	0	0.00	3 (27.3)	3	1.03	4 (14.8)	4	0.40	5 (21.7)	6	0.75	2 (50.0)	2	1.29
Other potentially immune-related TEAEs	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	1 (3.7)	1	0.10	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Arthralgia	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	1 (4.3)	1	0.12	0 (0.0)	0	0.00
Arthritis	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00	1 (3.7)	1	0.10	0 (0.0)	0	0.00	0 (0.0)	0	0.00

DFA102

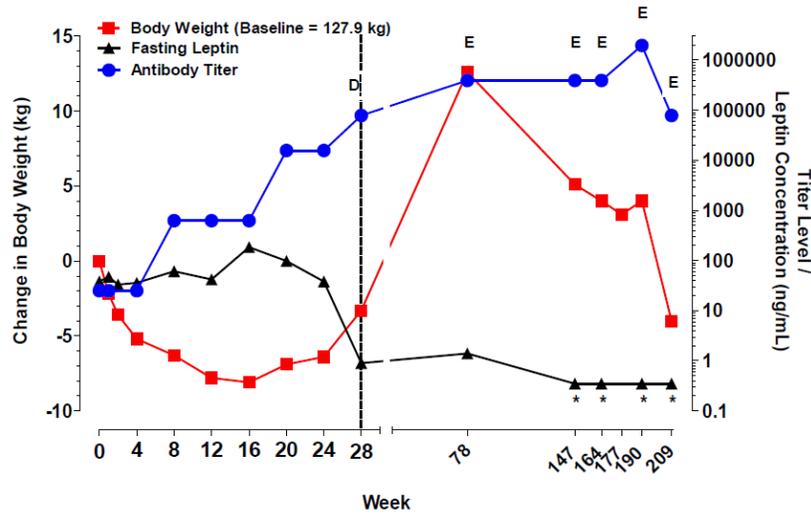
Of 446 subjects treated with metreleptin, 96% developed antibodies. Peak antibody level was reached at week 16. Those subjects with higher titers had higher fasting levels of leptin. As antibody levels became higher than 625, the percent weight loss decreased (although the number of subjects with higher antibody levels decreased as well). Incidence of TEAEs and immune-related TEAEs increased with increasing titers, and the majority of immune-related reactions were injection site reactions. Eight subjects experienced hypersensitivity reactions, but one was associated with a levaquin allergy. The Sponsor also argues that one subject already had a history of urticaria and also argues that as the basophil activation tests were negative in all six cases tested, these reactions were unlikely IgE-mediated.

Table 40. Treatment-Emergent Adverse Events Summarized by Adverse Event Category, Subcategory, Preferred Term, and Peak Titer of Treatment-Emergent Antibodies to Metreleptin (Study DFA102: Intent-to-Treat Population [N = 608])

Adverse Event Category [1] Adverse Event Sub-Category Preferred Term [2]	Placebo (N = 152)		≤5 (N = 54)		25 (N = 31)		125 (N = 140)		625 (N = 174)		3125 (N = 45)		≥15625 (N = 2)	
	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER
All TEAEs	126 (82.9)	454 50.46	44 (81.5)	128 111.05	28 (90.3)	73 70.06	124 (88.6)	483 61.49	164 (94.3)	733 62.06	43 (100.0)	228 70.22	2 (100.0)	12 78.27
All Potentially Immune-Related TEAEs	27 (17.8)	41 4.56	23 (42.6)	39 33.84	16 (51.6)	21 19.62	65 (46.4)	118 15.02	123 (70.7)	229 19.39	38 (84.4)	88 27.10	2 (100.0)	6 39.13
Anaphylaxis, Angioedema, Severe Cutaneous Reaction TEAEs	3 (2.0)	3 0.33	2 (3.7)	3 2.60	0 (0.0)	0 0.00	3 (2.1)	3 0.38	6 (3.4)	7 0.59	1 (2.2)	1 0.31	0 (0.0)	0 0.00
Angioedema	0 (0.0)	0 0.00	1 (1.9)	1 0.87	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Drug hypersensitivity	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.6)	1 0.08	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Hypersensitivity	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	2 (1.1)	2 0.17	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Rash	0 (0.0)	0 0.00	1 (1.9)	1 0.87	0 (0.0)	0 0.00	0 (0.0)	0 0.00	2 (1.1)	2 0.17	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Rash erythematous	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (2.2)	1 0.31	0 (0.0)	0 0.00
Rash macular	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.7)	1 0.13	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Rash maculo-papular	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Rash pruritic	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Urticaria	0 (0.0)	0 0.00	1 (1.9)	1 0.87	0 (0.0)	0 0.00	2 (1.4)	2 0.25	2 (1.1)	2 0.17	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Inflammatory Injection Site TEAEs	20 (13.2)	29 3.22	21 (38.9)	35 30.37	15 (48.4)	20 18.68	60 (42.9)	106 13.49	117 (67.2)	206 17.44	38 (84.4)	86 26.49	2 (100.0)	6 39.13
Injection site erythema	8 (5.3)	9 1.00	9 (16.7)	12 10.41	7 (22.6)	7 6.54	29 (20.7)	33 4.20	42 (24.1)	47 3.98	12 (26.7)	19 5.85	1 (50.0)	3 19.57
Injection site induration	5 (3.3)	5 0.56	1 (1.9)	1 0.87	0 (0.0)	0 0.00	3 (2.1)	4 0.51	6 (3.4)	6 0.51	6 (13.5)	8 2.46	0 (0.0)	0 0.00
Injection site inflammation	0 (0.0)	0 0.00	1 (1.9)	1 0.87	0 (0.0)	0 0.00	3 (2.1)	3 0.38	10 (5.7)	11 0.95	4 (8.9)	7 2.16	0 (0.0)	0 0.00
Injection site nodule	5 (3.3)	5 0.56	0 (0.0)	0 0.00	1 (3.2)	1 0.93	12 (8.6)	14 1.78	18 (10.3)	19 1.61	5 (11.1)	7 2.16	1 (50.0)	1 6.52
Injection site oedema	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.7)	1 0.13	1 (0.6)	1 0.08	1 (2.2)	1 0.31	0 (0.0)	0 0.00
Injection site papule	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.7)	1 0.13	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Injection site pruritus	5 (3.3)	5 0.56	11 (20.4)	11 9.54	4 (12.9)	4 3.74	26 (18.6)	28 3.56	42 (24.1)	46 3.89	19 (42.2)	25 7.70	2 (100.0)	2 13.04
Injection site rash	2 (1.3)	2 0.22	3 (5.6)	3 2.60	5 (16.1)	5 4.67	8 (5.7)	11 1.40	29 (16.7)	36 3.05	7 (15.6)	8 2.46	0 (0.0)	0 0.00
Injection site swelling	0 (0.0)	0 0.00	1 (1.9)	1 0.87	0 (0.0)	0 0.00	0 (0.0)	0 0.00	3 (1.7)	3 0.25	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Injection site urticaria	2 (1.3)	2 0.22	6 (11.1)	6 5.21	3 (9.7)	3 2.80	10 (7.1)	11 1.40	35 (20.1)	36 3.05	10 (22.2)	11 3.39	0 (0.0)	0 0.00
Injection site warmth	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.6)	1 0.08	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Other Potentially Immune-Related TEAEs	8 (5.3)	9 1.00	1 (1.9)	1 0.87	1 (3.2)	1 0.93	8 (5.7)	9 1.15	15 (8.6)	16 1.35	1 (2.2)	1 0.31	0 (0.0)	0 0.00
Arthralgia	5 (3.3)	5 0.56	0 (0.0)	0 0.00	1 (3.2)	1 0.93	7 (5.0)	8 1.02	6 (3.4)	6 0.51	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Arthritis	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	3 (1.7)	3 0.25	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Asthma	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Eosinophilia	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.7)	1 0.13	2 (1.1)	2 0.17	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Face oedema	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.6)	1 0.08	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Joint swelling	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.6)	1 0.08	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Lip swelling	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	2 (1.1)	2 0.17	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Local swelling	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Pruritus	0 (0.0)	0 0.00	1 (1.9)	1 0.87	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (0.6)	1 0.08	1 (2.2)	1 0.31	0 (0.0)	0 0.00
Pruritus generalised	1 (0.7)	1 0.11	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00

Two subjects (130019 and 12001) experienced weight gain after initial weight loss during a period of peak antibody production and subsequent decreased leptin levels to below the limit of detection. These antibodies tested positive for neutralization. In follow-up of one of these subjects (130019), the subject continued to have neutralizing antibodies and low leptin levels at week 209 (follow-up for the other subject was not available.) However, weight gain stabilized to 4 kg below baseline weight, and HgbA1c improved from 6.9 at week 147 to 5.7 at week 177. This data is shown below.

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



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

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

- Week 177 antibody/plasma leptin samples were lost.

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

DFA104

DF104 was terminated early due to discovery of neutralizing antibodies in subjects in DFA102. Duration of study exposure ranged from 1 to 30 days, and based on such a relatively short exposure, fewer subjects than in other studies developed antibodies. Following cessation of study medication, antibodies to metreleptin were detectable in 47% of subjects at the 2 month follow-up visit and this decreased to 29% at the six month follow-up visit. No subject developed neutralizing antibodies. The overall incidence of TEAEs was higher in the antibody positive group but potentially immune-related TEAEs did not vary between placebo and antibody positive groups as shown in the table below provided by the Sponsor.

Table 42. Treatment-Emergent Adverse Events Summarized by Adverse Event Category, Subcategory, Preferred Term, and Peak Titer of Treatment-Emergent Antibodies to Metreleptin (Study DFA104; Intent-to-Treat Population [N = 72])

Adverse Event Category [1] Adverse Event Sub-Category Preferred Term [2]	Pramlintide + Metreleptin (N = 36)													
	Placebo (N = 36)		Negative (N = 21)		25 (N = 3)		125 (N = 6)		625 (N = 3)		3125 (N = 2)		15625 (N = 1)	
	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER
All TEAEs	6 (16.7)	7 5.95	4 (19.0)	6 13.61	2 (66.7)	6 44.72	3 (50.0)	5 22.83	2 (66.7)	5 29.46	1 (50.0)	4 50.38	1 (100.0)	3 36.53
All Potentially Immune-Related TEAEs	0 (0.0)	0 0.00	1 (4.8)	1 2.27	0 (0.0)	0 0.00	1 (16.7)	2 9.13	1 (33.3)	1 5.89	1 (50.0)	1 12.59	1 (100.0)	1 12.18
Anaphylaxis, Angioedema, Severe Cutaneous Reaction TEAEs	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Inflammatory Injection Site TEAEs	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (16.7)	2 9.13	1 (33.3)	1 5.89	1 (50.0)	1 12.59	1 (100.0)	1 12.18
Injection site induration	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (16.7)	1 4.57	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (100.0)	1 12.18
Injection site pruritus	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (16.7)	1 4.57	1 (33.3)	1 5.89	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Injection site rash	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (50.0)	1 12.59	0 (0.0)	0 0.00
Other potentially immune-related TEAEs	0 (0.0)	0 0.00	1 (4.8)	1 2.27	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Arthralgia	0 (0.0)	0 0.00	1 (4.8)	1 2.27	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
All Other TEAEs	6 (16.7)	7 5.95	4 (19.0)	5 11.34	2 (66.7)	6 44.72	3 (50.0)	3 13.70	2 (66.7)	4 23.56	1 (50.0)	3 37.78	1 (100.0)	2 24.35
Mechanical Injection Site TEAEs	0 (0.0)	0 0.00	1 (4.8)	1 2.27	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (33.3)	1 5.89	1 (50.0)	1 12.59	0 (0.0)	0 0.00
Injection site haematoma	0 (0.0)	0 0.00	1 (4.8)	1 2.27	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (33.3)	1 5.89	1 (50.0)	1 12.59	0 (0.0)	0 0.00
Nausea	1 (2.8)	1 0.85	2 (9.5)	2 4.54	2 (66.7)	3 22.36	0 (0.0)	0 0.00	1 (33.3)	1 5.89	1 (50.0)	1 12.59	1 (100.0)	2 24.35
Other TEAEs	5 (13.9)	6 5.10	2 (9.5)	2 4.54	2 (66.7)	3 22.36	3 (50.0)	3 13.70	2 (66.7)	2 11.78	1 (50.0)	1 12.59	0 (0.0)	0 0.00

Footnotes on next page.

Post-treatment AEs were also observed equally amongst groups as seen in the table below provided by the Sponsor.

Table 43. Post-Treatment Adverse Events Summarized by Adverse Event Category, Subcategory, Preferred Term, and Peak Titer of Treatment-Emergent Binding Antibodies to Metreleptin (Study DFA104; Population: Intent-to-Treat Subjects [N = 72])

Adverse Event Category [1] Adverse Event Sub-Category Preferred Term [2]	Pramlintide + Metreleptin (N = 36)													
	Placebo (N = 36)		Negative (N = 21)		25 (N = 3)		125 (N = 6)		625 (N = 3)		3125 (N = 2)		15625 (N = 1)	
	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER	n (%)	EAER
All PTAEs	13 (36.1)	22 18.69	7 (33.3)	18 40.84	3 (100.0)	6 44.72	4 (66.7)	10 45.66	2 (66.7)	2 11.78	0 (0.0)	0 0.00	0 (0.0)	0 0.00
All Potentially Immune-Related PTAEs	3 (8.3)	3 2.55	1 (4.8)	1 2.27	1 (33.3)	1 7.45	1 (16.7)	1 4.57	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Anaphylaxis, Angioedema, Severe Cutaneous Reaction PTAEs	1 (2.8)	1 0.85	1 (4.8)	1 2.27	0 (0.0)	0 0.00	1 (16.7)	1 4.57	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Hypersensitivity	1 (2.8)	1 0.85	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (16.7)	1 4.57	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Rash	0 (0.0)	0 0.00	1 (4.8)	1 2.27	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Inflammatory Injection Site PTAEs	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Other potentially immune-related PTAEs	2 (5.6)	2 1.70	0 (0.0)	0 0.00	1 (33.3)	1 7.45	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Arthralgia	2 (5.6)	2 1.70	0 (0.0)	0 0.00	1 (33.3)	1 7.45	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
All Other PTAEs	13 (36.1)	19 16.14	6 (28.6)	17 38.57	3 (100.0)	5 37.27	3 (50.0)	9 41.09	2 (66.7)	2 11.78	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Mechanical Injection Site PTAEs	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Nausea	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00	1 (16.7)	1 4.57	0 (0.0)	0 0.00	0 (0.0)	0 0.00	0 (0.0)	0 0.00
Other PTAEs	13 (36.1)	19 16.14	6 (28.6)	17 38.57	3 (100.0)	5 37.27	3 (50.0)	8 36.53	2 (66.7)	2 11.78	0 (0.0)	0 0.00	0 (0.0)	0 0.00

AE = adverse event.

Notes: Post-treatment Adverse Events (PTAEs) are defined as those with an onset date after the date of last dose (imputed if not available) of randomized study medication.

- n=number of subjects who experienced a given AE. Percentages are based on number of subjects with each peak titer.

- Ev=number of events (a subject may be counted more than once).

- EAER=Exposure Adjusted Event Rate, derived by dividing events by patient years of exposure.

- Antibody data generated using the Amylin assay method as described in Section 4.1.1.1.

- Subjects with missing peak treatment-emergent anti-leptin antibody titer are not included in this table.

- No Subjects had peak treatment-emergent anti-leptin antibody titer of 5.

[1] A list of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms identified by Amylin was used to search for AE categories and subcategories.

[2] MedDRA Version 14.0 terms.

Cross-Reference: CSR DFA104 SDS 3.2.7.4.

This study was conducted in January 2012 to determine if additional subjects from DFA101 or 102 developed neutralizing antibodies and was part of the risk management plan agreed upon with the Agency on May 4, 2012. The majority of subjects (80.9%) were antibody negative at the safety follow-up, and most titers were less than 625.

One subject (139005) displayed significant neutralizing activity; she had been exposed for 183 days, had no neutralizing antibodies at the end of the study, and was off the drug for 3.1 years. Her antibody titer rose from 625 at the end of the study to 9,765,625 at the safety follow-up. Her leptin was within normal limits at the end of the study but was below the lower level of detection at the safety follow-up, and concurrently, she saw an endocrinologist for evaluation of weight gain during that time. A second follow-up visit was conducted in June 2012 which showed continued high antibody titer, neutralizing activity, leptin levels below the level of detection, type 2 diabetes mellitus, hypertension, dyspnea, hypoxia, fatigue, and amenorrhea. No other medical history for this subject was provided. A third visit in December 2012 occurred, but the data are not yet available.

In comparing the treated groups and a pooled comparator group, the adverse events of special interest (weight gain, diabetes, hypertriglyceridemia, and infection) were similar (12%) versus (14%). In comparing antibody status, a higher percentage of antibody positive subjects experienced weight gain (6.5% versus 4.2%), and a higher percentage of antibody negative subjects, developed diabetes (6.1% versus 3.2%).

Table 44. Adverse Events of Special Interest Summarized by Treatment and Titer of Binding Antibodies to Metreleptin (Study DFA106, Enrolled Population [N = 419])

Event	Pooled Placebo and Pramlintide Only (N = 93) n (%) Events	Metreleptin [1]					
		Negative (N = 262) n (%) Events	Titer at Safety Follow-up Visit				
			5 (N = 7) n (%) Events	25 (N = 31) n (%) Events	125 (N = 21) n (%) Events	625 (N = 2) n (%) Events	≥15625 [2] (N = 1) n (%) Events
Any Adverse Event of Special Interest	13 (14.0) 15	32 (12.2) 32	1 (14.3) 1	3 (9.7) 3	2 (9.5) 2	0 (0.0) 0	1 (100.0) 1
>10% Weight Gain from Baseline in DFA101 or DFA102	7 (7.5) 7	11 (4.2) 11	0 (0.0) 0	1 (3.2) 1	2 (9.5) 2	0 (0.0) 0	1 (100.0) 1
Diabetes	5 (5.4) 5	16 (6.1) 16	1 (14.3) 1	1 (3.2) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Hypertriglyceridemia	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (3.2) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Infection Leading to Hospitalization	3 (3.2) 3	5 (1.9) 5	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

AE = adverse event.

Notes: For statistic n, subjects experiencing multiple episodes of a given AE are counted once in each relevant category.

- Antibody data generated using the Amylin assay method as described in Section 4.1.1.1.
- Subjects with missing binding antibodies to metreleptin are not included in this table.
- No subjects had titer of binding antibody to metreleptin of 3125.

[1] Includes metreleptin monotherapy and metreleptin+pramlintide combination.

[2] Subject 139005 had a titer of binding antibodies to metreleptin of 9765625. Additional data from a subsequent safety follow-up visit for this subject are not included in this table (presented in Section 8.4.4).

Cross-References: CSR DFA106 SDS 3.2.5.

Literature reports

Further information on neutralizing activity has been found in several published reports. In one study of 8 lipodystrophy subjects, two subjects were described as metreleptin-resistant, and 1 of the 2 subjects had positive neutralizing antibodies². Neutralizing activity was also described in 2 subjects receiving metreleptin for congenital leptin deficiency, and both experienced loss of efficacy which was overcome by increasing the dose³.

Assessment of immunogenicity

Almost all subjects who received metreleptin therapy developed antibodies (in the various studies, this ranged from 85-100%). In lipodystrophy subjects, HgbA1c and triglyceride levels still seemed to improve overall, despite presence of antibodies. However, there was an increased incidence of immune-mediated reactions, notably injection site reactions in those subjects with positive antibodies (but this was difficult to ascertain as almost all subjects had antibodies). In subjects with obesity, weight loss did not vary between those treated with metreleptin and those on placebo, and similar to lipodystrophy subjects, there was an increase in immune-related reactions, notably injection site reactions (but, once again, difficult to ascertain.).

With few exceptions, leptin levels continually rose with increasing antibody levels. This is consistent with previous PK studies in mice and dogs that showed metreleptin exposure tended to increase over time following repeat SC dosing. However, this is inconsistent with the typical decrease in drug levels found in those with antibodies against biologics^{5,6}. It is hypothesized that antibodies bind metreleptin interfering with renal clearance, but it should also be noted that in the human studies, the assay could not detect metreleptin from leptin. Thus, it is difficult to discern if increased exposure caused a build-up of metreleptin product or increases in endogenous leptin.

A small number of subjects developed neutralizing antibodies. In the lipodystrophy subjects, one subject displayed metreleptin resistance, although there are published reports of 4 other subjects receiving metreleptin for lipodystrophy or leptin deficiency that were metreleptin resistant. In addition, a recent report of a subject in the NIH study showed positive neutralizing antibodies with an initially elevated level that decreased substantially with elevated antibody titers. This subject more closely parallels three subjects with obesity who developed neutralizing antibodies. These subjects, too, experienced severely decreased leptin levels and decreased efficacy (accompanying weight gain.) Thus, the development of neutralizing antibodies may be related to a loss of efficacy which is consistent with what is typically observed with anti-drug antibodies such as with biologics^{5,6}.

As described, leptin deficiency is associated with increased Treg cell populations and activity. Three cases of non-Hodgkin's lymphoma (T-cell) have been diagnosed in subjects with acquired lipodystrophy treated with metreleptin (one case is discussed in this Clinical Addendum.) Treg cells are clearly involved in tumor immune-responses, although they appear to play both a positive or negative role, depending on the type of cancer.⁴ Thus, in subjects who have altered amounts of leptin due to metreleptin treatment, there could be an alteration in tumor suppression activity with subsequent increased risk of cancer. In addition, high leptin levels would lead to a lack of Treg function, potentially increasing susceptibility to autoimmune diseases.

Finally, a leptin deficient state causes an increased susceptibility to infections in animal models. The most recent case of a lipodystrophy subject with positive neutralizing antibodies and lowered leptin levels who was hospitalized for sepsis on two separate occasions may also point to the increased risk of infection with treatment if significant neutralizing antibodies develop.

II. Questions Submitted to DPARP

1. What is the clinical relevance of antibody formation with metreleptin therapy, and how does it apply to the lipodystrophy indication?

This product has proven to be highly immunogenic. In the clinical development program, 58/65 subjects (89%) developed antibodies, and 6/65 (9.2%) developed neutralizing activity. Based on this information, it is highly likely that most patients will develop antibodies, and a small portion will develop neutralizing ability.

Most subjects in the lipodystrophy program who developed neutralizing antibodies experienced increased leptin levels and no loss of efficacy, similar to those with non-neutralizing antibodies. However, this August, another subject was found with neutralizing antibodies who had a similar clinical outcome as those patients in the obesity programs with neutralizing antibodies. She ultimately developed decreased leptin levels with an increase in the antibody titer and decreased efficacy. In addition, case reports have identified subjects treated with metreleptin who have experienced a decrease in efficacy as well.

So although those patients with lipodystrophy who develop neutralizing antibodies will likely have high leptin levels (with a potential for a decreased susceptibility to infection and an increased susceptibility to autoimmune diseases), they may behave more like those in the obesity program and develop low leptin levels (with a potential for an increased susceptibility to infection and a decreased susceptibility to autoimmune disease.) Given the complex nature of Treg function in oncologic processes, it is difficult to predict if these patients would be at a higher risk for cancer, but this may be the case. It may also be that these patients have a higher likelihood of experiencing immune-related TEAEs such as urticaria and injection site reactions as is consistent with the behavior of biologics that cause anti-drug antibody formation^{5,6}.

Thus, this is a highly immunogenic product, with the potential to cause further leptin deficiency as well as an alteration in the susceptibility to infection, autoimmunity, and cancer. Significant consideration should be given to the risk/benefit analysis of the subjects who would be receiving metreleptin versus conventional treatments for diabetes and hypertriglyceridemia.

2. What is the immunogenicity risk to a subject without a low-leptin condition – in other words, with normal or above-normal concentrations of endogenous leptin – who may be prescribed metreleptin off-label for another indication?

In those subjects exposed to metreleptin for obesity, most will develop antibodies. As seen in the lipodystrophy program, this occurred with an increase in leptin levels and no change in efficacy. In those few subjects who developed neutralizing activity, however, leptin levels decreased to undetectable levels. The subjects experienced weight gain and also seemed to have higher immune-related TEAEs. One patient seems to have developed type II diabetes. With low leptin levels, these patients may experience an increased risk of infection and decrease risk of autoimmunity.

Once neutralizing antibodies are present, it is unknown how long they would persist. Thus, obese patients, already in a leptin resistant state, could experience not only weight gain but an alteration in their ability to fight infection or cancer.

3. Given leptin's role in the immune system, are there specific safety concerns (e.g., autoimmunity, malignancy) with the use of metreleptin in subjects with autoimmune diseases (i.e., certain types of acquired lipodystrophy)?

If a subject develops antibodies, then higher leptin levels likely will occur. This could lead to a decrease of Treg cell function leading to a potential increase in autoimmune disease. Those with autoimmune conditions may be at a higher risk as they already have abnormal Treg function.

4. Do you have any recommendations for additional studies or monitoring?

Even if an assay was commercially available, there is no clear limit as to when the drug should be discontinued. In addition, once antibodies are present, there is no ability to reverse this process. Patients may be at an increased risk of infection (low leptin state), autoimmunity (high leptin state), and cancer. Prescribing physicians should be informed of this potential, but as this is largely based on animal model data, additional activities may be unwarranted at this time.

5. We would like your recommendations of potential AC members with the appropriate expertise to address these issues. (We have considered the authors of a recent NEJM paper on JAKs and STATs in immunity, immunodeficiency, and cancer as potential candidates.)

III. References

1. Matarese G, *et al.* Regulatory T cells in obesity: the leptin connection. *Trends Mol Med.* 2010 Jun;16(6):247-56.
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3. Farooqi IS, *et al.* Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest.* 2002 Oct 15;110 (8):1093-103.
4. Whiteside, TL. What are regulatory T cells (Treg) regulating in cancer and why? *Semin Cancer Biol.* 2021 Aug 22(4):327-34.
5. Chamberlain, P. Assessing immunogenicity of biosimilar therapeutic monoclonal antibodies: regulatory and bioanalytical considerations. *Bioanalysis.* 2013 5 (5), 561-574.
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/s/

TRACY L KRUZICK
02/21/2014

BANU A KARIMI SHAH
02/21/2014

LYDIA I GILBERT MCCLAIN
02/21/2014
I concur



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

From: Donna L. Snyder, MD
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff (PMHS)

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Metreleptin (Myalept®) Injection
Recommended dosage to be given by injection:
≤ 40 kg (males and females) - 0.06 mg/kg as a daily dose
> 40 kg males - 2.5 mg as a daily dose
> 40 kg females - 5 mg as a daily dose

BLA: 125390

Sponsor: Amylin Pharmaceuticals

Proposed Indication: For treatment of pediatric and adult patients with:
(1) Generalized lipodystrophy
(2) Metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia, inadequately controlled diabetes on current therapy, and/or evidence of hepatic steatosis.

Consult Request: PMHS-Pediatrics has been asked to review the labeling and medication guide.

Materials Reviewed:

- Proposed Myalept® (metreleptin) labeling dated November 12, 2013
- Medical Review of BLA 125390, dated November 18, 2013, DARRTS Reference ID: 3408513

- PMHS- Pediatric and Maternal Health Team (MHT) consult request dated November 19, 2013, DARRTS Reference ID: 3409449

Background:

Amylin Pharmaceuticals has submitted a Biologics License Application (BLA 125390) for Myalept® (metreleptin). This BLA was submitted in different modules under the rolling review program with the final module submitted on March 27, 2013. The proposed indication is for the treatment of adult and pediatric patients with generalized lipodystrophy and metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia, diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis. Metreleptin received orphan designation for the treatment of metabolic disorders secondary to lipodystrophy on August 22, 2001. Currently there are no approved treatments for lipodystrophy.

Lipodystrophy can be acquired or congenital and is associated with selective loss of body fat. Patients may have a generalized form or a more localized variety. The congenital form has an inherited, genetic basis, for which 11 genetic loci have been discovered to date. The genetic forms are rare with about 1000 cases reported worldwide. Patients have metabolic complications such as diabetes, increased triglycerides and hepatic steatosis.¹

Metreleptin is a recombinant analog of human leptin. Leptin is a hormone that is primarily secreted by adipose tissue and provides feedback to the central nervous system on the status of the body's energy stores. Patients with lipodystrophy are known to have a deficiency in endogenous leptin levels which has led to the development of metreleptin as a therapy for lipodystrophy.²

The Division of Metabolism and Endocrine Products (DMEP) consulted the Pediatric and Maternal Health Staff (PMHS) to review the Pediatric Use subsection in Myalept® (metreleptin) labeling.

Drug Development Program³

After the discovery of the leptin gene in 1996, an analog of human leptin was developed and evaluated in several conditions, including obesity and lipodystrophy. In 2000, the National Institutes of Health (NIH) began a trial starting with a small cohort of patients with lipodystrophy. Because of the significant improvements in glucose metabolism and triglycerides seen in the initial phase of the placebo-controlled study, the continued use of a placebo control was considered to be unethical. This NIH study has continued as a single-arm, open-label study since 2000 and is used as the basis of approval for this application. At the time of submission of the application, the study included 72 patients with generalized and partial lipodystrophy available for safety and efficacy evaluations. The following table includes the study results.

¹ Garg A. Lipodystrophies: genetic and acquired body fat disorders. *J Clin Endocrinol Metab.* 2011;96(11):3313–25.

² Oral EA, Chan JL. Rationale for leptin-replacement therapy for severe lipodystrophy. *Endocr Pract.* 2010;16(2):324–33.

³ Medical Review of BLA 125390, dated November 18, 2013, DARRTS Reference ID: 3408513

Changes in HbA1c, fasting glucose and triglycerides after 12 months of treatment with metreleptin for patients with generalized and partial lipodystrophy:

HbA1c, %	All			Baseline HbA1c ≥ 7%		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	29	8.7 (0.4)	-2.0 (0.3)	24	9.3 (0.3)	-2.4 (0.5)
Partial	21	7.5 (0.5)	-0.4 (0.2)	11	9.2 (0.5)	-1.0 (0.4)

Fasting glucose, mg/dL	All			Baseline FPG ≥ 126 mg/dL		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	31	179.5 (15.9)	-48.3 (16.9)	21	218.6 (17.8)	-82.1 (16.5)
Partial	21	155.8 (19.3)	-32.1 (14.8)	11	220.9 (22.5)	-68.6 (23.2)

TG, mg/dL	All			Baseline TG ≥ 500 mg/dL		
	n	Baseline Median	Δ from baseline at Month 12 Median	n	Baseline Median	Δ from baseline at Month 12 Median
Generalized	30	414.5	-246.5	12	1526.5	-1117.0
Partial	21	357.0	-74.0	7	1237.0	-499.0

(From: Medical Review of BLA 125390, dated November 18, 2013, DARRTS Reference ID: 3408513)

Patients with generalized lipodystrophy had larger reductions in HbA1c, fasting glucose and triglycerides compared to patients with partial lipodystrophy. In some cases, patients with generalized lipodystrophy were able to discontinue anti-hyperglycemic or lipid lowering therapies. Patients with partial lipodystrophy were a more heterogeneous group. Patients with partial lipodystrophy and low baseline leptin levels had a greater reduction in HbA1c, fasting glucose and triglycerides levels compared to patients with partial lipodystrophy and higher baseline leptin levels. For example, HbA1c at month 12 decreased 0.9% for patients with low baseline leptin levels and partial lipodystrophy compared to 0.1% for patients with high baseline leptin levels and partial lipodystrophy. However, these differences were much smaller than the reduction in HbA1c in patients with generalized lipodystrophy at month 12.

Lymphoma has been identified as a possible risk with use of metreleptin. Three cases of T-cell lymphoma have been reported in patients in the NIH trials. Two of the cases occurred in patients with hematological disease who were on confounding medications, such as G-CSF and erythropoietin. The third patient did not have any other risk factors for development of lymphoma other than lipodystrophy.

Immunogenicity has also been identified in the trial. The long-term implications of antibody development are not known. The possibility of maternal-fetal transfer of antibodies is also a concern; it is theoretically possible that an infant could develop a congenital leptin deficiency-like condition because of development of immunogenicity in a pregnant woman receiving treatment with metreleptin.

Other adverse events of interest identified in the trial are hypoglycemia, pancreatitis, liver abnormalities and proteinuric nephropathy. Of note, lipodystrophy patients are predisposed to acute pancreatitis and all the patients with liver abnormalities had some

liver abnormalities at baseline. Additionally, proteinuric nephropathy has been associated with lipodystrophy. The lack of a control group in the trial makes it difficult to determine what adverse events may be associated with the underlying disease or with metreleptin treatment.

Reviewer Comment: Patients with generalized lipodystrophy had greater reductions in HbA1c, fasting glucose and triglycerides compared to patients with partial lipodystrophy with treatment in the trial. DMEP is considering whether the data in patients with partial lipodystrophy are sufficient to support approval of the product in this population or whether the indication should be limited to patients with generalized lipodystrophy.

The sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) program with a restricted distribution system to include prescriber certification, pharmacy certification, and documentation of safe use conditions via a prescription authorization form because of the risks of lymphoma and serious adverse sequelae caused by the development of neutralizing antibodies in non-lipodystrophy patients. The Office of Medication Error Prevention and Risk Management agrees with the sponsor's proposal and also recommends that the REMS include identifying patients by baseline leptin concentration, monitoring leptin concentrations, and/or monitoring antibody titers. This additional monitoring would be particularly important if a partial lipodystrophy indication is granted.

PMHS-Maternal Health Team was also consulted during the review of this application and will provide information on and recommended monitoring of pregnant women treated with metreleptin.

Pediatric Review:

Under the Pediatric Research Equity Act (PREA), all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must include a pediatric assessment that is adequate to assess the safety and effectiveness of the product and to support dosing and administration for all relevant pediatric populations, unless requirement is waived, deferred, or inapplicable. Since Myalept® (metreleptin) has orphan designation, PREA does not apply.

Pediatric Use Labeling:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

It is important to note the product proposed by this sponsor when reconstituted with bacteriostatic water for injection (BWHI) contains benzyl alcohol. Benzyl alcohol 0.9% when used in flush solutions has been shown to cause severe metabolic acidosis,

encephalopathy and respiratory depression with gasping leading to death in infants at doses of 99 to 234 mg/kg/day.⁴ Benzyl alcohol toxicity occurs in infants, particularly in low birth-weight infants, because greater dose of benzyl alcohol relative to body weight, and because the metabolic and excretory pathways for benzyl alcohol are still immature.⁵ Additionally, infants in hospital settings may be exposed to benzyl alcohol through routine administration of multiple medications and may be at increased risk of toxicity.⁶

In May 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and CDC issued a Drug Bulletin⁷ containing strong recommendations to warn pediatricians and hospital personnel against using fluids and diluents preserved with benzyl alcohol in newborn infants. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible.⁸ In 1997, the AAP Committee on Drugs published a review of the available published literature on neonatal benzyl alcohol toxicity and reported that most therapeutic agents, other than large-volume fluids, contain amounts of benzyl alcohol smaller than those associated with neonatal death; however, the effects of lower amounts of benzyl alcohol have not been adequately studied.⁹

In 2009, PMHS developed standard pediatric use warning language for neonates and infants in labeling for drugs that contain benzyl alcohol either as an active ingredient or as a preservative. Prior to 2009, the pediatric use warning language varied among drug products. This revised warning language is placed in labeling when product that contains benzyl alcohol as an active ingredient or preservative. In addition, if a drug product is available in more than one presentation and a benzyl alcohol-free formulation is available, the recommendation to use the benzyl alcohol-free formulation in pediatric patients, if available, is also placed in labeling. Furthermore, PMHS would recommend the neonate and infant warning be placed in any drug product in which benzyl alcohol is present intentionally as an ingredient or unintentionally as a byproduct of manufacturing. The following is an example of the neonate and infant benzyl alcohol warning use in drug products that contain benzyl alcohol as a preservative:

"Preservative-free [Tradename], when available, is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its

⁴ Gershanik, J et al. The Gasping Syndrome and Benzyl Alcohol Poisoning. NEJM 1982; 307:1384-1388.

⁵ Hiller J, Benda G, Rahatzad M, et al. Benzyl alcohol Toxicity: Impact on mortality and intraventricular hemorrhage among very low birth-weight infants. 1986; 77(4):500-6.

⁶ Anderson C, Ng J, et al. Benzyl alcohol poisoning in a premature newborn infant. Am J Obstet Gynecol. 1984;148:344-346.

⁷ FDA Drug Bulletin, August 1982.

⁸ American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. Pediatrics. 1983;72(3):356-8

⁹ AAP Committee on Drugs. Inactive ingredients in pharmaceutical products: update. Pediatrics 1997;99(2);268-78.

metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gaspings syndrome," the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources."

PMHS-PEDIATRIC TEAM RECOMMENDATIONS FOR LABELING

Note: these labeling recommendations are based on draft labeling from November 12, 2013. (See attached Appendix 1 with Sponsor's draft labeling and Appendix 2 with PMHS tracked changed suggestions to labeling).

See approval letter for final approved labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----- WARNINGS AND PRECAUTIONS -----

- Benzyl Alcohol Toxicity: Preservative-free Water for Injection recommended for neonates and infants. (5.7)

2 DOSAGE AND ADMINISTRATION

2.3 Administration

MYALEPT Preparation and Storage

Instruct patients to store the vials of lyophilized powder in their carton in the refrigerator as soon as received [see *How Supplied/Storage and Handling (16.2)*].

MYALEPT is reconstituted aseptically with 2.2 mL of sterile Bacteriostatic Water for Injection (BWFI), USP (0.9% benzyl alcohol). For preservative-free MYALEPT, which is recommended for use in neonates and infants, reconstitute with 2.2 mL of sterile Water for Injection (WFI) [see *Warnings and Precautions (5.7)* and *Use in Specific Populations (8.4)*].

Allow the MYALEPT vial to warm to room temperature prior to use.

When reconstituted in BWFI, MYALEPT solution can be used within 3 days when stored in the refrigerator between 36°F and 46°F (2°C and 8°C) and protected from light [see *How Supplied/Storage and Handling (16.2)*]. Discard unused reconstituted solution after

3 days. When reconstituted in sterile WFI unused reconstituted solution should be discarded after 4 hours. Attach the supplied sticker to the vial and enter the discard date.

Reconstitution of the Lyophilized Powder

Instruct patients to follow the directions below for reconstitution of the lyophilized powder:

- a) Remove the vial containing the MYALEPT lyophilized powder from the refrigerator and allow the vial to warm to room temperature prior to use.
- b) Visually inspect the vial containing MYALEPT. The cake of lyophilized powder should be intact and white in color.
- c) Using a 3 mL syringe with a 22-gauge or smaller diameter needle, withdraw 2.2 mL of the supplied sterile Bacteriostatic Water for Injection (BWFI) or, for preservative free MYALEPT, sterile Water for Injection. Do not reconstitute MYALEPT with other diluents.
- d) Slowly inject the BWFI or WFI into the sides of the vial containing the lyophilized powder of MYALEPT. It is normal for some bubbles to form.
- e) Remove the needle and syringe from the vial and **gently swirl** the contents to reconstitute. **Do not shake or vigorously agitate.** When properly mixed the MYALEPT reconstituted solution should be clear and free of clumps, dry powder, bubbles, or foam. Do not use the solution if discolored or cloudy, or if particulate matter remains.
- f) Compatibility of MYALEPT reconstituted solution with other solutions:
 - Do not mix with, or transfer into, the contents of another vial of MYALEPT.
 - Do not add other medication including insulin. Use a separate syringe for insulin injections (may inject both medications in the same area using two different injection sites).

See the MYALEPT Instructions for Use for complete preparation and administration instructions. The instructions can also be found at www.myalept.com.

5 WARNINGS AND PRECAUTIONS

5.7 Benzyl Alcohol Toxicity

MYALEPT when reconstituted with BWFI contains benzyl alcohol. Myalept when reconstituted with Water for Injection (WFI) contains no preservative. Preservative-free MYALEPT is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death in pediatric patients, particularly in neonates and premature infants [see Use in Specific Populations (8.4)]

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatrics

The MYALEPT study included a total of 35 pediatric patients (73%) with an age range from 1 to 17 years. No clinically meaningful differences were observed in the efficacy and safety of MYALEPT between pediatric and adult patients.

MYALEPT, when reconstituted with BWFI, contains benzyl alcohol. Preservative-free MYALEPT, when available, is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome," the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources. When reconstituted with 2.2 mL of BWFI, MYALEPT contains 1.76 mg of benzyl alcohol per mg of metreleptin or 9 mg of benzyl alcohol per mL of reconstituted product.

140 Pages of Draft Labeling have been
Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

DONNA L SNYDER
02/05/2014

HARI C SACHS
02/05/2014

LYNNE P YAO
02/10/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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Pediatric and Maternal Health Staff – Maternal Health Review

Date: February 5, 2014

From: Tamara Johnson, MD, MS, Medical Officer
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader- Maternal Health
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Metabolism and Endocrinology Products (DMEP)

BLA: 125390/000

Drug: MYALEPT (metreleptin)

Applicant: Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)

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

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

- Consult Request:**
1. “Potential risks of metreleptin include lymphoma and immunogenicity (including a question of the maternal transfer of neutralizing antibodies).”
 2. “This drug is likely to be used in pediatrics and pregnant women. Please review and comment on the PI and Medguide.”

Materials Reviewed:

- Original BLA 125390, Myalept (metreleptin), received March 27, 2013
- Draft Myalept (metreleptin) Labeling, submitted March 27, 2013
- Primary Clinical Review by J. Golden, MD, dated November 15, 2013
- Primary Nonclinical Review by F. Basso, PhD, dated November 5, 2013

INTRODUCTION

The original marketing application for metreleptin is submitted as a rolling submission as agreed upon by the Agency and the Applicant, Amylin Pharmaceuticals, LLC, a subsidiary of Bristol-Myers Squibb Company. The final submission was received on March 27, 2013. The application is presented to the Agency with clinical evidence from two open-label trials and an expanded access program. Metreleptin was granted orphan designation on August 22, 2001.

The review division, Division of Metabolism and Endocrinology Products (DMEP), requests input from the Maternal Health Team on the potential risks of maternal transfer of neutralizing antibodies to the developing fetus or neonate. In addition, DMEP requests assistance in review of the full prescribing information and the medication guide.

This review discusses the risk of maternal transfer of antibodies to the developing fetus or neonate based upon clinical information from similar human hormone drug products found in the medical literature. The review also provides recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Generalized and Partial Lipodystrophy

Generalized and partial lipodystrophies may be inherited or may be an acquired disorder.¹ Patients with lipodystrophy lack adipose tissue and, because the leptin hormone is primarily secreted from adipose tissue, these patients are also leptin-deficient. Leptin is responsible for the regulation of energy homeostasis, fat and glucose metabolism, as well as neuroendocrine and reproductive systems. Without leptin, patients exhibit hyperphagia, excess energy intake, and develop metabolic abnormalities such as insulin

¹ Chan JL, Lutz K, Cochran E, Huang W, Peters Y, Weyer C, Gorden P. Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. *Endocr Pract.* 2011 Nov-Dec;17(6):922-32.

resistance. They also accumulate fat in the bloodstream (leading to hypertriglyceridemia) and have ectopic fat deposition in non-adipose tissues such as the liver and muscle. The severity of the disease is related to the degree of adipose tissue loss, and thereby, degree of leptin deficiency.

Inherited forms of lipodystrophy are rare. Congenital generalized lipodystrophy (CGL) is inherited in an autosomal recessive manner and has an estimated worldwide prevalence of 1 in 10 million.² CGL patients lack adipose tissue and are insulin resistant from birth with metabolic derangements. In addition to muscular hypertrophy and hepatomegaly, clinical features may also include acromegaloid features, mild mental retardation, abnormal pituitary function, acanthosis nigricans, hypertrophic cardiomyopathy, hypertension, nonalcoholic fatty liver disease, kidney disease, and polycystic ovarian syndrome in female patients.³ Both LH and FSH are decreased, therefore, only a few affected women have successful pregnancies. Affected men have normal fertility.² Additional inherited forms include familial partial lipodystrophy (FPL) and mandibuloacral dysplasia.

Acquired lipodystrophy are more common than inherited forms and may result in generalized, partial, or localized loss of adipose. Acquired lipodystrophy may be associated with autoimmune disorder, panniculitis, HIV infection, or may be idiopathic. Patients with acquired partial lipodystrophy may have normal leptin levels.

Clinical management of lipodystrophy is supportive; there are no FDA-approved therapies specific for treatment of lipodystrophy.

Metreleptin

Metreleptin is a recombinant analog of the human hormone leptin that is intended as replacement therapy to correct the metabolic abnormalities associated with leptin deficiency in patients with generalized or partial lipodystrophy. The metreleptin protein differs from the endogenous human leptin amino acid sequence by one additional amino acid, methionine, located at the amino-terminal end. Metreleptin was approved for treatment of lipodystrophy in Japan in March 2013.⁴

DISCUSSION

Maternal Transfer of Neutralizing Antibodies of Exogenous Therapeutic Proteins

DMEP requests advice regarding the risk of maternal-fetal transfer of neutralizing antibodies (NAb) and whether a baby born to a mother with neutralizing antibodies could develop a congenital leptin deficiency-like condition. In the metreleptin clinical program (lipodystrophy and obesity studies), six patients developed persistent NAb (IgG). Of the six patients, the three who participated in the obesity studies were noted to have

² Garg, A. Acquired and inherited lipodystrophies. *New Eng. J. Med.* 350: 1220-1234, 2004.

³ Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 608594; February 17, 2011. World Wide Web URL: <http://omim.org/>

⁴ Chou K, Perry CM. Metreleptin: first global approval. *Drugs.* 2013 Jun;73(9):989-97. Abstract.

decreased levels of endogenous leptin. Therefore, DMEP is concerned that this scenario will occur with maternal transfer of NAb to the developing fetus or neonate, potentially leading to a leptin deficiency-like condition.

Because transfer of maternal antibodies occurs through the placenta (IgG) to the fetus and through breastmilk (IgA) to the neonate, it is plausible that NAb may transfer to the fetus and interfere with the action of endogenous leptin. Of the three lipodystrophy patients who developed NAb, none were reported to be pregnant during the course of the clinical trials. In addition, amongst those infants born to mothers who continued metreleptin treatment during pregnancy, no data on metreleptin antibody levels in the infants were collected. Therefore, there is no objective evidence of a leptin deficiency-like condition in an infant, although the theoretical risk of this adverse event remains.

A review of the literature found no information on metreleptin and the maternal transfer of metreleptin-related NAb to the fetus/neonate. There was also little evidence of a congenital deficiency-like condition associated with maternal use of other recombinant human hormones like insulin or levothyroxine. However, a rare condition of transient congenital hypothyroidism has among one of its etiologies placental transfer of TSH receptor antibodies from maternal autoimmune thyroid disease.⁵ Infants with this type of transient congenital hypothyroidism require hormone replacement for the first few months or years of life, although clearing the TSH receptor antibodies by three months of age.

No concerns were mentioned in the LactMed database related to discontinuation of insulin or levothyroxine while breastfeeding. The LactMed database provides information for FDA-approved drugs when available on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered, and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

DMEP's additional concern of the tumorigenic potential of metreleptin is raised due to negative *in vitro* assays, the lack of a two-year carcinogenicity study in rodents, literature reports of leptin promoting cell proliferation and tumor progression, and three cases of T-cell lymphoma reported in lipodystrophy patients. This concern was also evaluated by FDA's Division of Hematology Products (DHP). Based on the fact that leptin activates the JAK-STAT intracellular pathway and other pathways that promote cell growth and survival and inhibits apoptosis, it is biologically plausible that metreleptin may contribute to the risk of lymphoma or other malignancy. The three cases of lymphoma, however, could not be clearly attributed to metreleptin.

In summary, no clear conclusions may be made at this time regarding the risks of maternal-fetal transfer of NAb and potential tumorigenicity from metreleptin exposure. The effect of metreleptin NAb on the developing fetus has not been described in the

⁵ Mengreli C, Maniati-Christidi M, Kanaka-Gantenbein C, Girginoudis P, Vagenakis AG, Dacou-Voutetakis C. Transient congenital hypothyroidism due to maternal autoimmune thyroid disease. *Hormones (Athens)*. 2003 Apr-Jun;2(2):113-9.

Applicant's submission or in the medical literature such that the outcome of a congenital leptin deficiency-like condition may be predicted. In addition, evidence of tumorigenesis may not be seen for years in patients or infants born to mothers on metreleptin. Because the data are sparse, the extent of these risks remains unknown. Therefore, until more substantial data is available, healthcare providers should inform mothers of these potential risks to the fetus/infant.

Pregnancy Data and Literature Review

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (PLLR) (published on May 29, 2008). As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers labeling subsections. In addition, the MHT works with the pharmacology/toxicology reviewers to present animal data, in the Pregnancy and Nursing Mothers subsections, to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

Although no teratogenicity was observed in animal embryo-fetal toxicity studies with metreleptin, there was some risk to both pregnant mice and pups demonstrated in other animal reproduction studies. In the reproductive and developmental toxicology studies, pregnant mice experienced prolonged gestation and difficult labor (dystocia) which lead to death of some laboring mice and low perinatal survival of pups. There was no dose-response relationship as these events were observed at all dose levels. Metreleptin did not affect fertility in mice.

No adequate and well-controlled study of metreleptin treatment in pregnant lipodystrophy patients was conducted, however, eight female patients with inherited generalized lipodystrophy (n = 4) or partial lipodystrophy (n = 4) became pregnant while enrolled in the metreleptin clinical program. Ten pregnancies were reported in these eight patients. Each patient had received metreleptin treatment varying from 2 months to 9 years prior to conception. Of the ten pregnancies, two resulted in full term (≥ 37 weeks gestational age) live births, one results in full term stillbirth (resuscitated), three resulted in preterm (32- <37 weeks GA) live births, two resulted in early preterm (20- <32 weeks GA) live births,

and two resulted in spontaneous abortions (< 20 weeks GA). In six pregnancies, patients continued metreleptin treatment during pregnancy and resulted in a term live birth, a term stillbirth (resuscitated), a preterm live birth at 32 weeks, two preterm deliveries of nonviable fetuses, and a spontaneous abortion. Table 1 (see Appendix A) further describes the specifics of these pregnancies.

Medical Officer Comments

It should be noted that the stillborn infant who was resuscitated experienced shoulder dystocia which lead to some trauma during the delivery. Shoulder dystocia is associated with a high risk fetal morbidity and mortality.⁶ Maternal obesity, diabetes, post-term pregnancy, and multiples are risk factors for fetal shoulder dystocia. Therefore, there was potential for a similar event amongst the lipodystrophy patients who became pregnant during the metreleptin clinical trials. The majority of these patients (7 out of 8) also had a comorbidity of diabetes mellitus.

Although an article by Moynihan, *et al.* 2006, describes an *in vitro* inhibitory effect of leptin on human myometrium contractility that may play a role in dysfunctional labor, it is difficult to conclude that metreleptin induces dystocia from the limited information reported in the ten pregnancies in lipodystrophy patients.⁷ In the clinical setting, a laboring woman may present with dystocia due to multiple factors (i.e. cephalopelvic disproportion, ineffective uterine contractions, inadequate cervical dilatation or fetal descent).⁸ Clinicians may utilize medications, such as oxytocin and prostaglandin E₂, to augment labor or prepare for Caesarian section. For patients with lipodystrophy, the medical literature recommends close obstetric care and monitoring, with a plan for elective early delivery. This is because lipodystrophy patients carry a risk of obstetrical complications such as gestational diabetes, macrosomia, eclampsia, intrauterine growth retardation, intrauterine death, and miscarriage.^{9, 10, 11}

In summary, there is no clear evidence of metreleptin's contribution to dystocia. The animal data raises concerns regarding dystocia and the potential of fetal harm due to traumatic birth. Nonetheless, the limited human data demonstrates pregnancy outcomes consistent with lipodystrophy and diabetes mellitus.

⁶ Leveno KJ, Hauth JC, Rouse DJ, Spong CY. Chapter 20. Abnormal Labor. In: Leveno KJ, Hauth JC, Rouse DJ, Spong CY, eds. *Williams Obstetrics*. 23rd ed. New York: McGraw-Hill; 2010. <http://www.accessmedicine.com/content.aspx?aID=6025698>. Accessed December 18, 2013.

⁷ Moynihan AT, Hehir MP, Glavey SV, Smith TJ, Morrison JJ. Inhibitory effect of leptin on human uterine contractility in vitro. *Am J Obstet Gynecol*. 2006 Aug;195(2):504-9. Epub 2006 May 2.

⁸ Leveno KJ, Hauth JC, Rouse DJ, Spong CY. Chapter 20. Abnormal Labor. In: Leveno KJ, Hauth JC, Rouse DJ, Spong CY, eds. *Williams Obstetrics*. 23rd ed. New York: McGraw-Hill; 2010. <http://www.accessmedicine.com/content.aspx?aID=6025698>. Accessed December 18, 2013.

⁹ Vantyghem MC, Vincent-Desplanques D, Defrance-Faivre F, Capeau J, Fermon C, Valat AS, Lascols O, Hecart AC, Pigny P, Delemer B, Vigouroux C, Wemeau JL. Fertility and obstetrical complications in women with LMNA-related familial partial lipodystrophy. *J Clin Endocrinol Metab*. 2008 Jun;93(6):2223-9. Epub 2008 Mar 25.

¹⁰ Maguire M, Lungu A, Gorden P, Cochran E, Stratton P. Pregnancy in a woman with congenital generalized lipodystrophy: leptin's vital role in reproduction. *Obstet Gynecol*. 2012 Feb;119(2 Pt 2):452-5.

¹¹ Akhter J, Qureshi R. Partial Lipodystrophy and Successful Pregnancy Outcome. *Journal of Pakistan Medical Association*. January 1995: 24.

The Applicant has proposed a

(b) (4)

However, a pregnancy category C classification more accurately reflects the animal findings observed in the pre- and post-natal animal studies. PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

Lactation Data and Literature Review

No information on the use of metreleptin during lactation was found in a review of published literature; however, due to the type and the 16.2 kDa molecular weight of the metreleptin molecule, it is unlikely to pass into breastmilk. Protein drugs with molecular weights higher than 800 Da (i.e. heparin, insulin, and interferons) are unlikely to be transferred to the infant via breastmilk.¹² Many, but not all, drugs transfer to breast milk. The transport of a drug into breast milk is largely a function of the drug's physicochemical properties and its concentration in maternal plasma. All of the following factors influence the amount of drug transfer into human milk: plasma and milk protein binding, molecular weight, mechanism of transport, degree of ionization, and clearance pathways. Factors that tend to produce higher human milk levels of drugs include: higher maternal plasma concentration, higher lipid solubility, higher pKa, lower protein binding, and lower molecular weight. The mean pH of human milk is 7.2, about 0.2 units lower than that of plasma. This difference influences the transfer of drugs into milk, more so for drugs that are weak bases with pKa values in that range. Drugs that are more lipid soluble may accumulate in the lipid fraction of the milk, leading to higher concentrations of drug in human milk than in maternal plasma. Most drugs move between maternal serum and human milk based on equilibrium forces. Drugs with higher molecular weights, especially those with weights greater than 800 Daltons, must generally be actively transported or dissolved in the cells lipid membranes.¹³

No formal lactation study of metreleptin treatment in nursing mothers has been conducted by the Applicant, however, three of the eight pregnant lipodystrophy patients (see Appendix A) continued to receive metreleptin during pregnancy and while breastfeeding their infants. The development of antibodies to metreleptin was not assessed in the three infants who were breastfed. The Applicant reports that these three infants showed normal development, "without health issues or adverse effects reported."

In summary, although the metreleptin molecule is unlikely to pass into human breastmilk, there are potential risks from metreleptin exposure to the nursing infant (including immunogenicity and tumorigenicity concerns). Without additional data to elucidate the extent of these risks, the use of metreleptin by nursing mothers cannot be safely recommended.

¹² Nice FJ, Luo AC. Medications and breastfeeding: Current concepts. J Am Pharm Assoc. 2012;52:86–94.

¹³ Hale T. Medications and Mothers' Milk, 12th ed, 2012.

CONCLUSIONS

There is insufficient evidence to accurately predict the development of neutralizing antibodies to endogenously produced leptin in unaffected infants born to lipodystrophy patients. In addition, the limited data provided from pregnant lipodystrophy patients does not lend to a clear conclusion about the risks of metreleptin treatment over those risks already known to pregnant lipodystrophy patients. A pregnancy surveillance program is recommended for the postmarketing period to monitor the outcomes of pregnant mothers and infants exposed to metreleptin. This pregnancy surveillance program may be incorporated into a postmarketing product registry.

In regards to labeling, PMHS-MHT structured the pregnancy and nursing mothers subsections of the Myalept labeling in the spirit of the proposed PLLR, while complying with current labeling regulations.

PMHS-MHT participated in the team and labeling meetings with DMEP held during December 2013 and January 2014. Final labeling will be negotiated with the applicant and may not fully reflect changes recommended here.

RECOMMENDATIONS

1. A Pregnancy Surveillance Program to monitor outcomes of women and infants who were exposed to metreleptin during pregnancy. (See Appendix B – Data Elements for Collecting Pregnancy Exposure Data.) PMHS-MHT has suggested language for this program to be included in Section 8.1 of the full prescribing information. See below.
2. PMHS-MHT recommends revisions to the Applicant's proposed labeling and medication guide. These labeling revisions are shown below; deleted text has a strikethrough, while new text is underlined. Recommendations made by the Pharmacology/Toxicology Review team, Dr. F. Basso and Dr. T. Boucier, are included in this version of the labeling.

(HIGHLIGHTS)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, may cause fetal harm. MYALEPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No adequate and well-controlled studies have been conducted with metreleptin in pregnant women (8.1).
- Nursing Mothers: (b) (4)
Discontinue drug or nursing depending on importance of drug to mother (8.3).

8.1 Pregnancy Category C

There is a Myalept product registry that monitors outcomes in women exposed to Myalept during pregnancy. Women who become pregnant during Myalept treatment are

encouraged to enroll. Patients or their physicians should call 1-XXX-XXX-XXXX to enroll.

Risk Summary

There are no adequate and well-controlled studies of ~~metreleptin~~ Myalept in pregnant women. (b) (4)

In animal reproduction studies in mice, administration of metreleptin during organogenesis was not teratogenic at doses up to 7-fold the clinical dose. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In a pre- and post-natal development study in mice, administration of metreleptin caused prolonged gestation and dystocia resulting in maternal death during parturition and lower survival of offspring in the immediate post-natal period at doses below the clinical dose. (b) (4) Myalept should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated Maternal and Fetal Risk

Myalept's contribution to obstetrical risks and complications is unknown compared to those already documented in the lipodystrophy patient population (i.e., gestational diabetes, macrosomia, eclampsia, intrauterine growth retardation, intrauterine death, and miscarriage).

Labor or Delivery

The effects of Myalept on labor and delivery in pregnant women are unknown. In an *in vitro* study of human myometrial tissue exposed to a recombinant leptin, human uterine contractility was inhibited. Furthermore, prolonged gestation and dystocia were observed in animal studies with metreleptin [see Animal Data].

Animal Data

Metreleptin administered to pregnant mice during the period of organogenesis was not teratogenic at doses up to 7-fold the clinical dose, based on body surface area.

In a pre- and post-natal development study in mice, metreleptin administered at doses of 3, 10 and 30 mg/kg (<1, 5, and 15-fold the clinical dose in a 60 kg subject, based on body surface area) from gestation day 6 to lactation day 21 caused prolonged gestation and dystocia at all doses, starting at below the clinical dose. Prolonged gestation resulted in the death of some females during parturition and lower survival of offspring within the immediate post-natal period. Decreased maternal body weight was observed from gestation throughout lactation at all metreleptin doses, and resulted in reduced weight of offspring at birth which persisted into adulthood. However, no developmental abnormalities were observed and reproductive performance of the first or second generations was not affected at any dose.

Placental transfer of metreleptin into the fetus was low (approximately 1%) following subcutaneous dosing from gestation days 11 to 17.

8.3 Nursing Mothers

(b) (4)

It is not known whether Myalept is present in human milk. Endogenous leptin is present in human milk. Because of the potential for serious adverse reactions from immunogenicity in nursing infants from Myalept, and the potential for tumorigenicity shown for leptin in *in vitro* and animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of drug to the mother [see Adverse Reactions (6.2) and Nonclinical Toxicology (13.1)].

(b) (4) — Nursing Mothers

(b) (4)

Advise nursing mothers that breastfeeding is not recommended with Myalept use [see Use in Specific Populations (8.3)].

(MEDICATION GUIDE)

Before you take MYALEPT, tell your healthcare provider if you:

- are pregnant, or plan to become pregnant. It is not known if Myalept will harm your unborn baby.
- are breastfeeding or plan to breast-feed. It is not known if MYALEPT passes into your breast milk. You and your healthcare provider should decide if you will take MYALEPT or breast-feed. You should not do both without talking with your healthcare provider first.

APPENDIX A

Table 1: Pregnancies in Lipodystrophy Patients on Metreleptin during Clinical Trials

Patient ID or Study type*	Age (yrs.)	Disease type [†]	Preconception metreleptin exposure	Pregnancy outcome [‡]	Perinatal conditions	Metreleptin exposure? Y/N		
						During pregnancy	Postpartum	While breastfeeding
NIH 90105 [‡]	23	CGL	9 years	Term stillbirth/resuscitated, elective induction, large for gestational age, vaginal delivery complicated by cephalopelvic disproportion – 37 weeks EGA	Respiratory distress, shoulder dystocia	Y	Y	Y, breastfed for 5 months
NIH 90156	25	CGL	3 years	Early preterm live delivery, cervical incompetence – 20 4/7 weeks EGA	Nonviable fetus	Y	Y	N/A
NIH 90140	19	CGL	3 years	Spontaneous abortion at 8 weeks EGA	N/A	Y?	Y	N/A
	21	CGL	5 years	Preterm live birth, pre-eclampsia, Caesarian section – 32 weeks EGA	None reported.	Y	Y	Y, breastfed for 12 months
NIH 90152	33	FPL	2 years	Spontaneous abortion per patient report – not confirmed	N/A	Y	N, patient removed from study	N/A

ITT	27	FPL	3 years	Term live birth, pre-eclampsia, Caesarian section – 37 weeks EGA	Hypoglycemia and respiratory distress	N	Y	N, breastfed for 9 months
NPP	20	CGL	4 years	Early preterm live twin birth, premature labor -- 23 2/7 weeks EGA	Nonviable fetuses	Y	Y	N/A
	21	CGL	5 years	Term live birth, vaginal delivery – 38 weeks EGA	None reported.	Y, stopped in the last month of pregnancy	Y	Y, breastfeeding ongoing as of 12/5/2013
NPP	27	FPL	2 months	Preterm live birth, pre-eclampsia, Caesarian section – 35 5/7 weeks EGA	Hypoglycemia	N, discontinued at month 2 of pregnancy	N	N
NPP	36	FPL	9 months	Preterm live birth, vaginal delivery – 35 weeks EGA	None reported.	N	Y	Unknown

Table based on summary of pregnancy data submitted by the Applicant in “Response to FDA Request for Information Dated 19-Nov-2013.”

*NIH: National Institutes of Health; ITT: investigator-initiated trial; NPP: named patient program

† CGL: Congenital Generalized Lipodystrophy; FPL: Familial Partial Lipodystrophy

‡ EGA: estimated gestational age

‡ Additional information from Metreleptin Clinical Study Report 991265 and 20010769, and Maguire M, *et al.* *Obstet Gynecol.* 2012 Feb;119(2 Pt 2):452-5.

APPENDIX B

PMHS Recommended Data Elements for Collecting Pregnancy Exposure Data

A. General

- Patient identifier
- Name of reporter at initial contact
- Date of initial contact
- Dates of any follow-up contacts
- Telephone number of reporter
- Additional contact names and phone numbers (if reporter is the patient)

B. Maternal Information

- Source of information (e.g., obstetrician, pregnant woman, other)
- Birth date
- Race
- Occupation
- Maternal medical history (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, allergic disorders, heart disease, connective disease, autoimmune disease, hepatitis, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures, other)
- Obstetrical History:
 - Number of pregnancies and outcome of each (live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy)
 - Previous maternal pregnancy complications
 - Previous fetal/neonatal abnormalities and type
- Current Pregnancy:
 - Date of last menstrual period
 - Complications during pregnancy (including any adverse drug reactions) and dates
 - Number of fetuses
 - Labor/delivery complications
 - Disease course(s) during pregnancy and any complications
 - Medical product exposures (prescription drugs, OTC products & dietary supplements):
 - Name
 - Dosage & route
 - Date of first use & duration
 - Indication
 - Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount
- Family History (specify type, maternal/paternal, etc.):
 - Spontaneous Abortions
 - Anomalies/Malformations
 - Multiple fetuses/births

C. Neonatal Information

Initial:

- Source of information (e.g., obstetrician, pediatrician, mother)
- Date of receipt of information
- Date of birth or termination
- Gestational age at birth or termination
- Gestational outcome (live born, fetal death/stillborn, spontaneous abortion, elective termination)
- Sex
- Pregnancy weight gain of mother
- Obstetric complications (e.g., pre-eclampsia, premature labor, premature delivery)
- Pregnancy order (singleton, twin, triplet)
- Results of neonatal physical examination including
- Anomalies diagnosed at birth or termination
- Anomalies diagnosed after birth
- Weight at birth indicating whether small, appropriate, or large for gestational age
- Length at birth
- Condition at birth (including when available Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
- Neonatal illnesses, hospitalizations, drug therapies

Follow-up:

- Source of information (e.g., pediatrician, mother)
- Date of receipt of information
- Anomalies diagnosed since initial report
- Developmental assessment
- Infant illnesses, hospitalizations, drug therapies

Note: Infants should be followed for 12 months with assessment times at birth, at 12 months, and some point in between.

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/s/

TAMARA N JOHNSON
02/05/2014

JEANINE A BEST
02/05/2014

LYNNE P YAO
02/10/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 5, 2014

To: Patricia Madara, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 125390
OPDP labeling comments for MYALEPT™ (metreleptin for injection), for subcutaneous use

OPDP has reviewed the proposed draft prescribing information (PI) and carton container labeling for MYALEPT™ (metreleptin for injection), for subcutaneous use submitted for consult on December 17, 2013.

OPDP's comments regarding the proposed draft PI are provided directly on the marked version attached. OPDP has no comments on the proposed draft carton and container labeling at this time.

Please note, OPDP's comments regarding the draft medication guide and instructions for use (IFU) were provided under separate cover on February 5, 2014, in conjunction with the Division of Medical Policy Programs (DMPP). Therefore, OPDP's comments regarding these materials are not included on the draft version of the PI.

Thank you for the opportunity to comment on the proposed draft PI and carton container labeling.

If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
02/05/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 05, 2014

To: Jean-Marc Guettier, MD
Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kendra Y. Jones
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: (Medication Guide (MG) and
Instructions for Use (IFU))

Drug Name (established name): MYALEPT (metreleptin for injection)

Dosage Form and Route: for subcutaneous use

Application Type/Number: BLA 125390

Applicant: Amylin Pharmaceuticals , Inc.

1 INTRODUCTION

On December 15, 2010, Amylin Pharmaceuticals Inc., submitted for the Agency's review a Biologics Licensing Application (BLA 125390) for MYALEPT (metreleptin for injection) for subcutaneous use, for the proposed indication of the treatment of diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on April 09, 2012 and December 17, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for MYALEPT (metreleptin for injection) for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed November 26, 2013.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DMEP under separate cover.

2 MATERIAL REVIEWED

- Draft MYALEPT (metreleptin for injection) MG and IFU received on April 02, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on January 29, 2014.
- Draft MYALEPT (metreleptin for injection) MG and IFU received on April 02, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on February 03, 2014.
- Draft MYALEPT (metreleptin for injection) Prescribing Information (PI) received on December 15, 2010, revised by the Review Division throughout the review cycle, and received by DMPP on January 29, 2014.
- Draft MYALEPT (metreleptin for injection) Prescribing Information (PI) received on December 15, 2010, revised by the Review Division throughout the review cycle, and received by OPDP on January 28, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication*

Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
02/05/2014

KENDRA Y JONES
02/05/2014

MELISSA I HULETT
02/05/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 24, 2013

TO: Julie Golden, M.D., Medical Officer
Eric Colman, M.D., Clinical Team Leader and Deputy Director
Patricia Madara, Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Leibenhaut, M.D. for
Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125390

APPLICANT: Amylin Pharmaceuticals, LLC

DRUG: metreleptin

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review with 3-month extension due to
submission of a major amendment

INDICATIONS: Treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy

CONSULTATION REQUEST DATE: May 30, 2013

CLINICAL INSPECTION SUMMARY GOAL DATE: December 27, 2013

DIVISION ACTION GOAL DATE: February 24, 2014

PDUFA DATE: February 24, 2014

I. BACKGROUND

Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb) is seeking approval of metreleptin (Myalept) for treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy. The pivotal dataset (n=72) is based on two open-label trials that were conducted at the National Institutes of Health (NIH): Protocol 991265 “*Efficacy of Leptin Replacement in Treatment of Lipodystrophy*” (Completed) and Protocol 20010769 “*Long Term Efficacy of Leptin Replacement in Treatment of Lipodystrophy*” (Ongoing), which were combined into a single dataset, given the similarity of the protocols and that seven of nine patients from the original trial were enrolled in the second ongoing trial.

As an additional means of making metreleptin available for expanded access to U.S. patients with lipodystrophy prior to an approved indication, the Sponsor initiated the open-label study FHA101 “*An Open-Label Treatment Protocol to Provide Metreleptin for the Treatment of Diabetes Mellitus and/or Hypertriglyceridemia Associated with Lipodystrophy*” (Ongoing), submitted in May 2008 via treatment IND 101,824 (n=28).

Study 991265 was an open-label, investigator-initiated pilot study (under IND 60,534) conducted from July 2000 to July 2002 at the NIH in Bethesda, MD and the University of Texas Southwestern Medical Center in Dallas, TX. Study 20010769 is an open-label, ongoing (i.e., open-ended, continued enrollment), investigator-initiated study (also under IND 60,534) conducted at the NIH in Bethesda, MD. Although conducted as separate studies, Study 991265 and 20010769 are considered as a single extended study since the two studies employed a similar protocol and most of the patients studied under the initial study continued long-term treatment in the second study. Thus, results from these 2 studies are summarized in a single study report. The total number of patients in the U.S. lipodystrophy trials combined is 100. The sites chosen for audit included 97 of those patients.

Study FHA101 is under a treatment IND 108,824. Although there are three sites so far that have enrolled patients in study FHA 101, the site chosen for inspection enrolled 25 of the 28 patients in this trial to-date.

(b) (4) was contracted to perform data management services including data entry (using DataFax[®] - an Intelligent Character Recognition [ICR] system for receiving paper case report forms from study sites by fax or

email), programming and validation of data exports, and preparation of the Data Management plan. Following the interim database locks for Study 991265 and Study 20010769, (b) (4) provided the CRFs, the locked database, data management plan, quality assurance audit reports, and other data management documents on hard media, (e.g., CD-ROM) for archiving. The Sponsor was responsible for medical coding, SAE reconciliation and data cleaning.

The three studies, the first of which dates back to 2000, were not originally intended to support a marketing application. For the NIH Studies 991265 and 20010769, the site followed both NIH and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Guidelines in accordance with applicable GCP for executing the protocol and collecting data from enrolled patients. Patient data was documented in patient medical records (electronic and/or paper) and stored at the site in NIH systems. Initially, patient data was collected on paper and stored in hard copy binders. Beginning in 2004, the NIH transitioned to electronic medical records.

In 2006, data were retrospectively captured by the sponsor at that time (Amylin Pharmaceuticals) into an industry-standard database with standardized conventions. Initially this involved the transcription of data from source documents onto paper case report forms (pCRF) which were then submitted to the contract research organization (CRO) (b) (4) for data entry into DataFax[®]. After patient data were transcribed onto pCRF, the data were then 100% verified against the source for accuracy by another member of the data collection team. If discrepancies were found during source data verification (SDV), the team member performing the SDV updated the pCRF with the appropriate data corrections (with dated initials next to the change), or met with site staff to clarify the appropriate data as needed.

Later in 2011, to simplify and streamline the process for the ongoing 20010769 study, the Sponsor transitioned to the use of (b) (4) system for data collection. Once the Sponsor transitioned to (b) (4) it was no longer necessary to contract (b) (4) for data management services and data entry into (b) (4) was performed by the sponsor-appointed data collection team.

The NIH PI was responsible for monitoring Studies 991265 and 20010769 to assure adherence to the NIH policies, applicable regulatory requirements, and the study protocol. There was no independent monitoring function during the conduct of the studies to oversee study conduct. FHA101 followed safety and clinical monitoring procedures/practices established by the Sponsor and described in the FHA Monitoring Guidelines. Sites received on-site monitoring visits and telephone monitoring.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of BLA 125390 in accordance with Compliance Program 7348.811 and 7348.810. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Preliminary Classification
Phillip Gorden, M.D. NIH Clinical Center Site #901	991265 and 20010769 72 Patients (as of July 11, 2011 data cut)	9/23/2013 – 10/04/2013	NAI
Elif Arioglu Oral, M.D. University of Michigan Site #648	FHA101 25 Patients (as of March 7, 2012 data cut)	9/16-20/2013	NAI
(b) (4)			

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending.

1. Phillip Gorden, M.D.
Clinical Endocrinology Branch
National Institute of Diabetes and
Digestive and Kidney Diseases (NIDDK)
National Institutes of Health
Clinical Center Building 10
CRC 6-5940
Bethesda, MD 20892

- a. **What was inspected:** Complete records for 33 of the patients enrolled were reviewed, including all nine subjects screened and consented into Study 991265. The review included informed consents, baseline and demographic data, subject eligibility, concomitant medications, treatment dates, visit dates, adverse events, study procedures, laboratory values including primary efficacy endpoint data as measured by changes in HbA1c, and fasting triglyceride levels. Institutional review board (IRB) approvals and renewals, staff training, certification of financial interests (Form FDA-3454) and drug accountability were also

reviewed. The NIH Clinical Records Information System (CRIS), scanned medical records, and hard copy files were reviewed for both studies.

- b. General observations/commentary:** The site has screened a total of 101 subjects for Studies 991265 and 20010769 as of the date of the inspection. The data for both studies have been combined and the sponsor used continuous numbering across both studies to identify subjects (starting with 90101). Nine subjects were screened and consented under Study 991265. Seven of these nine subjects in addition to 92 subjects were enrolled into Study 20010769. As of the 2009 interim data cut-off point, the combined studies had enrolled 55 subjects. As of the inspection date, 68 patients were considered active. Study 20010769 is still on-going. There are 17 international patients being treated. Study visit timelines for these international patients and some national patients are not adhered to strictly.

There were no issues with regard to inaccurate records; however, navigating study subjects records was difficult. Most of the enrollees' records were extremely large files, study information within these files was not organized and included non-related study information (some of the study's subjects were also Dr. Gorden's and/or other National Institutes of Health [NIH] physicians' patients and all NIH visits were aggregated in the same file), and complete patient records are stored in three different systems at the NIH (hard copy files, the electronic systems Chart View, and the Clinical Research Information System [CRIS]).

There were no discrepancies regarding adverse event reporting in the files reviewed. Subjects met inclusion/exclusion criteria and had documented treated as per protocol. Concomitant medications were recorded. The primary efficacy endpoints HbA1c, fasting plasma glucose (FPG), and triglyceride (TG) levels were verifiable. There were three protocol violations noted and all had been reported.

No Form FDA-483, Inspectional Observations, was issued. However, there were three discussion items at the end of the inspection that were discussed:

1.  (b) (4)



Written metreleptin injection steps were provided to some patients. The patients were trained during inpatient visits by NIH nurses as well as the subinvestigators.

2. Non-study related data was reported as study data to FDA for patients 90101 to 90111. Some of the study subjects were regular patients of the CI. The sponsor reported off-site visits conducted by these subjects as study related visits before study 20010769 began. The study coordinator stated initially that there was no system in place at the NIH that could control access to patient records by the visit.
3. Two patients (90102 and 90103), who were enrolled in study 991265, never enrolled (and no consents found) into study 20010769 but were reported as having been enrolled into that study by the sponsor. The two patients were granted a compassionate exemption to continue metreleptin therapy. Communications to the sponsor explaining their status was documented.*

*This is further explained in the Clinical Efficacy Update report dated 10 Feb 2013. *The duration of Study 991265 was initially 4 months (Original Protocol), extended to up to 8 months (Amendment 1) and subsequently extended beyond 8 months (Amendment 2). It should be noted that 3 patients (90101, 90102, and 90103) reached 8 months of metreleptin treatment prior to the approval of Amendment 2 and were granted exemption by the IRB to receive bridging metreleptin treatment under a Compassionate Use Exemption protocol (01-DK-9970) under the same IND. Of these 3 patients, patient 90101 enrolled into Study 20010769, patient 90102 was withdrawn during the compassionate use exemption due to non-compliance, and patient 90103 elected not to enroll into Study 20010769.*

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Elif Arioglu Oral, M.D.
University of Michigan
Department of Internal Medicine
Division of Endocrinology and Metabolism
24 Frank Lloyd Wright Dr.
Lobby G1500
Ann Arbor, MI 48106

- a. **What was inspected:** All 27 subjects' records were reviewed. The inspection covered informed consent documents, inclusion/exclusion criteria, adverse event review, laboratory results (including study endpoints), IRB approvals, 1572s, delegation of duties, financial disclosure forms, staff training, drug storage/handling and drug accountability (although a full reconciliation of investigational product receipt, use and return was not performed due to time restraints).
- b. **General observations/commentary:** The study, FHA101, is on-going with 27 patients screened and enrolled from 3/30/09 – 7/9/13. There are 19 subjects active in the study. Two additional subjects had enrolled since the data cut-off period. Since the last sponsor submission on 3/7/12, there had been four more terminations, including Subjects 648015, 648017, 648020, and 648021.

Comparison of the individual source records to the sponsor data line listings for safety and efficacy endpoints, including fast metabolic parameters HbA1c, triglycerides and glucose did not find any deviations.

The inspection revealed adequate adherence to the regulations and there was no FDA Form-483 issued. However, there were two discussion points:

1. Enrollment test results were not received prior to dosing. Many subjects came from long distances and the CI mailed them the Informed Consent and discussed by phone prior to the Day 1 visit. The CI received background files from the subjects' private physicians. The protocol does not give any windows for testing or visit dates. On Day 1, laboratory testing was done but some subjects were dosed before the results were available. One subject (648011) had an eGFR reading of 33 mL/min. (Inclusion criteria #5 required calculated renal clearance > 40 mL/min. The test result could be < 40 mL/min but the Medical Monitor needed to be contacted to adjust dosing.) The lab results did not come back until after dosing. Repeat testing in one week was 38 mL/min. There was no documentation of medical monitor communication.

Another subject (648007) had a glucose reading of 36 mg/dL. The patient was diabetic and reported no unusual symptoms at the Day 1 exam at 9 a.m. The labs were drawn at 9:20 a.m. and the subject was dosed at 10:30 a.m. Dr. Oral called the subject at 2:00 p.m. when she received the test results and again at 6:00 p.m.; the subject reported a glucose reading at home of 137 mg/dL.

2. There were several errors made in the Pharmacy Log. Comparing Individual Subject Dispensing Logs with the Investigational Supplies Inventory noted several discrepancies. For example, Kits 10546 through 10549 were issued to Subject 648002, not to Subject 64801. Kits 10464 and 10465 were issued to Subject 648002, not to Subject 648022. The subjects' individual inventories were correct at the site. The Pharmacy reviewed their records and made the necessary corrections on 9/18/2013 during the inspection.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3



- a. **What was inspected:** All the firm's activities relative to clinical trial data collected for BLA #125390/0 and its formal contract responsibilities of this CRO with the Sponsor were evaluated. Training records and qualifications of staff were reviewed. All data transfer was assessed, including the data transfer specification documents and assessing that the transfer process was thoroughly tested prior to implementation. Also assessed was how the transfer was reviewed to ensure all transferred data matched the database (i.e., quality control process steps) in addition to compliance with the Data Management Plan (DMP) and the firm's own Standard Operating Procedures (SOPs).

The FDA ORA inspector randomly selected the following subjects' printed case report forms (CRFs) and SAS[®] data to review against the sponsor's data listings:

- Study #991265: 90109, 90104
- Study #20010769: 90122, 90111, 90106, 90130, 90154, 90150, 90115, 90119, 90115, 90128

Primary Efficacy Data review focused on the following sponsor data listings:

- Subject Disposition
- Metreleptin Dosing

- HbA1c
- Fasting Lipids
- Fasting Glucose
- Liver Volume
- ALT/AST
- Adverse Events/Serious Adverse Events

Initially only printed paper CRF records were available at the time of inspection to review. (b) (4) does not keep the original DataFax[®] data and images after the DataFax receipt, review of CRFs, and verification of data. When the database data has been converted to SAS[®] for complete transfer, the original data is no longer accessible in DataFax[®]. SAS[®] data and CRF images are printed and maintained in files). Original DataFax[®] CRF images were not available for review until the older version of DataFax[®] from that time could be migrated from the server. On 10/24/13, the migration was completed and original electronic DataFax[®] data was available for review and verification on 10/25/13.

Since there was limited information provided in the clinical study reports as to what exact methods were being used for collecting the clinical data, OSI requested from the sponsor any SOPs, user-guides, manuals, or training materials to cover data entry procedures that were used in the trials. An unofficial response to FDA Request for Information dated 27-AUG-2013 was received 22-SEPT-2013 and officially received 27-SEPT 2013 eCTD Sequence Number: 0034. Request for additional SOPs were received 11-NOV-2013 eCTD Sequence Number: 0045. This additional information was forwarded to the FDA inspector for review.

- b. General observations/commentary:** The firm was contracted two times from 2006 to 2011 by the sponsor for specific responsibilities, which can be summarized as developing case report forms (CRFs), receiving completed CRFs via fax or email from the clinical site, entering the data from CRFs into a database, exporting data to SAS[®] and transferring data to the Sponsor. In addition, in January and February of 2011, (b) (4) was contracted to amend the DMP for NIH Study 20010769. The firm was not responsible for ClinicalTrials.gov, monitoring the clinical site or selection of clinical investigators. There were no outside vendors or contractors utilized by (b) (4) to fulfill their obligations.

The data reviewed during this inspection revealed that there were quality control checks in place for data accuracy as well as missing data. The firm had several levels of internal verification of data receipt, entry and exportation. Training records were reviewed and no discrepancies were observed. Data received was de-identified. There was no personal data at the CRO level. There were no security breaches. It did not appear that there was any under-reporting of adverse events. The primary endpoints were verifiable.

There were several items discussed which led to a teleconference between the FDA ORA inspector, (b) (4) and Amylin, Bristol-Myer Squibb and Astra Zeneca representatives. Items discussed included all database locking and unlocking, (b) (4) and CRF data discrepancies of two subjects' test article dose data, and the number of subjects enrolled in the 20010769 study.

- There were additional dates of database unlocking and locking mentioned in the Clinical Study Report (CSR) discovered to be unrelated to (b) (4) database unlocking and locking activities. They occurred from 4/14/2008 to 4/29/2008 when Amylin unlocked and locked without involving (b) (4) and also 10/6/2010 when the same occurred. Amylin's response was that once Amylin had received the databases from (b) (4), Amylin had unlocked the databases to include new additional data and make corrections to data.

With this discovery during the inspection, the Sponsor acknowledged discrepancies in the 2010 CSR (BLA125390 Serial 0000, Module 5.3.5.1) regarding database unlocks and relocks and provided corrections in a written response to FDA Request for Information 27 Aug 2013. (The CSR says 4/10/2008 lock date for Studies 991265 and 20010769 but the corrected unlock-lock dates were 4/14-29/2008. The CSR says 9/30/2010 unlock-lock date for Study 20010769 but the corrected unlock-lock date was 10/6/2010). The response also included a summary of the database activities for both (b) (4) and Amylin.

There have been a total of five formal analyses of data for the NIH studies, where data from the two studies (991265 and 20010769) were pooled for summarization purposes. All data locks were performed to support these five formal analyses of the data.

There were no discrepancies observed in the (b) (4) CRF to SAS® data conversion. It is unclear what format Amylin stored, exported or maintained the SAS® datasets that (b) (4) provided to them. No data was ever transferred back to (b) (4) at any time. To summarize all dates of database unlocking and locking noted during the inspection:

Date	Study Database	(b) (4)	Amylin Activity
9/20/06	991265		
9/20/06-4/20/07	991265		
10/9/06	20010769		

Date	Study Database	(b) (4)	Amylin Activity
10/9/06-4/20/07	20010769		
4/20/07	991265 & 20010769		
4/20/07	991265 & 20010769		
4/20/07	991265 & 20010769		
4/14/08	991265 & 20010769		Unlock database at Amylin
4/29/08	991265 & 20010769		Relock database at Amylin
5/12/10	20010769		
5/12/10-6/4/10	20010769		
6/4/10	20010769		
6/4/10	20010769		
10/6/10	20010769		Unlock database at Amylin
10/6/10	20010769		Relock database at Amylin

On 11/4/2013, the (b) (4) DataFax® database was queried to confirm activities (b) (4) performed in between the database locks and unlocks. A set of queries of audit trails were run. There were no activities to the (b) (4) DataFax® database whatsoever at (b) (4) between 4/21/07 - 5/11/2010 or after 6/4/2010. Therefore, there were also no (b) (4) DataFax® database activities between Amylin database unlock and lock activities:

Study	Amylin Database Unlock	Amylin Database Lock
991265	4/14/2008	4/29/2008
20010769	4/14/2008	4/29/2008
20010769	9/30/2010	10/6/2010

These queries confirmed that the (b) (4) DataFax® database was inactive at (b) (4) outside their described contract dates. The (b) (4) DataFax® database was closed on the dates the firm provided and the final closure dates are indicated on the database stored file name on the headers of the stored files.

Regarding the Sponsor’s activities, the Sponsor was asked to send their SOP regarding database locking and unlocking to define the procedures employed when locking and unlocking a clinical trial database. The

Sponsor submitted an SOP titled “SOP-QUC-110 - Locking and Unlocking the Clinical Trial Databases,” (Version 04), which was signed off Jan 2012. All previous SOP versions were then requested and reviewed.

- Version 1: SOP-QUC-110 Effective Date – 07 Apr 2006
- Version 2: SOP-QUC-110 Effective Date – 10 Oct 2008
- Version 3: SOP-QUC-110 Effective Date – 28 Jul 2011
- Version 4: SOP-QUC-110 Effective Date – 03 Feb 2012 (current)

Language noted in all: *“This SOP may not apply to protocols for investigator-initiated trials or to those conducted by corporate partners”*.

- Clarification of data discrepancies between [REDACTED] (b) (4) and [REDACTED] (b) (4). There were two discrepancies noted during the inspection.

Study 20010769, Subject 90119: The original “Test Article Administration” CRF that was received through DataFax[®] and also the SAS[®] dataset that was transferred to Amylin by [REDACTED] (b) (4) were reviewed. The last recorded information shows a dose of 0.90 mL QD with Dose Start Date 05DEC2005 and Dose Stop Date Blank. The “Start Date/Stop Date” CRF data does not match the data line listing. According to Amylin’s response, the dates displayed on the first row of each dosing record shows the Start Date and Stop Date as entered from the CRF, while the second row displays the Start Date and Stop Date after converting to a numeric SAS date and imputation (if needed) is done. The imputation of Start Date and Stop Date is required to perform dosing duration computations. Dates are entered into the database as character strings to accommodate incomplete dates. Footnote to the listing states *“Start date with missing day is imputed to last day of the month; stop date with missing day is imputed to first day of the month, complete missing stop date is set to start date if not the last dose record, set to data cutoff date (31JUL2009) if last dose record and patient is still in study”*. It appeared that the 31 JUL2009 date was imputed because the date was blank on the CRF. No further clarification was pursued due to lack of time at the [REDACTED] (b) (4) inspection.

Study 20010769, Subject 90128: The original “Test Article Administration” CRFs that were received through DataFax[®] and also the SAS[®] dataset that was transferred to Amylin by [REDACTED] (b) (4) were reviewed. The “Start Date/Stop Date” data (which was StartDate 21JUL2004 crossed out) does not match the data listing. Subsequent

Test Article Administration CRF pages for Subject 90128 do not contain a dose record with start date 21JUL2004. According to Amylin's response for Subject 90128, this particular dose record was programmatically added to the database as part of the second database unlock for study 20010769 (database re-lock date 06OCT2010), based upon the site's response to a data query. This second database unlock was handled internally at Amylin and had no involvement by (b) (4), which explains the difference between the dosing information reflected on the (b) (4) CRF for Subject 90128, versus the dosing information reflected in the data line listings.

In conclusion, data that was collected, queried or changed after (b) (4)'s last data transfer in 2010 could not be verified with the sponsor data listings for those two above examples.

- The FDA inspector was asked to carefully document actual enrollment as the CSR has both 54 and 55 patients. The Sponsor acknowledged a discrepancy in patient enrollment numbers reported in the 2010 CSR for Study 20010769 between Section 9.7.3 (Data Management, page 25) and Patient Disposition Section 10.1 (Patient Disposition, page 36). The CSR submission captures data with an error in the number of subjects enrolled as 55. Subsequently an additional subject was identified as not participating in 20010769 (subject 90102) and therefore the updated number should be 54. Thus the error within the CSR resides within the Section 9.7.3 Data Management Section and was missed during QC of the data management section within the CSR.

The inspectional findings indicate adequate adherence to good clinical practice regulations. No Form FDA-483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this CRO appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this BLA consisted of two domestic sites as well as a contract research organization (CRO). There were no significant deviations noted at these sites and all inspections have been classified as No Action Indicated (NAI).

The Sponsor was able to explain the apparent inconsistencies in the clinical study report for database locking and unlocking and some of the discrepancies regarding the case report forms and the line listings that were discovered during the inspection of the contract research organization (b) (4). The Sponsor clarifications were shared with the review team and

submitted to the BLA.

Observations noted above for Drs. Gordon and Oral, and the CRO (b) (4) are based on the preliminary review of the Establishment Inspection Reports. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

{See appended electronic signature page}

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/s/

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12/24/2013

SUSAN LEIBENHAUT
12/24/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

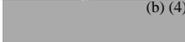
Label, Labeling and Packaging Review

Date: November 26, 2013

Reviewer: Reasol S. Agustin, Pharm D
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Myalept (Metreleptin)
For Injection
 (b) (4)

Application Type/Number: BLA 125390

Applicant/sponsor: Amylin Pharmaceuticals

OSE RCM #: 2012-902 and 2013-823

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the Human Factors/Usability Study results, proposed container label, carton and insert labeling, and instructions for use (IFU) for Myalept (Metreleptin) for Injection, BLA 125390, for areas of design that can lead to medication errors.

1.1 BACKGROUND

On December 15, 2010, Amylin Pharmaceuticals, Inc. submitted the initial application of a rolling Biologics License Application (BLA) for Orphan Designations for Myalept (Metreleptin) for Injection.

1.2 PRODUCT INFORMATION

Myalept (Metreleptin)

- Active Ingredient: Metreleptin
- Indication of Use: Indicated for the treatment of diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy.
- Route of Administration: Subcutaneous Injection
- Dosage Form: Lyophilized powder
- Strength: (b) (4)
- Dose and Frequency:
 - 2.5 mg (0.5 mL) once daily (men)
 - 5 mg (1 mL) once daily (women)
 - 0.06 mg/kg (0.012 mL/kg) once daily (less than 40 kg)
- How Supplied: 5 mL multi-dose vial. The materials needed to prepare and administer the product (i.e. syringes, needles, bacteriostatic water for reconstitution, alcohol wipes, and sharps container for disposal) will be supplied by the single-source specialty pharmacy.
- Preparation and Administration: Myalept (Metreleptin) is prepared and administered by the patient or their caregiver, after receiving proper training.
- Storage: Store under refrigeration 36° F to 46° F (2° C to 8° C) and protect from light until ready for use. Once product is reconstituted the vial can be used for multiple doses within 3 days when stored under refrigeration 36° F to 46° F (2° C to 8° C) and protected from light.
- Container and Closure Systems: Primary container closure is a 5 mL glass vial, rubber stopper, and aluminum seal with a plastic flip-off cap.

2 MATERIALS REVIEWED

We reviewed the Myalept Human Factors/Usability Report, container label, carton and insert labeling, and IFU submitted by the Applicant on April 10, 2012 in order to evaluate the potential for medication errors.

2.1 HUMAN FACTORS/USABILITY STUDY

- A. Human Factor Study Design Overview (see Appendix D for the summary of the results)
 - a. Study Objective: To evaluate the effectiveness of the IFU to instruct patients and caregivers to prepare and administer the injection of Metreleptin.
 - b. Study Population and Training: The study includes a broad population of patient and caregiver participants including injection naïve and injection experienced anticipated users of Myalept. Participants also varied in gender, age, race, level of education, body mass index (BMI). See Table 1 for detailed participant demographic summary. All of the participants were trained regarding how to inject the product prior to testing.

Table 1: Participant Recruitment Target¹ and Demographic Summary

Attribute		Recruitment Target	Result N (%)																					
Total number completing Days One and Two ²		90	93																					
Gender	Female Male	70% 30%	66 (71%) Female 27 (29%) Male																					
Age (yrs)		<table border="1"> <tr> <td>16-30</td> <td>≥40%</td> </tr> <tr> <td>16-20</td> <td>≤30%</td> </tr> <tr> <td>21-30</td> <td>≤30%</td> </tr> <tr> <td>31-65</td> <td>≤60%</td> </tr> <tr> <td>31-40</td> <td>≤30%</td> </tr> <tr> <td>41-50</td> <td>≤30%</td> </tr> <tr> <td>51-65</td> <td>≤30%</td> </tr> </table>	16-30	≥40%	16-20	≤30%	21-30	≤30%	31-65	≤60%	31-40	≤30%	41-50	≤30%	51-65	≤30%	<table border="1"> <tr> <td>37 (40%)</td> </tr> <tr> <td>11 (13%)</td> </tr> <tr> <td>24 (27%)</td> </tr> <tr> <td>56 (60%)</td> </tr> <tr> <td>27 (29%)</td> </tr> <tr> <td>21 (24%)</td> </tr> <tr> <td>8 (8%)</td> </tr> </table>	37 (40%)	11 (13%)	24 (27%)	56 (60%)	27 (29%)	21 (24%)	8 (8%)
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11 (13%)																								
24 (27%)																								
56 (60%)																								
27 (29%)																								
21 (24%)																								
8 (8%)																								
Race	Caucasian Non-Caucasian	≤80% ≥20%	Caucasian – 70 (75%) Non-Caucasian – 23 (25%)																					
Education	HS degree or less No HS degree HS degree At least some college	≥25% 5-10% NS ³ ≤70%	HS grad or less – 33 (35%) No-HS degree – 8 (9%) HS degree 25 (27%) At least some college – 60 (65%)																					
BMI (kg/m ²) ≤20		At least 20% will have a BMI of ≤20; participants with a BMI > 35 will be excluded from the study	≤20 BMI – 19 (20%)																					
Injection experienced	Naïve Familiar	50% 50%	48 (53%) Naïve 45 (47%) Familiar																					

¹ Participants who are blind were excluded, but visually impaired participants were allowed so long as they were able to read the IFU with vision correction. Participants with functional loss of a hand, i.e. amputation or CVA with paralysis, were excluded. Participants were required to be able to communicate (speak and read) in English.

² Approximately 30% additional people were planned to be recruited to allow for drop-outs and no-shows.

³ NS: Not Specified

The participant population is appropriate because the Applicant recruited patients and caregivers who are the intended population for this product. We also consider that training all of the participants is appropriate since training is a part of labeling for this product. Furthermore, although the HCPs were not represented in this study, HCPs do not need to be tested since HCPs reconstitute different drugs and extract an appropriate dose for administration in their routine practice.

c. Study Design:

- i. The study was conducted over two days:

1. Day One consisted of introduction and training of all participants by a facilitator, which was designed to simulate anticipated use conditions.
2. Participants were asked to return for testing in order to simulate training decay. Day Two consisted on participants performing the tasks without the help of the facilitator. Patients were instructed to contact Customer Support Center for assistance to simulate real life scenario.

Applicant's study design is adequate and decay period is appropriate given the fact that this drug is used once daily.

ii. Critical Steps:

1. Fill the 3 mL syringe for reconstitution of the product with 2.2 mL of diluent without air pockets or large bubbles (Step 2i in the IFU)
2. Mix liquid and powder together, to yield a clear, colorless solution without clumps, dry powder or foam (Step 3c in the IFU)
3. Draw medicine into delivery syringe to the assigned dose line (0.75 mL was chosen for all participants in the HF Study), without air pockets or large bubbles (Step 4i in the IFU)
4. Deliver dose of medication (Step 5c in the IFU)

The Critical steps in the study are appropriate because performing either one of these steps incorrectly can potentially result in overdoses and underdoses that may have clinically significant adverse events.

d. Human Factors Study Results Summary and Evaluation ::

Of the 93 total participants, majority (n= 77 or 83%) were able to complete all four critical tasks with no assistance. The remaining participants either required assistance (n =2 or 2%) or did not complete the task correctly (n =14 or 15%). See Appendix D or details.

i. The following failures occurred with the 4 critical tasks evaluated:

- Task #1: Fill the mixing syringe with 2.2 mL of diluent, without any air pockets or large bubbles (step 2i). (Failure n=9)
 1. Five participants incorrectly lined up the plunger. The range of diluent volume drawn into the syringe was 2 mL to 2.3 mL, instead of the intended 2.2 mL, causing an error of 0.1 mL to 0.2 mL.
 2. Four participants were observed to have air pockets/bubbles estimated to be 0.05 mL to 0.1 mL in size.

Although these failures occurred, they would result in the 4.5% to 9% underdose or overdose. According to clinical team, the dosing errors under 10% are not clinically significant. As a result, the task results are still acceptable.

- Task #2: Mix liquid and powder together (step 3c) (Failure n=1)
 1. One participant did not fully mix the diluent with the product powder, resulting in formation of the bubbles. Once bubbles settled, no negative consequences were observed. As a result, this task result is acceptable.
- Task #3: Draw medicine into syringe to the assigned dose line, without any air pockets or large bubbles (step 4i) (Failure n=8)
 1. Three participants were observed lining up the plunger incorrectly, where the measurement errors were 0.01 mL, 0.02 mL, and 0.1 mL
 2. Five participants were observed to have air pockets/bubbles in their syringes when they moved on to the next step. Majority of air pockets/bubbles were estimated to be 0.1 mL to 0.04 mL. One participant had a larger air pocket of approximately 0.1 mL.

Similarly to the failures during the task of filling the mixing syringe, these task failures would also result in the 4.5% to 9% underdose or overdose. According to clinical team, the dosing errors under 10% are not clinically significant and would not result in harm. As a result, the task results are still acceptable.

- Task #4: Deliver dose of medication (step 5c) (Failure n=0)

Myalept will be reconstituted and administered by patients at home. Prior to self-administration at home, all patients will be trained by a healthy care provider according to the product's labeling which requires patient training. In terms of the product requiring reconstitution in the vial, this setting of use is not unique to this product. Other products such as Somatropin (e.g., Genotropin, Norditropin, Omnitrope) are also reconstituted and administered at home by patients or caregivers. However, Somatropin need to be reconstituted with the entire vials of diluents where in Myalept's case, a certain amount of diluent needs to be drawn out, which complicates the reconstitution procedure. Thus, reconstitution procedure for Myalept is more complicated than with majority of the marketed products.

The Human Factors Validation Study results demonstrate that with training patients understand the correct amount of diluent needed for reconstitution and the correct amount of diluted product needed for administration. However, some patients have difficulty lining the

plunger correctly or eliminating bubbles from the syringe, which results in the wrong volume of diluent or the reconstituted product by 0.05 mL to 0.1 mL. These errors would result in overdoses or underdoses below 10%, which is not clinically significant and will not result in patient harm. Furthermore, per conversation with clinical team, the dose up to 10 mg of Myalept daily (i.e., the entire vial) is the maximum allowable daily dose from clinical trials. Thus, even if the patient were to administer the entire vial of the diluted product, no clinically significant harm would occur. As a result, Human Factors Study results support the safe use of this product from the medication error perspective.

However, since this product's preparation is still difficult for patients to perform and requires manipulation of the vials and needles, we recommend the Applicant considers simplifying the use of this product by developing an autoinjector device for patients' use.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 10, 2012 (Appendix)
- Carton Labeling submitted April 10, 2012 (Appendix B)
- Instructions for Use submitted April 10, 2012 (Appendix C)
- Human Factors/Usability Report Summary submitted April 10, 2012 (Appendix D)
- Response to FDA Request for Information submitted on April 25, 2013 (Appendix E)

3 CONCLUSIONS

DMEPA concludes that with proper education and training prior to first injection, Myalept can be used safely and effectively. However, since this product's preparation is difficult and requires manipulation of the vials and needles, we recommend the Applicant considers simplifying the use of this product by developing an autoinjector device for patients' use.

Additionally, the proposed IFU, container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA/ANDA/supplement:

A. Comments to the Applicant

1. Container Closure System

Myalept's preparation is difficult and requires manipulation of the vials and needles. Although training appears to be an effective means to help patients' to understand the correct amount of diluent and dose to withdraw, the Human Factors Study results demonstrate that patients have difficulty lining the plunger correctly or eliminating bubbles from the syringe. As a result, we recommend you simplify the use of this product by developing an autoinjector device for patients' use.

2. Container Label

- a. Revise the presentation of the proprietary name from all lowercase (e.g. myalept) to title case (e.g. Myalept) to increase readability of the proprietary name.
- b. Ensure the proper name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the proper name should have a prominence commensurate with the prominence of the proprietary name.
- c. Remove the dosage form “for injection” in parenthesis with the proper name [i.e. (metreleptin for injection)] and relocate so it appears below the proprietary name. For example:

Myalept

(metreleptin)

For Injection

(b) (4)

- d. Bold the statement “Must be used within 3 days of reconstitution” to increase prominence of this important information. If feasible, add spacing between the statements “Multi-dose vial. Requires reconstitution” and “Must be used within 3 days.” to increase prominence of the expiration period.

3. Carton Labeling

- a. See comment 1.a and 1.c.
- b. Change the font color of the proper name (b) (4). As currently presented, it is the same color as background color, thus decreasing readability of the proper name and route of administration. In addition, the proper name should be

presented with same prominence (i.e. font color, size, bolding) as the proprietary name. See comment 1.b.

- c. Increase the color contrast between the text and the background color to increase prominence and readability of the important information on the carton.

4. Instructions for Use

- a. See comment 2.a, 2.b. and 2.c.
- b. Add quantitative descriptions of the syringes used in preparation and administration (i.e. 3 mL and 1 mL). For example, revise the description “Syringe to mix the medicine” to read “3 mL Syringe to mix medicine” and “Syringe to inject medicine” to read “1 mL Syringe to inject medicine.” Ensure that these descriptions are revised throughout the IFU (i.e. page 2, 4, 5, 6, 9, 15, etc.).
- c. Delete all trailing zeros (i.e., 2.0 mL to 2 mL on page 4 and 1.0 mL to 1 mL on page 5). The use of trailing zeros (i.e., 1.0 mL) can lead to 10 fold overdoses if the decimal is not seen.
- d. On page 11 and 21, use the actual picture of the Myalept vial.
- e. On page 12, Step 1: Add a step between 1b and 1c to “Check Expiration date.” For example:

1b Take one vial with powder out of the refrigerator

1c Check the expiration date on the vial. It is labeled EXP.

1d Wash your hands with soap and water.

Etc.

- f. On page 15, Step 2: It states “Syringe to mix the medicine ^{(b) (4)} needle base with longer needle.” ^{(b) (4)}
^{(b) (4)} from this statement to prevent confusion.
- g. On page 19, add the picture of large air bubbles and small air bubbles (from page 46 of the IFU) to this page. This will help end users determine the acceptable air bubbles/pockets prior to proceeding to the next steps. In the Usability report, most “incompletes” were due to air bubbles/pockets.
- h. On page 25, Step 4: It states “Syringe to inject the medicine ^{(b) (4)}
^{(b) (4)} from this statement to prevent confusion.

- i. On page 25, Step 4: Remove [REDACTED] (b) (4)
- j. On page 34 Step 5: The information on this page refers to vial storage after use and discard date. This page should be its own step (i.e., Step 6 Storing the medicine). Thus, making the current Step 6 Using a vial of mixed medicine as Step 7.

B. Comment to the Division

a. The Dosage and Administration section contains dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert². As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:

- Revise all instances of the symbol '<' or '>' in the text. The 'greater than' and 'less than' symbols are dangerous abbreviations that could be interpreted opposite of its intended meaning.
- Revise all instances of the abbreviation 'SC' to read subcutaneous. The 'SC' abbreviation can be misinterpreted as SL (sublingual).
- Remove all trailing zeros (i.e., 5.0 mg to 5 mg, 1.0 mL to 1 mL). The use of trailing zeros (i.e., 1.0 mL) can lead to 10 fold overdoses if the decimal is not seen.

b. Instructions for Use, Section 2.2: Myalept Preparation

- Revise the last paragraph to include the term "preparation." For example, "See the MYALEPT Instructions for Use for complete preparation and administration instructions. The instructions can also be found at www.myalept.com). In addition, relocate this last paragraph so it is immediately under Section 2.2 Administration.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX D: Human Factors/Usability Report

1 INTRODUCTION

The objective of this report is to present the results of a Usability Study to evaluate the metreleptin Instructions for Use (IFU). This Usability Study was conducted in accordance with the approved protocol RESPL110098.

The Usability Study was designed to evaluate the effectiveness of the IFU to instruct users to prepare and administer an injection of metreleptin. Assessment of metreleptin and package literature such as Prescribing Information (PI), Medication Guide and container labeling were out of the scope of this study.

2 MATERIALS AND METHODS

- Minimum of 360 (*three hundred sixty*) vials of metreleptin lyophilized powder, lot #631303F, manufactured Mar2008. No injections were given. Materials were void of corporate identification but had a label the same size and shape to replicate the commercial product labeled "Not For Human Use".
- Minimum of 360 BD 3 ml syringes with 22 gauge × 1 inch needles, part #309572
- Minimum of 360 BD 1 ml syringe with 26 gauge × 3/8 inch needles, part #309625
- Minimum of 60 Patient Instructions for Use booklets
- Minimum of 60 Product Supplies Checklists
- Minimum of 60 IFU Closure Band for use with the IFU
- Minimum of 360 vials of bacteriostatic water for injection, 30mL, (b) (4) catalog #NC9591368
- Minimum of 720 packets of alcohol wipes, PDI, part #06-669-73
- Injection aid or injection balls, which were used to help simulate an actual injection, 2-3 per site
- Sharps disposal containers (2-3 per site)

The IFU was used for each participant in the study. The IFUs used in the study were the same size, shape, format, and layout as expected in commercial production. No brand or company identifier information was included on the IFU or any of the study materials.

Moderators were trained on the requirements of the protocol, the Observation Worksheet and essential training elements to provide a standard approach to implementation of the study for both Day One and Day Two.

Pre-conditions: The study material was refrigerated as per IFU storage requirements.

2.1 Day One

To start the session the study facilitator asked a few unscripted questions at the onset of the participant study session. The purpose of these questions was for the facilitator to establish rapport with the participant, and to help put the participant at ease by allowing him or her to talk about their own personal situation with injections and/or current medications. All participants were informed that they would not be giving themselves or anyone else an injection.

Each participant was provided with all required supplies. The metreleptin vial was warmed to ambient temperature as directed in the IFU in advance of participant testing. To begin the instruction the study facilitator demonstrated to the participant the five IFU steps (*Getting Started through Injecting the Medicine*) necessary to prepare and inject a dose. The study facilitator then walked the participant through each step, using the IFU, allowing the participant to practice measuring correctly with empty syringes. The participant then used the IFU to prepare a dose for simulated self-administration while the facilitator observed and coached. The participant was allowed to ask the facilitator questions to simulate actual user training. Once a dose was prepared the participant was instructed to simulate dose administration using an injection aid. Participants were observed, with no proactive facilitator discussion, for their ability to perform each of the fundamental steps required for accurate dose preparation and administration.

The dose selected, 0.75 mL, was intended to require study participants to draw to a less prominent mark on the syringe, thereby allowing a thorough assessment of the IFU content and its ability to provide clear direction on this fundamental step. The 4 (*four*) fundamental steps to prepare and administer an accurate dose included:

- Fill the 3 mL syringe with 2.2 mL of diluent, without any air pockets or large bubbles (Step 2i in the IFU)
- Mix liquid and powder together, to yield a clear, colorless solution without clumps, dry powder or foam (Step 3c in the IFU)
- Draw medicine into syringe to the assigned dose line (0.75 mL), without any air pockets or large bubbles (Step 4i in the IFU)
- Deliver dose of medication (Step 5c in the IFU)

These four steps were selected as each was deemed critical for a patient to prepare and administer an accurate dose. If one of these steps was incomplete a patient would not be able to successfully deliver a full dose of medication.

The study facilitator was present at all times to ensure no participant attempted to give themselves an actual injection. If the participant performed an action that could potentially put them at risk for a needle stick the study facilitator would have intervened to correct the situation, and noted the action on the Observation Worksheet.

The study facilitator objectively observed and recorded use errors, operational difficulties, or close calls and documented completion of each fundamental step, on the Observation Worksheet which was used to assess if the participant met the established acceptance criteria for each step. The study facilitator asked to view the mixing syringe at the completion of IFU Step 2j to assess if the participant pulled to the correct line (2.2 mL) with minimal amounts of air. The study facilitator asked to view the vial of mixed medicine at the completion of IFU Step 3d to assess if the participant mixed the solution correctly. The study facilitator asked to view the dosing syringe at the completion of IFU Step 4j to assess if the participant pulled to the correct dose line (0.75 mL) with minimal amounts of air. These assessments were noted on the Observation Worksheet. The participant then proceeded to simulate an injection.

If a participant was unable to complete a step while preparing a dose for simulated injection, they could seek assistance from the study facilitator. Such a request was documented as “Assistance Requested”. If the participant did not request assistance and attempted to proceed with the next step without successfully completing a step, the facilitator intervened to provide guidance in completing the step, and correct technique. The facilitator documented this as “Assistance Offered”. If after facilitator intervention the step was still not performed, then it was scored as incomplete.

Once the participant completed the steps of the operation as outlined in the IFU to the best of his or her ability, the Day One testing was complete. The overall study session lasted no more than 45 minutes. Regardless of Day One training results, all participants were asked to return one day later for Day Two evaluation and study completion. The participants were not allowed to take the materials home overnight.

2.2 Day Two

To start the session, the study facilitator informed participants they would be preparing a dose of medication and simulating an injection unaided. All participants were informed that they would not be giving themselves or anyone else an injection. They were also instructed to locate the Customer Support Center telephone number on the IFU if they needed any assistance during the session. After locating the telephone number, they could request assistance by asking a specific question to the study facilitator. The study facilitator provided a standardized response to the question using only the IFU in a manner similar to what the Customer Support Center would be expected to provide.

Each participant was provided with all required supplies. The metreleptin vial was warmed to ambient temperature as directed in the IFU in advance of participant testing to eliminate the 15 minute waiting period.

The study facilitator instructed the participant to prepare a dose for simulated self-injection using the IFU as the only source of information. The facilitator did not provide any guidance to the participant unless assistance was requested via a “simulated Customer Center call.”

Once a dose was prepared the participant was instructed to simulate dose administration using an injection aid. Participants were observed for their ability to perform each of the fundamental steps required for accurate dose preparation and administration. The four fundamental steps to prepare and administer an accurate dose are described in [Section 2.1](#) above.

The study facilitator was present at all times to ensure no participant attempted to give themselves an injection. If the participant had performed an action that could potentially put them at risk for a needle stick the study facilitator would have intervened to correct the situation.

The study facilitator objectively observed and recorded use errors, operational difficulties, or close calls and documented completion of each fundamental step on the Observation Worksheet which was used to assess if the participant met the established acceptance criteria for each step. The four fundamental steps on the Observation Worksheet are 2i, 3c, 4i and 5c. The study facilitator asked to view the mixing syringe at the completion of IFU Step 2i to assess if the participant pulled to the correct line observation 2i (2.2 mL) with minimal amounts of air. The study facilitator asked to view the mixing vial at the completion of IFU Step 3d, to assess if the participant mixed the solution correctly. The study facilitator asked to view the dosing syringe at the completion of IFU Step 4i, to assess if the participant pulled to the correct dose line (0.75 mL) with minimal amounts of air. The study facilitator observed simulation of delivering a dose at the completion of Step 5c. These assessments were noted on the Observation Worksheet. The moderators used the same evaluation criteria on Day 2 as they did on Day 1.

A simulated Customer Support Center telephone call in which the participant seeks assistance from the study facilitator was documented on the Observation Worksheet as “assistance needed”. If the participant did not request assistance and attempted to proceed with the next step, thus omitting a step, it was documented as “incomplete”. If this was a fundamental step as defined in [Section 2.1](#) they were counted as Fail.

Once the participant completed the steps of operation as outlined in the IFU to the best of his or her ability, the study facilitator asked the participant to complete the written questionnaire regarding the subjective elements of the product. For questionnaire items for which the participant responded as “disagree” the study facilitator could, for informational purposes, query the participant as to why he or she disagreed with the items.

The overall study session, including the simulated use task and administration of the subjective elements questionnaire, lasted no more than 30 minutes.

Results:

Table 2: Summary Completion Data (all 4 critical steps combined)

	Completed without assistance	Completed with assistance ¹	Incomplete
Number of Participants (%)	77 (83%)	2 (2%)	14 (15%)
Total number of participants	93		

¹Completed with assistance indicates that participant contacted the simulated Customer Support 1-800 number.

Table 3: Completion Data for Four Fundamental Steps

Usability Study Element	Total (N=93)		
	Completed w/o assistance N (%)	Completed with assistance N (%)	Incomplete N (%)
Fill the mixing syringe with 2.2 mL of diluent, without any air pockets or large bubbles (step 2i in the IFU)	83 (89%)	1 (1%)	9 (10%)
Mix liquid and powder together (step 3c in the IFU)	91 (98%)	1 (1%)	1 (1%)
Draw medicine into syringe to the assigned dose line, without any air pockets or large bubbles (step 4i in the IFU)	85 (91%)	0	8 (9%)
Deliver dose of medication (step 5c in the IFU)	93 (100%)	0	0

APPENDIX E: Response to FDA Request for Information

QUESTION 1

Please indicate your intended packaging configuration(s) for marketing. If one of the configurations will be a kit, please indicate the contents of the kit, and provide proposed labels and labeling for all components of the kit.

RESPONSE

The intended Myalept packaging configuration for marketing consists of a single multi-dose, clear glass vial, containing lyophilized metreleptin powder for reconstitution prior to the first injection, housed inside a carton. Proposed primary and secondary container labeling have been submitted with the final portion of the rolling BLA, on 27 March 2013, Serial 0017 ([Draft Carton](#) and [Vial Label](#) located in Module 1.14.1.1).

QUESTION 2

If Myalept will not be marketed as a kit, where will patients acquire the materials needed (e.g. syringe and bacteriostatic water) to properly use Myalept?

RESPONSE

A contracted single-source specialty pharmacy will provide and co-ship all necessary materials to properly use Mylept (syringes, needles, bacteriostatic water for reconstitution, alcohol wipes, sharps container for disposal etc.) along with Metreleptin Instructions for Use to patients at the time Myalept is dispensed.

QUESTION 3

Is the current proposed product configuration (e.g. multi-use vial) the same product configuration used during clinical trial(s)? If yes, please provide pharmacovigilance and medication error data from the clinical trial(s).

RESPONSE

The current proposed commercial product configuration is similar to the product configuration used in clinical trials (multi-use vial containing lyophilized powder for reconstitution prior to first injection). The primary difference in the product configuration from that used for clinical trials is that vials were packaged in kits of approximately 30 vials for clinical trials whereas each vial is packaged in a separate carton for the proposed commercial product configuration. Pharmacovigilance (i.e. adverse events) and any available data on medication errors (which were not systematically collected) in the clinical studies were included in the final portion of the rolling BLA submitted 27 March 2013, Serial 0017 (Module 5.3.5.3: Clinical Safety Update Section 4.3 and 4.4.6).

QUESTION 4

Is training required prior to initial use of the product? If so, how does Amylin plan to ensure that patient education and training will occur prior to initial patient use?

RESPONSE

The proposed prescribing information states that the first dose of Myalept should be administered by under the supervision of a Healthcare Professional and training will be provided to patients and caregivers prior to initial self-use of the product. The Sponsor plans to utilize trained nurse specialists who will provide education and training to healthcare professionals and/or patients starting MYALEPT. The education will be focused on the Myalept FDA-approved Instructions for Use, which describes proper product reconstitution, aseptic, and injection techniques. This proposed training will be facilitated through the specialty pharmacy which will coordinate this training effort upon receipt of a notification for a new therapy start being submitted for product dispensation. A case file would be created in the system and a nurse specialist will be assigned to the case, who will then communicate with the prescribing physician and/or the patient in order to coordinate the time and place for the aforementioned training to take place, based on shipment location for the initial prescription.

QUESTION 5

Are there any special disposal or handling procedures for Myalept? (e.g. must wear gloves to handle during preparation and/or requires disposal in special handling containers etc.)?

RESPONSE

Patients will be trained on proper product reconstitution, aseptic, and injection techniques, as well as proper syringe/needle disposal method via sharps container.

QUESTION 6

In your Human Factors study you indicate that the trial took two days: on the first day training was provided and on the second day participants were using the device on their own after reading the IFU. However, it appears that your results section provides success and failure data from both days without breaking the data down by day. Please separate the results from day 1 and 2 of the study and provide the results data to us that way, so that it is easier to extract the important information.

RESPONSE

Per the Agency's request, in addition to the Day Two results provided in Usability Study Report (REST120038), Appendix 1 contains a separate table with the Day One results. The [REST120038](#) report was submitted to the FDA in BLA125390 (Serial 0003, Section 1.11.4) on 02 April 2012.

The Metreleptin Instructions for Use (IFU) Usability Study was designed to evaluate the effectiveness of the IFU to instruct users to self prepare and administer an injection of metreleptin under simulated use conditions. These simulated use conditions were designed to mimic the healthcare professional training and retention of training (i.e. memory decay)

anticipated with real world use, consistent with recommendations from the 2001 draft FDA Guidance, Applying Human Factors and Usability Engineering to Optimize Medical Device Design.

The draft Myalept (metreleptin for injection) prescribing information recommends that all patients and caregivers receive proper training in how to prepare and administer the correct dose of metreleptin prior to self-administration. The draft labeling further states, “the first dose of metreleptin should be administered by the patient or caregiver under the supervision of a qualified healthcare professional”. For consistency with this recommendation, the Usability Study employed a Day One training session to simulate the type of training a patient should receive from their a healthcare professional prior to initial use.

During the Day One training the study facilitator demonstrated the five steps necessary to prepare and inject a dose. The facilitator then walked the participant through each step allowing the participant to practice measuring a dose and to seek assistance throughout the process. The study facilitator was directed to objectively observe and record use errors or operational difficulties, however, these data were not used to calculate overall study results.

The Day Two assessment period consisted of participants preparing a dose for simulated self-injection using the IFU as the only source of information and was designed to serve as the basis for the study results. No training or other proactive interventions were allowed on Day Two. Participants could only seek assistance by simulating a call to the Customer Service Call center. Therefore, the Day Two study results represent an unbiased assessment of the effectiveness of the IFU to instruct the participants on preparation and administration of a dose when accounting for memory decay of previous training. Day One data were not used in calculation of the overall study results as they did not measure memory decay and therefore did not support the objective of the study.

QUESTION 7

In your clinical studies, did patients self-administer the product or was the product administered to them by a healthcare professional?

RESPONSE

In clinical studies, patients/caregivers received training on proper product preparation and administration prior to the first use. Following this initial training, patients either self-administered the injection, or received the injections from a care-giver/guardian in the case of pediatric patients.

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

/s/

REASOL AGUSTIN
11/26/2013

YELENA L MASLOV
11/26/2013

KELLIE A TAYLOR
11/26/2013

CDER Consult Memo
Division of Gastroenterology & Inborn Error Products

Date: November 12, 2013

To: Julie Golden, MD, Medical Officer
Division of Metabolism and Endocrinology Products, CDER

From: Lauren Weintraub, MD, Medical Officer
Division of Gastroenterology and Inborn Errors Products

Through: Lara Dimick-Santos, MD, FACS, Medical Team Leader
Andrew E. Mulberg, MD, FAAP, Division Deputy Director
Division of Gastroenterology and Inborn Errors Products

Subject: Medical Officer Consultation: Evaluation of safety and efficacy of metreleptin on hepatic parameters

Application: BLA 125390

Applicant/Sponsor: Amylin Pharmaceuticals

Drug Product: Myalept (metreleptin)

Proposed Indication: Treatment of pediatric and adult patients with generalized lipodystrophy; and for the metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis

Date of Request: August 27, 2013

1 Introduction

This review is in response to a consult from the Division of Metabolism and Endocrinology Products regarding a BLA submission for treatment of patients with lipodystrophy. The Division asked us to review and comment on the data submitted concerning evaluation of fatty liver disease that is common in this patient population, and to make recommendations on the Sponsor's request for labeling for an indication of steatosis in lipodystrophy patients. Section 4 contains the data analysis and Section 5, starting on page 21, contains the Divisions questions and DGIEP's responses.

2 Background

Lipodystrophy: The lipodystrophies are a group of rare metabolic disorders characterized by loss of adipose tissue with ectopic fat deposition. Metabolic derangements, including insulin resistance, diabetes mellitus, and dyslipidemia are also features of the disease. Lipodystrophy subtypes are characterized according to underlying etiology (acquired or inherited) and

distribution of fat loss (generalized or partial). The most common form of lipodystrophy is an acquired form seen in patients with the human immunodeficiency virus receiving protease inhibitors; however, these patients are not included in these studies.

Generalized Lipodystrophy:

Patients with generalized lipodystrophy (congenital or acquired) experience total loss of subcutaneous and visceral fat, resulting in a lack of metabolically active adipose tissue. Thus, patients typically have extremely low levels of the adipocyte-derived hormones, leptin and adiponectin. Hyperinsulinemia and diabetes mellitus are universal findings, as is hypertriglyceridemia, though lipid levels may not necessarily correlate with disease severity. Circulating fatty acids deposit in other tissues, typically targeting muscle and liver tissue, and hepatocellular fat deposition, or steatosis, can evolve into non-alcoholic steatohepatitis (NASH), a chronic necroinflammatory condition which can progress to cirrhosis.

Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder with an estimated prevalence of 1 in 10,000,000. The complete absence of adipose tissue is present at birth, and the ectopic fat deposition creates a striking muscular appearance, often accompanied by hepatomegaly and steatosis. Early symptoms include voracious appetite, accelerated growth, and advanced bone age. Severe hyperinsulinemia and hypertriglyceridemia typically develop by adolescence or young adulthood, leading to diabetes mellitus often with poor glycemic control. Disease complications mimic those of the metabolic syndrome, including the liver manifestations of non-alcoholic fatty liver disease (NAFLD). Cirrhosis is common in this patient population and may occur during childhood in patients with particular genotypes.

The acquired form of generalized lipodystrophy (AGL) typically presents with onset of progressive, severe loss of fat in childhood or adolescence. Male-to-female ratio is 1:3. 50% of cases are idiopathic, while 25% of cases are preceded by an episode of panniculitis followed by a mixed inflammatory infiltration of adipose tissue. The remaining 25% of patients with AGL also have associated autoimmune diseases, including autoimmune hepatitis. Cirrhosis occurs in ~20% of patients as a late sequela of hepatic steatosis or autoimmune hepatitis.

Partial lipodystrophy

The partial lipodystrophies represent a heterogeneous group of disorders with diverse patterns of fat loss and varying degrees of metabolic abnormalities. Like generalized lipodystrophy, both genetic and acquired forms exist. Familial partial lipodystrophy (FPL) is an autosomal dominant disorder with several known genotypes, and although mutations occur equally in both genders, women are more severely affected than men. Typically, patients have normal distribution of body fat during childhood with gradual disappearance of subcutaneous fat from the extremities, which can later progress to include the anterior abdomen and chest. Insulin resistance, diabetes, and hypertriglyceridemia may occur, though usually after the second decade. Fatty liver may occur, but cirrhosis has not been reported in these patients.

Acquired partial lipodystrophy (APL) usually presents during childhood or adolescence and has a male-to-female ratio of 1:4. Fat loss occurs in a cephalo-caudal pattern, in which there is loss of fat in the upper body and deposits in areas in the lower body. Insulin resistance occurs less frequently in APL than in other subtypes of lipodystrophy and metabolic abnormalities can vary. Patients have low serum C3 levels with presence of circulating C3 nephritic factor, and 20% of patients develop membranoproliferative glomerulonephritis. Other autoimmune disorders such

as systemic lupus erythematosus and juvenile dermatomyositis have been diagnosed in patients with APL. Leptin levels in both APL and FPL are more variable than the generalized forms.

Leptin:

Leptin is a cytokine secreted by adipose tissue which participates in many endogenous metabolic and immunomodulatory processes. Leptin receptors are expressed on cells primarily in the hypothalamus and on various white blood cells. Leptin attenuates many of the actions of insulin, including its effects on lipid metabolism, glycogen synthesis, and gluconeogenesis.[1] It also has appetite suppressive effects, which are clearly evident by the marked hyperphagia experienced by patients with generalized lipodystrophy. Leptin resistance, in addition to insulin resistance, has been implicated in obesity and the development of the metabolic syndrome.

Leptin also has broad immune-stimulatory effects, which include upregulation of phagocytic function, stimulation of pro-inflammatory cytokine secretion, chemotaxis of polymorphonuclear cells, and the differentiation, proliferation, activation, and cytotoxicity of NK cells.[2] The effect of leptin on the development of autoimmunity is unclear, but animal models of leptin deficiency demonstrate a protective effect against experimentally-induced autoimmune disease, which disappears with leptin replacement.[3]

Leptin deficiency has become a therapeutic target for the metabolic abnormalities in patients with lipodystrophy. Metreleptin (Myalept) is recombinant human methionyl leptin which is administered subcutaneously. Patients with various phenotypes of lipodystrophy have been receiving metreleptin treatment through study participation at the National Institutes of Health (NIH).

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH):

NAFLD encompasses a spectrum of fatty liver disease, ranging from simple steatosis (fatty infiltration of the liver) to steatohepatitis (fatty liver accompanied by liver inflammation and hepatocyte necrosis). The term nonalcoholic steatohepatitis (NASH) is used to describe the steatohepatitis of NAFLD, but the term metabolic steatohepatitis would be more accurate terminology. NAFLD is certainly not specific to lipodystrophy. In fact, NAFLD is now the most common cause of liver disease in the western world. In the general population, NAFLD is closely associated with the metabolic syndrome. More than 90% of patients have at least one feature of metabolic syndrome (obesity, insulin resistance, hyperlipidemia), and many meet full criteria for the syndrome. NAFLD is strongly linked to insulin resistance, a feature shared by the patients with lipodystrophy. Hyperinsulinemia promotes hepatic lipogenesis, while insulin resistance impairs suppression of adipose tissue lipolysis, causing increased efflux of free fatty acids from adipose tissue to the liver.

While simple steatosis is believed to be a relatively benign process, steatohepatitis is a chronic inflammatory process which can lead to hepatic fibrosis and cirrhosis. Patients are frequently asymptomatic; therefore NASH is thought to be a principal cause of cryptogenic cirrhosis. The transformation of steatosis to steatohepatitis requires activation of a complex inflammatory process in response to the steatosis. The inciting event resulting in NASH may involve oxidative or metabolic stress, dysregulated cytokine production, and/or hepatic mitochondrial dysfunction.[4] Other postulated mechanisms include lipid peroxidation and release of toxic products, depleted hepatic antioxidants, direct effects of adipocytokines (i.e. leptin and

adiponectin), ATP depletion in mitochondria, and toxic effects of bacterial toxins (lipopolysaccharide).[5]

Most patients with NAFLD are diagnosed as the result of an incidental discovery of elevated ALT level on routine laboratory examination. The majority of patients are asymptomatic, but when symptoms occur, they are usually nonspecific symptoms such as vague right upper quadrant abdominal pain, fatigue, and malaise. Transaminase elevations are typically mild, and the degree of ALT elevation does not correlate with histologic severity of hepatic inflammation or fibrosis.

The differential diagnosis of NASH includes alcoholic steatohepatitis, which can be difficult to distinguish from NASH as the pathologic appearance of NASH and alcohol induced fatty liver disease is very similar. The patient's history of alcohol intake is generally used to distinguish the two diseases, though both can exist in the same patient. Diagnosis also requires evaluation for other hepatitides, such as autoimmune and viral hepatitis, though these conditions are typically not associated with steatosis. While the majority of cases of NAFLD occur in the context of the metabolic syndrome, other less common causes include rapid weight loss, parenteral nutrition, toxic exposures, drug-induced steatosis (glucocorticoids, synthetic estrogens and tamoxifen, antiretroviral agents, amiodarone, diltiazem), and endocrine disorders (PCOS, hypothyroidism, hypopituitarism). While non-invasive methods are currently under development for diagnosing NAFLD, definitive diagnosis currently requires liver biopsy.

Pathology of NAFLD- Simple steatosis is predominantly macrovesicular steatosis, which develops as a result of hepatocellular accumulation of triglycerides. However, a diagnosis of NASH depends on evaluation for multiple independent histologic criteria, which, at a minimum, include (1) steatosis, (2) hepatocellular ballooning injury, and (3) parenchymal inflammation. The inflammatory process of NASH is predominantly lobular with a zone 3 injury pattern, with development of zone 3 pericellular/perivenular fibrosis over time. Portal inflammation is usually minimal to mild in adults with NAFLD; therefore, the presence of disproportionately dense portal inflammation should raise suspicion for concomitant liver disease, such as autoimmune or viral hepatitis, chronic biliary disease. In children, the typical pattern of inflammation and injury is predominantly zone 1 injury with portal inflammation. [5, 6]

Hepatocytic ballooning is the swelling and enlargement of hepatocytes with cytoplasmic alterations indicative of hepatocellular injury and is helpful for distinguishing progressive NAFLD from less aggressive forms. The swelling and enlargement of the hepatocytes results in loss of normal hexagonal shape along with cytoplasmic alterations indicative of cell injury. [5, 6]

Fibrosis is common in patients with NASH, and the degree of fibrosis on biopsy is variable as a function of the chronic and insidious nature of the condition.

While not required for diagnosis, the following pathologic features may help distinguish between simple steatosis and NASH. Since these findings are indicative of cellular injury and/or metabolic dysfunction, they are rarely seen in patients with simple steatosis.

- Mallory Bodies (also Mallory-Denk bodies or Mallory's hyaline): These are dense, irregularly shaped, eosinophilic, intracytoplasmic inclusions, commonly found in ballooned hepatocytes. They consist of clumps of intermediate filament components such as cytokeratin, which develop as a result of impaired proteosomal degradation of cytoplasmic proteins. Mallory bodies are a manifestation of hepatocyte injury and also occur in various other types of liver injury including Wilson's disease and primary biliary cirrhosis. [7]

- **Megamitochondria:** Swollen mitochondria with structural changes including multilamellar membranes, loss of cristae, and intramitochondrial paracrystalline bodies, which are most commonly seen in chronic alcoholic steatohepatitis, but are also a feature of NASH. The structural changes seen on biopsy are the consequence of altered mitochondrial function. [6]
- **Microvesicular steatosis:** A variant of hepatocellular fat accumulation also resulting from severe mitochondrial dysfunction, as the result of impaired beta oxidation of fatty acids, either inherited or acquired. This finding is also commonly associated with acute fatty liver of pregnancy, alcoholic hepatitis, and certain drug toxicities, as well as Reye’s syndrome, mitochondrial disorders, and urea cycle defects. [5,6]

NAFLD Activity Score: The NAFLD activity score (NAS) is composite scoring system calculated by the sum of its three individual components -- steatosis, lobular inflammation, and hepatocyte ballooning—plus a separate evaluation of fibrosis. (Table 1) The NAS was developed as a tool by the NASH-CRN (NASH Clinical Research Network), for use in clinical trials to measure changes in NAFLD and decrease inter-observer differences in pathological classification.[8] The diagnosis of steatohepatitis should be made by overall histologic assessment and cannot be inferred from the NAS alone. The NAS is helpful to grade disease activity, is sensitive to clinical changes, and is relatively reproducible, thus making it a useful tool for comparing repeated measures in the same patient. However, the NAS has not been validated as a marker for progression to cirrhosis or mortality.

TABLE 1:
NASH Clinical Research Network Scoring System for NAFLD
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An NAS ≥ 4 or more is associated with increasing likelihood of steatohepatitis, and scores of 5-8 are largely diagnostic of NASH. Scores of 0-2 occur mostly in patients without NASH; however scores of 3-4 were evenly divided among patients with definite, borderline, and no NASH in validation studies. [8]

3 Overview of BLA Submission:

In this BLA (125390), the applicant is proposing approval of metreleptin for treatment of patients with lipodystrophy, including the treatment of liver manifestations, particularly NAFLD.

The primary review division (DMEP) has requested consultation regarding the effect of metreleptin treatment on hepatic parameters and the appropriateness of this treatment indication.

Clinical Studies: The submitted safety and efficacy data to support this BLA were obtained from three open-label NIH studies of metreleptin in patients with lipodystrophy.

- NIH 991265: An 8-month, open-label, dose escalation study aimed to determine (1) the safety of subcutaneous metreleptin treatment in patients with generalized lipodystrophy and (2) to determine the effectiveness of metreleptin treatment to improve insulin sensitivity, lower blood glucose, and control hyperlipidemia. Nine patients, including one non-generalized FPL patient, enrolled in the study between July 2000 and September 2001. Eight of nine patients completed the 8-month protocol, 7 of which enrolled in Study 20010769. One patient withdrew from this study, but later enrolled in Study 20010769.
- NIH 20010769: An open-label, open-ended study (enrollment from March 2001 to May 2011) aimed to assess the effectiveness of metreleptin in patients with less severe forms of lipodystrophy and to lower plasma glucose and lipids in patients with lipodystrophy as young as 6 months old. Combined enrollment of studies 991265 and 20010769 was 72 patients. One patient participated only in study 991265.
- FHA101 (IND): An open-label, open-ended trial, started in March 2009, to provide metreleptin under an investigational treatment protocol to patients with lipodystrophy that is associated with diabetes mellitus and/or hypertriglyceridemia. Twenty-eight patients were included in the data analysis for this BLA submission.

Sample size in analyses:

- **Total 100 subjects:**
 - **n=72: Studies 991265 and 20010769 (source of liver volume and biopsy data)**
 - **n=28: FHA101**

Primary efficacy endpoints under consideration for this BLA are HbA1c, fasting plasma glucose, and triglyceride concentrations. The applicant has submitted supportive data evaluating the effect of treatment on “hepatic parameters.”

The original BLA submission included measurements of:

- (1) Serial transaminase levels: note that only ALT levels are included in this report because fewer ALT levels were missing from the submitted data. All 100 patients had baseline ALT levels, but 17 patients do not have post-treatment ALT levels appropriate for these analyses.
- (2) Liver volume measured by MRI in a subset of patients (n=27)
- (3) Liver biopsy data - 16 baseline biopsies with 14 paired biopsies

The applicant also submitted the publication by Zadeh *et al.* (J Hepatol 2013) [9] in support of their application. This publication included analyses of biopsy data obtained from metreleptin-treated patients enrolled in Studies 991265 and 20010769. The authors report decreased NASH with metreleptin treatment (86% at baseline vs. 33% after leptin replacement), with improvements in steatosis grade, ballooning injury, and mean NAFLD activity score. Fibrosis scores were stable. The authors also reported corresponding improvements in metabolic profile, ALT and AST.

An information request was sent to the applicant asking them to provide the raw data from Zadeh *et al.*[9], including pathology reports, NAS composite scores and component breakdowns. Any

additional available liver MRI data, including fat content analyses, were also requested. A response was submitted on October 31, including the pathology reports and scores from 50 patients with baseline biopsies and post-treatment biopsies for 27 patients, plus 4 with autoimmune hepatitis. Additional liver volume data was provided for 10 patients, but MRI fat content analyses were not available. This data was combined with the original BLA data for analysis and inclusion in this consultation report.

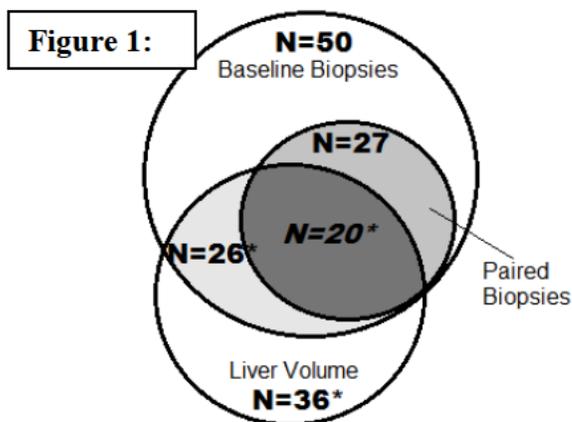
Amylin Pharmaceuticals has proposed the following labeling indications for metreleptin (BLA 125390):

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

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

4 Data Analyses:

3.1 Available liver data: Liver volume and pathology data is available for some patients in studies 991265 and 20010769, and only ~1/4 had complete data for all liver parameters. (Figure 1)



* The liver volume data set includes 37 baseline measurements and 33 paired (baseline and post-treatment) measurements. I excluded one of the baseline measurements of a pediatric patient whose MRI was performed 2 years prior to enrollment.

Of the 36 patients included in the analyses, 26 patients also had available biopsy data, 20 of which had paired biopsy data.

Three of the patients with liver volume measurements had only baseline studies performed. Therefore, 24/26 patients with biopsies have paired liver volume measurements and 19/20 of those with paired biopsies also have paired liver volume measurements.

3.2 Issues with data consistency and/or reliability: In addition to large amounts of missing data (noted above in Figure 1), other data inconsistencies decrease confidence in the findings detailed in this consultation report.

- Data collection time points differed between Studies 991265/20010769 and FHA 101. For purposes of data analyses, ALT values from Month 8 in patients in Studies 991265 and 20010769 were combined with Month 6 ALT levels from FHA 101.

- Even for the data collection time points noted above, several ALT values were missing. Interpolation from other time points was performed only in patients with multiple similar levels at close time points, leaving several remaining missing follow-up values.
- Missing data was also a problem for important baseline patient characteristics such as fasting insulin levels and leptin levels.
- Selection bias is likely due to lack of patient randomization to determine who would undergo the procedures from which data is obtained in these studies
- The inclusion of numerous disease phenotypes results in population heterogeneity; therefore dissimilar patient characteristics among disease subtypes, and even within the diagnosis subgroups, compromises the interpretation of patient outcome information and detection of treatment effect.
- The overall study sample is small due to the fact that lipodystrophy is a rare disease. Further subsetting of the study population results in tiny sample sizes in whom valid inter-group comparisons can not be performed.
- Baseline and outcome data among patients within different subgroups is highly variable (very large standard deviations) and often skewed (mean \neq median values). Detection of treatment effect is difficult in small patient populations without a comparison control group unless data is consistent and treatment effect is dramatic.

3.3 Liver endpoint efficacy analyses

(1) **Transaminase levels:** Elevated transaminase levels are present in 55% of study patients, but <20% are significantly abnormal (defined as > 3x ULN). Because LFTs are sensitive to minor changes in clinical condition and often vary acutely in NASH patients, we generally recommend that at least two baseline measurements are taken at least one week apart to establish a baseline with greater accuracy. Repeat baseline levels were not performed prior to initiation of metreleptin therapy in these trials.

Table 2: Frequency of baseline transaminase level by diagnosis (ULN=upper limit of normal)

	Normal (<40 IU/L)	1-3x ULN (41-120 IU/L)	3-5x ULN (121-199 IU/L)	>5x ULN (>201 IU/L)
All dx (n=100)	45 (45%)	36 (36%)	9 (9%)	10 (10%)
AGL (n=20)	4 (20%)	8 (40%)	3 (15%)	5 (25%)
CGL (n=33)	10 (30%)	15 (45%)	5 (15%)	3 (9%)
FPL (n=41)	29 (71%)	11 (27%)	0 (0%)	1 (2%)
APL (n=6)	2 (33%)	2 (33%)	1 (17%)	1 (17%)

Note: For this review, the ULN for ALT level was set at 40 IU/L; however, the upper limit of the normal range for ALT varies among different laboratories, with normal ranges up to 55 IU/L.

Table 3: Transaminase levels before and after initiation of metreleptin treatment

		All	AGL	CGL	FPL	APL
ALT baseline (n=100)	Mean ± SD	84.5 ± 104.1	157.6 ± 170.4	95.3 ± 87.2	38.4 ± 33.1	93.8 ± 87.2
	Median	46	100	62	32	76
	Range	14 - 726	19 - 726	18 - 386	14 - 221	18-232
ALT post-rx (n=83)	Mean ± SD	47.8 ± 54.8	71.0 ± 92.8	38.5 ± 20.5	36.5 ± 35.5	103.4 ± 96.8
	Median	30	41	37	25.5	68
	Range	8 - 396	16 - 396	8 - 92	12-165	16-264

(2) **Liver Volume:** measurements were obtained by MRI and reported in milliliter (mL) units. Normal adult liver volume correlates with body weight, and averages ~1400 mL in adult women and ~1800 mL in adult men. Liver volume approaches near adult size around 10-12 years of age and is highest in early adulthood. Liver volume normally correlates with body weight [10], but the liver sizes in this study population did not correlate with variables dependently associated with body weight, i.e. gender and age.

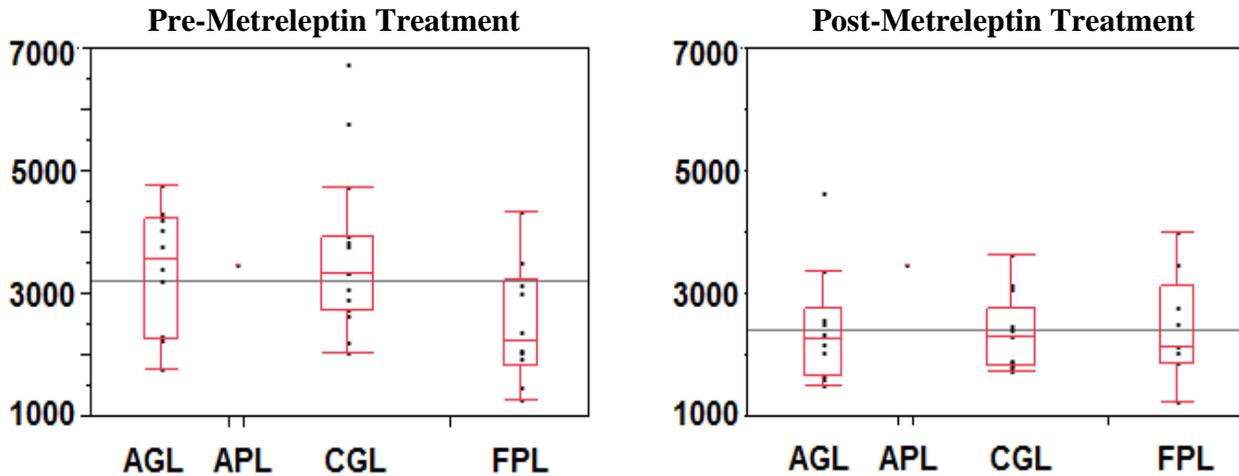
Liver volume data are summarized in Table 4, along with corresponding ALT levels in this subgroup of study patients. Larger baseline liver volume and greater reduction in liver volume occurred among the patients with the generalized forms of lipodystrophy (AGL and CGL), though subgroup standard deviations were marked (~1000 mL).

Table 4: Patients with pre- and post- metreleptin liver volume measurement and their ALT levels

	Liver Volume (mL)				ALT (IU/L)	
	Baseline	Post-rx	Change	Change (%)	Baseline	Post-Rx
All dx (n=33)	3171 ± 1068	2423±785	747.5 ± 836	-20.7 ± 18.5%	78.5 ± 86.4	48.6 ± 72.6
AGL (n=10)	3398 ± 1014	2440 ± 945	958 ± 986	25.7±23	109.5 ± 83.4	85.2 ± 121.6
CGL (n=13)	3349 ± 1174	2326 ± 609	1023 ± 847	27.8 ± 15.7	72.7 ± 99.1	23.6 ± 11.1
FPL (n=9)	2630 ± 942	2431 ± 870	199 ± 193	7.1 ± 5.9	45.8 ± 65.8	40.4 ± 47.5
APL (n=1)	3457	3461	-4	-0.1%	140	117

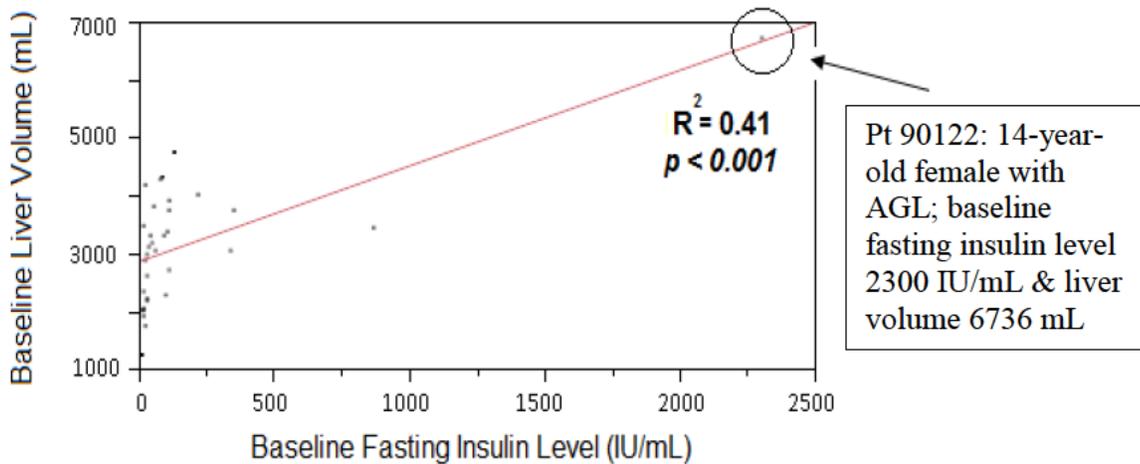
There was no significant change in liver volume in the FPL patients and the one APL patient. At baseline, the AGL and CGL patients have higher liver volumes than the FPL patients, but post-treatment liver volumes are similar among the groups. (Figure 2)

Figure 2: Liver volume by lipodystrophy subgroup:

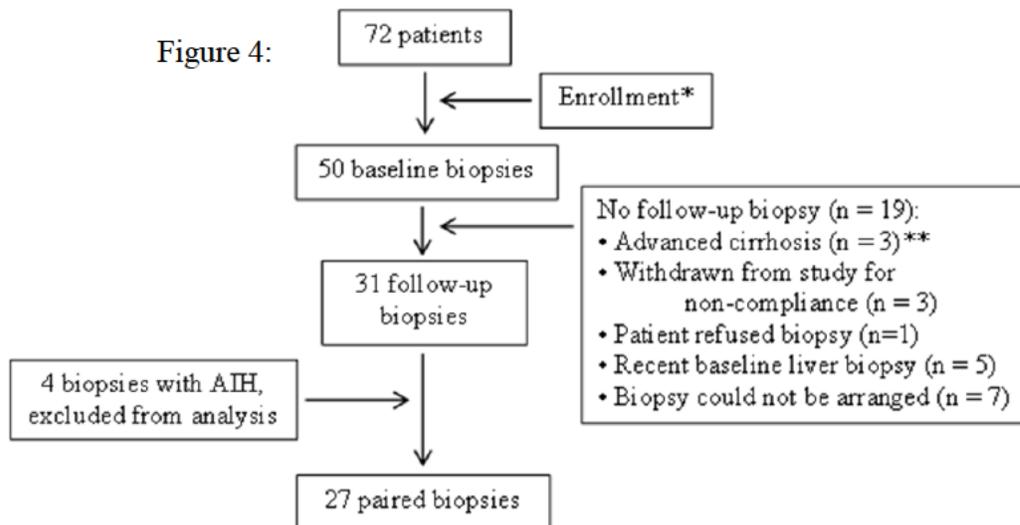


In the general population, hepatomegaly is not recognized to be a prominent feature of NASH. While liver enlargement can be observed in patients with NASH, it rarely approaches the degree of liver enlargement seen in many of these lipodystrophy study subjects.[11] On the other hand, glycogenosis which is a consequence of hepatocellular glycogen accumulation, resulting from increased hepatocyte glucose during episodes of hyperglycemia combined with supraphysiologic levels of insulin increasing glycogen synthesis.[12] Glycogenosis can occur in patients with type II diabetes presenting with severe insulin resistance, or in patients with poorly-controlled type I or II insulin-dependent diabetes with intermittent episodes of hyperglycemia and high-dose insulin administration. The primary clinical manifestation of this phenomenon is hepatomegaly and may be associated with mildly increased transaminase levels, both of which improve with proper glycemic control. [12, 13] Glycogenosis is observed routinely on liver biopsies of patients with lipodystrophy with poor glycemic control. Therefore, the contribution of hepatic steatosis to the liver enlargement in study patients cannot be accurately determined. Liver size does not correlate with ALT level, in the data submitted for this application, and reduction in liver size is observed in patients regardless of improvement in steatosis. A possible correlation may exist between fasting insulin level and liver volume and is shown in Figure 3. However, this analysis may be overly influenced by outlying data points.

Figure 3: Baseline liver volume by baseline fasting insulin level



(3) **Liver biopsies:** Fifty baseline liver biopsies and 27 paired (baseline and post-treatment) biopsies were included in the analyses reported by Zadeh *et al.* (J Hepatol 2013).[9] All biopsies were obtained from patients participating in the NIH studies 991265 and 20010769. According to Zadeh *et al.*[9], one of the patients who had NASH at baseline had concomitant chronic hepatitis B, and one patient had autoimmune hepatitis at baseline without histologic evidence of steatosis or NASH. The subject ID of these patients cannot be determined from the biopsy reports provided by the applicant. Following treatment, 4 patients were diagnosed with autoimmune hepatitis (AIH) on their follow-up biopsies, and these results were excluded from analysis. Limited information is provided to explain the incomplete nature of the biopsy data (Figure 4), despite plans for both pre- and post-treatment liver biopsies in the NIH study protocols.



* - Baseline biopsy of patient 90105 was performed 3 years after initiation of metreleptin treatment though reportedly following a treatment hiatus

- Baseline biopsies of the 4 patients diagnosed with AIH on follow-up biopsy were performed 19 months (ID 90103), 14 months (ID 90109), 23 months (ID 90110), and 4 months (ID 90150) prior to study enrollment.

** 3 patients with advanced fibrosis did not undergo follow-up biopsy, 3 others did undergo a repeat procedure. Factors affecting the decision whether to perform a biopsy in these patients are not known.

Since patients were not randomly selected to undergo liver biopsy, analyses using this data are subject to investigator selection bias. To determine whether this subgroup is representative of the entire study population, comparison of some key baseline laboratory values and patient characteristics were performed. (Table 5, next page) The boxed numbers highlight the median values which are most disparate from corresponding mean values.

Note that Zadeh *et al.* reported average data with mean and standard error calculations only. [9]

Table 5: Demographics of patients with biopsies vs. patients without biopsies:

		Biopsy (n=50)	No biopsy (n=50)	Paired biopsy (n=27)	No paired bx (n=73)
Age (years)	<i>Mean ± SD</i>	25 ± 15.8	33.4 ± 20.4	28.3 ± 16.0	29.5 ± 19.6
	<i>Median</i>	18	34.5	29	25
	<i>Range</i>	(7 - 68)	(1 - 67)	(7 - 68)	(1 - 67)
% Generalized	----	62%	44%	55.6%	52.1%
% Female	----	84%	88%	77.8%	89%
Years with dx	<i>Mean ± SD</i>	9.9 ± 9.7	7.10 ± 9.82	13.6 ± 11.1	6.25 ± 8.3
	<i>Median</i>	8.1	3.35	9.7	3.35
	<i>Range</i>	(0 - 40.6)	(0 - 43.8)	(0.4 - 40.6)	(0 - 43.8)
Baseline ALT (IU/L)	<i>Mean ± SD</i>	104.3 ± 124.5	64.4 ± 74.0	96.5 ± 97.5	79.8 ± 106.6
	<i>Median</i>	70.5	36.5	56	43
	<i>Range</i>	(18 - 726)	(14 - 419)	(18 - 386)	(14 - 726)
Post-Rx ALT (IU/L)	<i>Mean ± SD</i>	55.6 ± 69.0	38.0 ± 26.46	46.3 ± 55.2	48.5 ± 55.1
	<i>Median</i>	30.5	31.5	28	34
	<i>Range</i>	(8 - 396)	(15 - 155)	(6 - 264)	(15 - 396)
Baseline Leptin (units)	<i>Mean ± SD</i>	2.75 ± 2.89	8.33 ± 9.58	2.48 ± 2.33	6.43 ± 8.29
	<i>Median</i>	1.31	4.28	1.48	3.08
	<i>Range</i>	(0.4 - 14.1)	(0.31 - 42.9)	(0.5 - 7.97)	(0.31 - 42.9)
Baseline Insulin (IU/mL)	<i>Mean ± SD</i>	79.7 ± 125.2	182.4 ± 484.4	83.3 ± 161.6	127.7 ± 342.0
	<i>Median</i>	50.2	45	43.9	50.7
	<i>Range</i>	(4.7 - 862)	(6.6 - 2300)	(4.7 - 862)	(6.6 - 2300)

Prior to data analyses, the biopsies were reviewed for adequacy summarized in Table 6. Most investigators require a minimum of 10 portal areas for a biopsy specimen to be deemed adequate.

Table 6

Number of biopsies with <10 portal areas		
BASELINE BIOPSIES n=49*	PAIRED BIOPSIES n=27	
	Baseline	Post-Rx
15	7**	9**

* One biopsy did not have information regarding number of portal areas

** 3 patients had baseline and post-treatment biopsies < 10 portal areas

The results of the 50 baseline liver biopsies are displayed in Tables 7A-D. These analyses include frequency of NASH diagnosis and pathologic features of NASH for the entire cohort and each of the diagnosis subtypes.

Table 7: Summary of baseline liver biopsy findings

7A				
	NASH Diagnosis Classification			
	No	Borderline	Definite	
All (n=50)	9 (18%)	7 (14%)	31 (62%)	
AGL (n=13)	4 (31%)	2 (15%)	7 (54%)	
CGL (n=18)	1 (6%)	5 (28%)	12 (67%)	
FPL (n=15)	4 (27%)	2 (13%)	9 (60%)	
APL (n=4)	0 (0%)	1 (25%)	3 (75%)	

7B				
	NAS Steatosis Score (0-3)			
	0	1	2	3
All (n=50)	5 (10%)	20 (40%)	13 (26%)	12 (24%)
AGL (n=13)	3 (23%)	6 (46%)	1 (8%)	3 (23%)
CGL (n=18)	1 (6%)	6 (33%)	8 (44%)	3 (17%)
FPL (n=15)	1 (7%)	7 (47%)	4 (27%)	3 (20%)
APL (n=4)	0 (0%)	1 (25%)	0 (0%)	3 (75%)

7C			
	Hepatocellular Ballooning Score (0-2)		
	0	1	2
All (n=50)	11 (22%)	18 (36%)	21 (42%)
AGL (n=13)	4 (31%)	3 (23%)	6 (46%)
CGL (n=18)	2 (11%)	6 (33%)	10 (56%)
FPL (n=15)	4 (27%)	8 (53%)	3 (20%)
APL (n=4)	1 (25%)	1 (25%)	2 (50%)

7D					
	NAS Fibrosis Score (0-4)				
	0	1	2	3	4
All (n=50)	7 (14%)	12 (24%)	10 (20%)	13 (26%)	8 (16%)
AGL (n=13)	2 (15%)	2 (15%)	2 (15%)	4 (31%)	3 (23%)
CGL (n=18)	0 (0%)	5 (28%)	3 (17%)	5 (28%)	5 (28%)
FPL (n=15)	5 (33%)	5 (33%)	3 (20%)	2 (13%)	0 (0%)
APL (n=4)	0 (0%)	0 (0%)	2 (50%)	2 (50%)	0 (0%)

Interestingly, despite a definitive NASH diagnosis in greater than half of all baseline biopsies, the other characteristic pathologic features of NASH, indicative of hepatocellular injury and dysfunction, were only rarely identified in these biopsies. (Table 8) Furthermore, portal inflammation is an almost universal finding among the biopsy patients, an uncharacteristic finding among most NASH patients.

Table 8: Frequency of Other NASH-Associated Pathologic on Baseline Biopsies

	Mallory Bodies	Mega-mitochondria	Microvesicular Steatosis	Portal Inflammation
All (n=50)	6 (12%)	7 (14%)	5 (10%)	44 (88%)
NASH dx (n=31)	6 (19%)	7 (23%)	4 (13%)	29 (94%)

The inconsistency between these biopsy findings and those expected in patients with NASH questions whether other difference in pathophysiology and prognosis may exist.

Table 9: Baseline pathology by serum transaminase level (ULN=upper limit of normal)

	Fibrosis (0-4)	NAFLD Score (NAS) (0-8)	Definite NASH	Cellular Ballooning (0-2)	Steatosis (0-3)	Lobular Inflammation (0-2)
			<i>Definite +Borderline</i>			
All (n=50)	2.0	4.16	62% 82%	1.2	1.6	1.3
ALT level						
Normal (n=17) (<i><40 IU/L</i>)	1.4	3.2	53% 71%	0.9	1.3	1.0
1-3x ULN (n=21) (<i>40-120 IU/L</i>)	2.3	4.4	71% 85%	1.3	1.8	1.3
3-5x ULN (n=5) (<i>121-200 IU/L</i>)	2.6	4.6	80% 80%	1.6	1.6	1.4
>5 ULN (n=7) (<i>>200 IU/L</i>)	2.6	5.2	43% 100%	1.6	1.9	2.14

The applicant has purported that an improvement in transaminase levels from the entire study population is indicative of an improvement in NAFLD due to metreleptin therapy. They suggest that the pathology data from a subset of study patients is sufficient to conclude that elevated transaminases correlate with underlying NAFLD, and a decrease in transaminase levels represents an improvement in liver disease due to metreleptin treatment. Analysis of the study data has led to several observations which challenge these claims.

First, patients with abnormal liver pathology were distributed across different ALT level groups, making it impossible to accurately predict pathology based on baseline transaminase levels, though patients with baseline ALT levels in the normal range do have slightly more favorable biopsy results. These include: lower rate of definite NASH diagnosis, as well as lower average NAS, cellular ballooning injury, and fibrosis scores.

While the patients with baseline ALT levels > 5 times the upper limit of normal had higher average NAS scores, this group also had a lower rate of definite NASH diagnosis. These patients are described in greater detail in Table 10 (next page). Of note, lobular inflammation scores in these patients are higher. Also notable is the observation that the portal inflammation scores are also higher in the 2 highest ALT groups (3-5 times ULN and >5 times ULN) scores (score range 0-2)—mean 1.3 and 1.4 in these groups vs. 1.1 and 0.88 in the 2 lowest groups (1-3 x ULN and normal), though these scores are not included in the NAS. In the patient with the highest ALT level, the inflammatory scores are inconsistent with ballooning injury and steatosis scores, and this patient was diagnosed 9 months later with AIH and progressed to cirrhosis. Furthermore, there is a suggestion of a co-existing liver condition in the biopsy report for patient 90218’s baseline study, though the final diagnosis was not provided.

Table 10: Description of the 7 patients in the ALT group >5 times ULN

Subject ID	Diagnosis subtype	ALT level		NASH*		Fibrosis (0-4)		
		Baseline	Improved?	Pre	Post	Pre	Post	
90150	AGL	726	Partial	BL	BL	3	4	See comment [#]
90134	CGL	386	Complete	Yes	No	3	3	
90140	CGL	330	Complete	BL	---	1	---	
90128	AGL	326	Complete	BL	---	1	2	See comment ^{##}
90167	CGL	261	Partial	BL	---	4	---	
90141	APL	232	No	Yes	Yes	3	3	
90138	FPL	221	No	Yes	Yes	3	3	

* Diagnosis by pathologic diagnosis (biopsy review by pathologist), not NAS score; *BL=borderline*

Patient 90150: diagnosed on post-treatment biopsy with AIH

- Baseline biopsy:

- NAS score 4 (range 0-8)
- mild steatohepatitis: steatosis score (range 0-3) =1
- balloon injury score (range 0-2) =0
- diffuse inflammation: lobular score (range 0-3) =3; portal score (range 0-2) =2
- fibrosis score (range 0-4)=3

- Follow-up biopsy:—**not included in analyses because patient diagnosed with AIH**

- NAS score=6
- mild steatosis: steatosis score=1
- diffuse inflammation: lobular score=3; portal score=2
- fibrosis score=4 (**cirrhosis**)

Baseline biopsy pattern not consistent with NASH alone—presence of centrilobular necrosis, diffuse inflammation—suspected AIH, less likely viral hepatitis, but final diagnosis not provided

- Baseline biopsy:

- NAS score 5
- Steatosis score: 0
- Inflammation: lobular score=3; portal score=1

- Follow-up biopsy:

- No evidence of NASH (NAS=2)
- Inflammation improved but persistent: lobular score=2, portal score=1

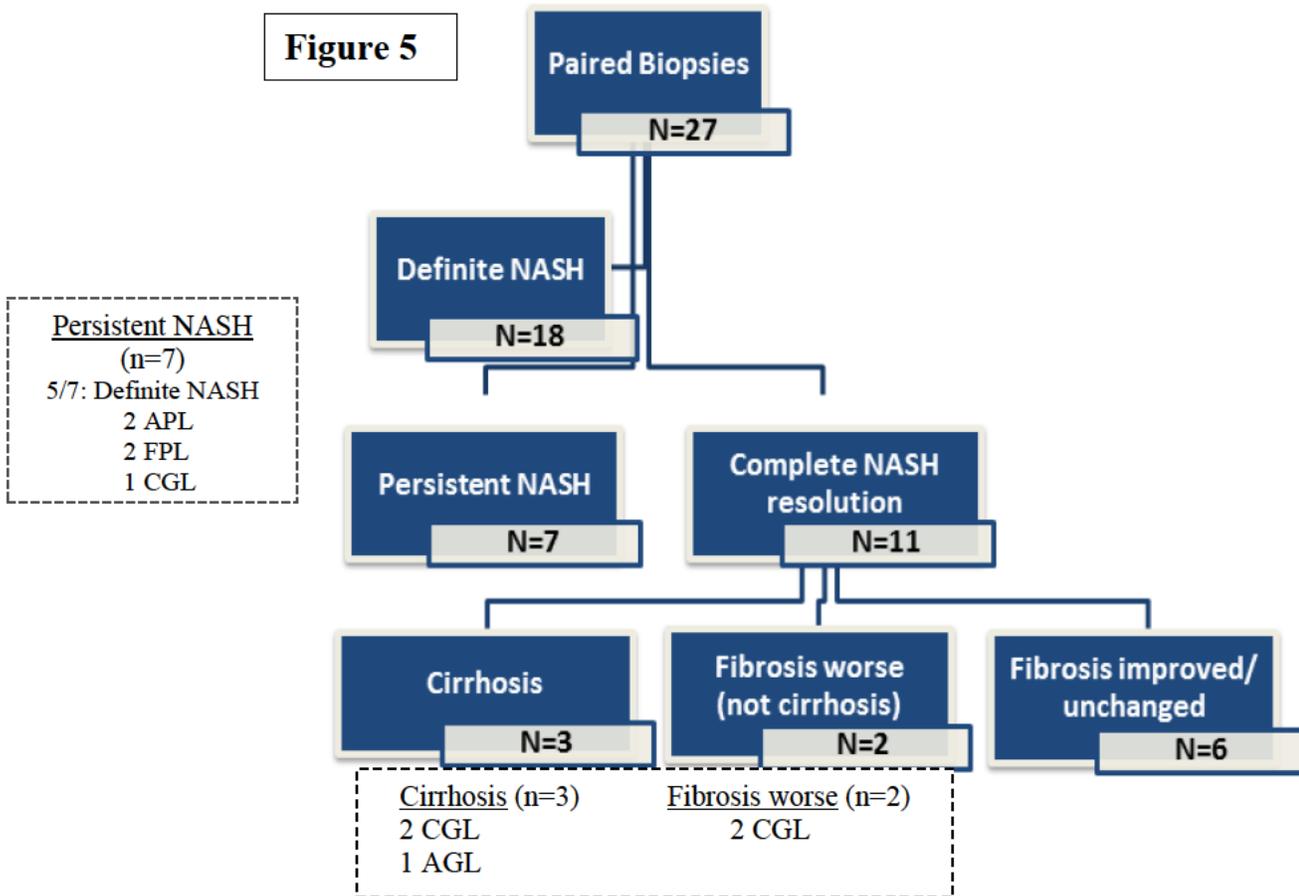
The comparison of baseline and post-treatment data, used in these efficacy analysis assess treatment effect of metreleptin on NAFLD in lipodystrophy, is not consistent among study patients, despite overall improvements in ALT levels. The paired biopsy results are summarized in Table 11 (next page). Due to the small the numbers of patients in each subgroup, this reviewer’s confidence in the following statements is limited. However, based on the comparison between the baseline and post-metreleptin biopsies, it appears that:

- A diagnosis of NASH is most consistent among the CGL patients
- The AGL patients demonstrated the greatest improvement in NASH after metreleptin treatment, followed by the CGL patients. However, some of these patients have worsening of their fibrosis which would not be considered a positive treatment response, particularly in patients with advanced fibrosis and cirrhosis since features of steatohepatitis often disappear in these patients (“burnt out liver”). (Figure 5) Of these patients with NASH resolution, 3 patients had cirrhosis (2 CGL, 1 AGL) and another 2 patients had worsening of fibrosis (2 CGL).
- NASH occurs in APL patients, but no improvement is observed following metreleptin treatment
- FPL patients have the lowest percentage of patients with NASH at baseline, but their resolution rate following metreleptin treatment is lower than the AGL and CGL patients
- Fibrosis occurs in all subtypes and may be more severe in the APL patients in this data set

Table 11: Pre- and post-treatment pathology in patients with paired biopsies

		NASH dx		NAS	Steatosis	Cellular Ballooning	Fibrosis	Lobular Inflammation
		Definite	Definite + Borderline					
All dx (n=27)	<i>Pre</i>	18 (67%)	23 (85%)	4.3	1.7	1.2	1.9	1.3
	<i>Post</i>	5 (19%)	9 (33%)	2.4	0.9	0.4	1.9	1.1
AGL (n=5)	<i>Pre</i>	3 (60%)	4 (80%)	4.8	1.6	1.2	2.2	2
	<i>Post</i>	0 (0%)	0 (0%)	1.4	0.2	0	2.2	1.2
CGL (n=10)	<i>Pre</i>	9 (90%)	10 (100%)	4.6	1.9	1.6	2.1	1.1
	<i>Post</i>	1 (10%)	3 (30%)	2.5	0.8	0.5	2.2	1.2
FPL (n=9)	<i>Pre</i>	4 (44%)	6 (67%)	3.3	1.3	0.8	1.3	1.2
	<i>Post</i>	2 (22%)	3 (33%)	2.2	0.8	0.44	1.2	1.0
APL (n=3)	<i>Pre</i>	2 (67%)	3 (100%)	5.7	3	1.3	2.7	1.3
	<i>Post</i>	2 (67%)	3 (100%)	4.7	2.3	1.0	2.7	1.3

Figure 5



(4) Comparison of all 3 liver parameters: The study results of the 19 patients with data for all three liver parameters are summarized in Table 12. In this small subgroup of patients, the 5 AGL and 6 CGL patients demonstrate improvements in all 3 parameters. By comparison, the single APL patient showed little improvement following treatment—ALT remained elevated, liver volume was essentially unchanged, and NASH was diagnosed on both biopsies.

Results in the 7 FPL patients were more equivocal. NASH was present in <50% of patients at baseline, and improved in 1 of the 3 patients. Liver volumes were similar at both time points. Mean ALT levels were slightly elevated at baseline and did not normalize completely. However, median values were entirely normal at both time points, suggesting that the means are skewed by outliers.

Table 12: Analysis of the 19 patients with ALT levels, MRI data, and paired biopsies

	NASH diagnosis*		ALT (IU/L)		Liver volume (mL)	
	<u>Yes</u>	<u>Persistent NASH</u>	<u>Baseline Mean Median</u>	<u>Post-rx Mean Median</u>	<u>Baseline Mean Range</u>	<u>Post-rx Mean Range</u>
All (n=19)	12/19	4/12	92.6 33.0	37.0 24.0	3113 (1274 - 4780)	2464 (1229 - 4012)
AGL (n=5)	3/5	1/3	133.0 97.0	30.4 23.0	3459 (2232 - 4780)	2397 (1597 - 3361)
CGL (n=6)	5/6	1/5	99.0 43.5	22.3 21.5	3120 (2029 - 3919)	2201 (1733 - 3081)
FPL (n=7)	3/7	1/3	51.2 25.0	42.8 24.0	2810 (1274 - 4327)	2594 (1229 - 4012)
APL (n=1)	1/1	1/1	140.0	117.0	3457	3461

* NASH diagnosis is based on formal pathologic diagnosis (pathologist biopsy reading, not NAS score)

(5) *Summary of metrelleptin effects on liver parameters:* The presence of NAFLD at baseline and improvement following metrelleptin treatment differ between the patients with the generalized and partial forms of lipodystrophy. Also, the applicant is seeking a separate indication for the partial lipodystrophy, specifically for the treatment of hepatic steatosis. Therefore, Table 13 provides a summary of the analyses for all three liver parameters for the generalized (n=53) vs. partial (n=47) lipodystrophy patients. Comparisons between analyses need to be judged carefully since each analysis is performed on a different subgroup of patients. Nevertheless, the composite data included in this table is consistent with others in this report.

- The average baseline ALT levels in the cohort of **generalized** lipodystrophy patients were mildly elevated and improved following metrelleptin treatment. This trend is consistent in the ALT analyses for subgroups of liver volume patients and liver biopsy patients.
- Average baseline liver volume in the **generalized** lipodystrophy patients is quite large, but, individual measurements within the cohort are extremely variable. Following metrelleptin treatment, these patients exhibit marked reduction in liver size.
- By comparison, liver volume in the **partial** lipodystrophy patients are not as large pre-treatment as the generalized lipodystrophy patients and do not change significantly, and neither do the ALT levels in this subgroup.
- NASH is present in most of the **generalized** lipodystrophy patients at baseline, and the features of NASH improve with treatment (NAS, steatosis, ballooning injury), though average fibrosis scores do not. Although 75% of patients with baseline NASH do not

have NASH on follow-up, only 50% improve without worsening fibrosis/cirrhosis. In these patients, like the others, ALT levels normalize following metreleptin treatment.

- In the **partial** lipodystrophy patients, NASH is still relatively common (50%), but the rate of resolution is lower. In addition, baseline and post-metreleptin ALT levels in this subgroup are unchanged.

Table 13: Summary of metreleptin effect on liver endpoints: generalized vs. partial lipodystrophy

	GENERALIZED LIPODYSTROPHY	PARTIAL LIPODYSTROPHY
Transaminase serum level (IU/L) (ALT)	n=53 <u>Pre → Post-rx serum ALT</u> • Mean: 119 → 49 • Median: 79 → 37.5	n=47 <u>Pre → Post-rx serum ALT</u> • Mean ALT level: 48.5 → 46.1 • Median ALT level: 32 → 29
Liver Volume (mL) (MRI)	n=23 <u>Pre → Post-rx liver volume</u> • Mean: 3370 → 2376 • Mean % change: 27% <u>Pre → Post-rx serum ALT (IU/L)</u> • Mean: 88.7 → 48.8 • Median: 54 → 24.5	n=10 <u>Pre → Post</u> • Mean liver volume 2713 → 2534 • Mean % change: 6% <u>Pre → Post-rx serum ALT (IU/L)</u> • Mean ALT level: 55.2 → 48.1 (IU/L) • Median ALT level: 25.5 → 27 (IU/L)
Liver Pathology (Biopsy)	n=15 <u>Paired biopsies</u> • NASH dx: pre: 12/15 (80%) - NASH resolution: 9/12 (75%) + without ↑ fibrosis/cirrhosis: 6/12 (50%) • NAS: 4.7 → 2.1 • Steatosis: 1.8 → 0.6 • Fibrosis: 2.1 → 2.1 • Ballooning: 1.5 → 0.3 <u>Pre → Post-rx serum ALT (IU/L)</u> • Mean ALT level: 115 → 29.6 • Median ALT level: 95 → 27	n=12 <u>Paired biopsies</u> • NASH dx: pre: 6/12 (50%) - NASH resolution: 2 /6 (33%) + without ↑ fibrosis/cirrhosis: 2/6 (33%) • NAS: 3.9 → 2.8 • Steatosis: 1.8 → 1.2 • Fibrosis: 1.7 → 1.6 • Ballooning: 0.9 → 0.6 <u>Pre → Post-rx serum ALT (IU/L)</u> • Mean ALT level: 73.2 → 67.1 • Median ALT level: 26.5 → 30.5

5 CONCLUSIONS:

Questions requested to be addressed in consultation report:

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.

DGIEP Response:

- (1) **Transaminase levels:** Although more than half of the subjects had baseline ALT levels >40 IU/L, only 10% had levels more than 5 times the upper limit of normal. (Table 2) Low-grade transaminitis is often clinically insignificant, in that it does not predict significant clinical morbidity or mortality. [14] In this population, ALT levels do not appear to correlate with liver histopathology. NASH biopsy features, including steatohepatitis, ballooning injury, and fibrosis were present in patients across different degrees of ALT elevation (see Table 9).
- (2) **Liver volume:** Hepatomegaly is a prominent clinical feature in many patients with generalized lipodystrophy, with the most severe elevations in patients with the CGL subtype. (Figure 3) Glycogenosis, a metabolic process typically associated with inherited glycogen storage disorders, is the result of hepatocellular glycogen accumulation. Glycogenosis can also occur in patients with diabetes mellitus presenting with severe hyperinsulinemia and insulin resistance resulting in massive hepatocellular glycogen storage and impaired glycogen breakdown. The glycogenosis and enlarged livers improve following insulin treatment in these diabetic patients. However, steatosis is likely not the primary etiology of liver enlargement in this population. Rather, glycogenosis is likely the primary causative process based on the following: (1) the degree of hepatomegaly does not consistently correlate with degree of steatosis; (2) improvement in liver volume can occur with treatment even if steatosis does not; and (3) NASH in non-lipodystrophy patients is not typically associated with severe hepatomegaly, which is consistent with the observation that patients with partial lipodystrophy may have NASH but have lower liver volumes. Glycogenosis is a recognized feature in hepatocytes of patients with lipodystrophy and can be associated with mild transaminase elevations.
- (3) **Biopsy Results:** It is impossible to draw reliable conclusions about the effect of metreleptin on liver histology in this trial for several reasons as noted below. In addition, these assessments may not be generalizable to the entire lipodystrophy population.
 - a) The first reason is the uncontrolled, non-randomized trial design that included a very heterogeneous patient population.
 - b) The second reason is that the number of available liver biopsies to assess treatment response was small (less than 1/3 of study subjects), and the patients with biopsies may not be a representative sample of the entire study population because the selection of biopsy patients was not randomized and therefore subject to bias. In addition, comparison of demographic and baseline characteristics between patients with and without biopsies detected several differences in these

groups (Table 5), though the clinical significance of these difference in the groups is unclear.

- c) **The third reason is that it is difficult to draw clear conclusions is that the response was inconsistent, even among the patients with generalized lipodystrophy, with only a fraction of patients demonstrating clear improvement. (see Figure 5 and Table 11) This is further complicated by the fact that up to 20% of placebo patients in NASH clinical trials have spontaneous improvement and/or resolution of their liver disease. [15]**

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?**

DGIEP Response:

Simple steatosis, in the absence of NASH, is not a clinically significant condition in the absence of transaminase elevations that persist chronically. In other words, “fatty liver” alone is not necessarily associated with an increase in morbidity or mortality and varies depending on the metabolic disease condition. Therefore, treatment for steatosis is typically not recommended since only medications with a negligible risk profile could satisfy the risk/benefit balance of treatment. Since we do not have clear understanding of what causes the transition from steatosis to NASH, we do not have the capability of predicting which patients may possibly benefit from pre-emptive treatment.

Similarly, it is impossible to predict which of these study patients is more likely to develop complications of NAFLD, particularly in the absence of consistent trial data. The NASH outcomes were secondary endpoints in this uncontrolled trial. To answer this question one would need to design a trial in which patients with lipodystrophy were biopsied and then followed longitudinally for long periods of time. Note that essentially all analyses in this review are observations of data trends. Therefore, confidence in our assessments is limited by the lack of statistical validation.

Overall, no improvements in liver parameters were seen following metreleptin therapy in the partial lipodystrophy cohort. However, improvements in liver parameters were observed following metreleptin therapy in the cohort with generalized lipodystrophy, though both baseline and outcome data were widely distributed and often skewed, limiting efficacy analyses. Treatment response may be specific to particular patients within the generalized lipodystrophy cohort, but subset sample sizes are much too small to be able to make outcome predictions. Furthermore, in the patients with inherited lipodystrophy, genotype-phenotype differences may account for some of the data variability; however, genetic testing results were not provided.

3. **Are there safety concerns with treating patients who have other liver diseases, such as autoimmune hepatitis with metreleptin?**

DGIEP Response:

The risks of metreleptin identified by the primary review team, such as the potential for hematologic malignancy and the development of neutralizing anti-drug antibodies, are compelling and would affect any risk/benefit analysis of treatment, including effects on liver parameters.

The immune-stimulatory effect of leptin raises concern, particularly because leptin had been implicated in the development of NASH in patients with NAFLD. Other considerations include the potential for metreleptin to trigger autoimmunity or its potential role in malignancy. Four study patients were diagnosed with biopsy-proven autoimmune hepatitis during study participation. However, all 4 of these cases occurred in patients with AGL, a known association, and one of these patients may have been exhibiting signs of AIH even before initiation of metreleptin.

De novo ALT levels elevations were uncommon (i.e. elevated ALT > 3 times ULN in patients with baseline ALT levels < 2 times ULN), as were recurrences of elevated ALT (i.e. ALT level > 3 times ULN after initial improvement (<2 times ULN)). Seven patients fit criteria for one of these categories, 3 of which were diagnosed with AIH post-treatment, 2 of which had no biopsy data at all, 1 of which underwent biopsies >2 years prior to the ALT elevation, and only 1 non-AIH patient who had biopsy data corresponding to the ALT elevation. Since corresponding pathology data was inconsistently collected, it is not possible to conclude whether the cause of transaminase elevations during treatment is treatment-related or due to the underlying disease, particularly since one of these patients withdrew for non-compliance and another “transferred to another program.”

Three cases of lymphoma and one case of adenocarcinoma occurred during clinical trials with metreleptin. Hepatocellular carcinoma is a known complication of NASH [11], and no cases of hepatocellular carcinoma were identified during clinical trials of metreleptin. One patient had a known hepatic tumor at baseline, described as a well-differentiated hepatic nodule with prominent ductular proliferation and fibrosis on pathology (differential diagnosis: dysplastic nodule, hepatocellular carcinoma, and focal nodular hyperplasia), and this patient continued treatment with metreleptin without known adverse effect on the tumor. Nevertheless, long-term safety data is needed to address these potential concerns.

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)?

DGIEP Response:

There is insufficient evidence to support

(b) (4)

The biopsy data from the clinical trial confirms that many patients with lipodystrophy have NAFLD and NASH, but response to treatment is variable. While some patients with NASH had resolution of pathologically defined disease, only 6/18 showed complete resolution WITHOUT worsening fibrosis or development of cirrhosis. The improvement in steatohepatitis in the remaining patients may be due to advancing liver disease (i.e., “burned out” cirrhosis), rather than positive metreleptin effect on the steatohepatitis process. Furthermore, if lipodystrophy-associated NAFLD follows a similar natural

history as NAFLD in the general population, in which a 20% spontaneous remission rate can be seen in placebo patients in NASH trials, a 33% improvement (particularly without a control group) (b) (4)

Improvements in ALT were noted in the generalized lipodystrophy subgroup but not in the partial lipodystrophy subgroup. However, it is difficult to correlate this improvement with improvement in NASH pathology. It appears from the limited data available that the improvement in ALT was most notable in the patients who had enlarged livers and responded with dramatic decrease in liver volume, therefore it is likely that the improvement in ALT in these patients was related to resolving glycogenosis not improvement in NASH.

In addition the applicant has requested an indication for treatment of steatosis in the generalized lipodystrophy population. We do not agree that this is indicated for the reasons noted above in the answer to question #2. Steatosis has a low rate of progression to steatohepatitis in NAFLD, and there are currently no prospective, predictive variables to determine which patients are at risk for progression of disease. In the opinion of DGIEP, the benefit/risk assessment for leptin treatment does not support an indication for treatment of steatosis in lipodystrophy.

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/s/

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11/15/2013

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11/15/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Sponsor's Patient Registry Summary

Date: September 30, 2013

Reviewer(s): Patricia L. Bright, M.S.P.H., Ph.D.,
Epidemiologist,
Division of Epidemiology 1 (DEPI 1),
Office of Pharmacovigilance and Epidemiology (OPE),
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Acting Division Director: Solomon Iyasu, M.D., M.P.H.,
Acting Division Director, DEPI 1, OPE, OSE

Subject: Review of the Sponsor's Proposed Metreleptin Patient
Registry FHA403 Protocol Summary (Appendix 3 of the
Risk Management Plan, dated March 8, 2012)

Drug Name(s): Metreleptin

Application Type/Number: BLA 125390

Applicant/sponsor: Amylin Pharmaceuticals, Inc.

OSE RCM #: 2013-1153

TSI #: Not Applicable

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EXECUTIVE SUMMARY

Lipodystrophy (genetic or acquired) is a group of disorders characterized by the loss of subcutaneous fat tissue. This loss of adipose tissue results in increased fat in the blood stream (hypertriglyceridemia) and accumulation of fat in non-adipose tissue, such as the liver and muscles (1).

The fat loss can be localized, partial (such as lost from a limb), or generalized -- involving nearly the entire body. Localized lipodystrophy may only have cosmetic implications. The extent of fat loss in partial and generalized lipodystrophy determines the severity of complications, however, including diabetes mellitus, hypertriglyceridemia, hepatic stenosis, polycystic ovaries, and acanthosis nigricans (2).

Metreleptin, a therapeutic protein, is a recombinant analog of human leptin administered by injection and is a new biological entity submitted to the FDA for the indication of diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy (3). It is not indicated for use in patients with HIV-related lipodystrophy or for use in patients with diabetes mellitus and/or hypertriglyceridemia without concurrent evidence of inherited or acquired lipodystrophy. Genetic and acquired lipodystrophies are rare and FDA granted the sponsor orphan designation for metreleptin.

Prior to metreleptin's approval, the sponsor, Amylin, provided a risk management plan and proposed that metreleptin (b) (4)

[REDACTED] As part of their risk management plan the sponsor included a three page Metreleptin Patient Registry Summary in Appendix 3, dated March 8, 2012.

The registry summary described a prospective, multicenter, observational, product exposure registry for patients with lipodystrophy receiving commercially available metreleptin. Patients with HIV-associated lipodystrophy or localized lipodystrophy would not be eligible for enrollment.

The primary objective of the registry would be to describe the occurrence of Adverse Events of Special Interest (AESI) among lipodystrophy patients who receive commercial metreleptin therapy. These AESI are acute pancreatitis, hematologic malignancy, severe hypoglycemia and generalized hypersensitivity.

The Division of Epidemiology 1 (DEPI1) provided recommendations to the sponsor about the proposed registry in section 6 of this review; however, in the absence of an FDA PMR and given the brevity of the sponsor's registry summary, no response to these comments is required from the sponsor. If metreleptin receives FDA approval and if a post-marketing observational study is required, the sponsor will be obligated to submit to the FDA a formal well-developed study protocol that evaluates the outcomes identified in the post-marketing requirement.

1. INTRODUCTION

The purpose of this review is for the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology 1 (OSE/OPE/DEPI1) to evaluate the sponsor's Metreleptin Patient Registry Summary included in Appendix 3 of their Risk Management Plan, dated March 8, 2012.

1.1 BACKGROUND

Metreleptin, a therapeutic protein, is a recombinant analog of human leptin administered by injection and is a new biological entity submitted to the FDA for the indication of diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy (3).

Lipodystrophy (genetic or acquired) is a group of disorders characterized by the loss of subcutaneous fat tissue. This loss of adipose tissue results in increased fat in the blood stream (hypertriglyceridemia) and accumulation of fat in non-adipose tissue, such as the liver and muscles (4).

The fat loss can be localized, partial (such as lost from a limb), or generalized -- involving nearly the entire body. Localized lipodystrophy may only have cosmetic implications. The extent of fat loss in partial and generalized lipodystrophy determines the severity of complications including diabetes mellitus, hypertriglyceridemia, hepatic stenosis, polycystic ovaries, and acanthosis nigricans (2).

The diagnosis of lipodystrophy is mainly clinical and is associated, particularly for "lean" patients with evidence of fat loss, with early diabetes, severe hypertriglyceridemia, hepatic steatosis, hepatosplenomegaly, acanthosis nigricans, and polycystic ovarian syndrome (2). The patient may also have extremities and hips with signs of fat loss and muscular prominence. "Patients with lipodystrophies should be differentiated from those with anorexia nervosa, cachexia, starvation, diencephalic syndrome, Cushing's syndrome, generalized and truncal obesity, multiple symmetric lipomatosis, and other rare progeroid syndromes and disorders affecting growth and development" (2).

Laboratory tests can provide supportive evidence; patients with suspected partial or general lipodystrophy should be tested for glucose intolerance, serum lipids, liver function, hyperuricemia, analysis of serum complement 3 and 4, and complement 3 nephritic factor and urinalysis for proteinuria (2). To assess for genetic lipodystrophies, an in-depth pedigree analysis should be conducted with careful examination of the male first-degree relatives. Genetic testing, including prenatal diagnosis, is available for AGPAT2, BSCL2, LMNA, ZMPSTE24, and PPARG (2).

Since adipose tissue secretes the hormone leptin, a low level of adipose tissue results in a low level of circulating leptin. The low leptin levels stimulate appetite, prompting the patient to overeat. Given the lack of adipose storage, the additional calories from overeating can worsen the patient's condition. Options currently available for patients with lipodystrophy are limited and include diet modification and use of oral anti-hyperglycemic agents, insulin, and/or lipid-lowering agents (5).

Genetic lipodystrophies have an estimated prevalence in the general population of less than one in one million (2). Acquired partial and generalized lipodystrophy cases are

also rare, with 250 and 100 cases reported in the literature, respectively (2). Acquired lipodystrophy is mainly idiopathic or autoimmune in origin, with females affected more often than males, and with symptoms first presenting in childhood or adolescence (2). Conversely, lipodystrophy induced by use of highly active antiretroviral therapy (HAART) containing protease inhibitors is relatively common and affects over 100,000 in the U.S. and worldwide (2).

Metreleptin is not indicated for use in patients with HIV-related lipodystrophy nor for use in patients with diabetes mellitus and/or hypertriglyceridemia without concurrent evidence of inherited or acquired lipodystrophy.

The sponsor proposed a risk management plan (b) (4)

[Redacted]

As part of their Risk Management Plan the sponsor included a Metreleptin Patient Registry Summary in Appendix 3, dated March 8, 2012.

The March 2012 risk management plan for metreleptin identifies the following four important risks:

[Redacted]



1.2 BRIEF REGULATORY HISTORY

- March 29, 1996: IND 50259 submitted by Amgen.
- June 5, 2000: IND 60534 submitted by Philip Gorden, M.D., Director, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health (NIH) to study metreleptin for lipodystrophy.
- August 22, 2001: Amgen was granted orphan designation for metreleptin for the treatment of metabolic disorders secondary to lipodystrophy.
- March 3, 2006: Amylin assumed sponsorship of metreleptin from Amgen.
- July 30, 2010: The FDA accepted a rolling submission time line.

- December 17, 2012: Pre-BLA meeting held to discuss outstanding clinical documents/data and non-clinical information required to complete BLA filing.
- April 30, 2013: FDA filing meeting held.
- September 18, 2013: FDA to hold mid-cycle meeting.
- December 11, 2013: Projected date for FDA to hold advisory committee meeting on metreleptin.

1.3 PRODUCT LABELING

- Metreleptin has not yet been approved and product labeling has not been finalized.

2 REVIEW METHODS AND MATERIALS

On March 27, 2013, the Division of Metabolism and Endocrinologic Products (DMEP) requested the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology 1 (OSE/OPE/DEPI1) review the sponsor's proposed product registry. The FDA has not received a fully developed protocol; however, the sponsor included a summary of the metreleptin patient registry, dated March 8, 2012, in Appendix 3 of their Risk Management Plan. In reviewing this registry, DEPI staff consulted "Registries for Evaluating Patient Outcomes: A User's Guide" (6).

3 REVIEW RESULTS



- references and appendices.

7 REGULATORY RECOMMENDATIONS TO DMEP

We are in agreement with the sponsor's general proposal for a product exposure registry and, if metreleptin receives approval, we endorse the use of a registry, enhanced pharmacovigilance, or both as PMRs. Given the rarity and severity of the disease and the small number of patients likely to be using the drug, a product registry or enhanced pharmacovigilance may be efficient methods for surveillance for some rare adverse events.

We anticipate that the AESI identified in the proposal would need to be expanded to include safety outcomes specified by the DMEP clinical reviewer (potentially all cancers [excluding non-melanoma skin cancer], autoimmune disease exacerbation, hepatic adverse events, and pregnancy outcome).

Although registry data would be easier to analyze for the more common outcomes, such as severe hypoglycemia, generalized hypersensitivity, and acute pancreatitis, the registry also has the potential to provide descriptive data on more rare outcomes, such as malignancies and pregnancies.

If the FDA clinical reviewer identifies malignancies as an outcome of interest, registry follow-up would need to be extended to allow for the evaluation of malignancy development.

8 REFERENCES

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² Garg A. Lipodystrophies: Genetic and Acquired Body Fat Disorders. *J Clin Endocrinol Metab*, 2011;96(11):3313-3325.

³ Metreleptin for Lipodystrophy Program Risk Management Plan, Amylin Pharmaceuticals, Inc., March 08, 2012, p 6.

⁴ FDA Clinical Pharmacology and Biopharmaceuticals BLA filing review, BLA number 125390, completed by Vaidyanathan, J., June 7, 2012.

⁵ FDA Clinical Filing Memorandum, BLA filing review, BLA number 125390, completed by Golden J., May 2, 2013.

⁶ Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcomes Sciences, Inc. d/b/a Outcome] under Contract No. HHS290200500351 TO3.) AHRQ Publication No. 10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010.

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09/30/2013

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09/30/2013



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 19, 2013

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Patricia J Madara, RPM
DMEP

Subject: QT-IRT Consult to BLA 125390

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated April 22, 2013 regarding the Sponsor's request to waive the requirement to conduct a thorough QT study for metreleptin. The QT-IRT received and reviewed the following materials:

- Your consult
- Investigator's Brochure (April 7, 2011)
- Highlight of Clinical Pharmacology Table
- Response to FDA Request for Information Dated 12-Apr-2013

QT-IRT Comments for DMEP

We agree that a TQT study is not needed for Metreleptin. Sponsor should continue collecting ECGs in ongoing and future studies. Sponsor should collect safety ECGs as clinically indicated.

BACKGROUND

Metreleptin is a recombinant human analog of leptin and has a molecular weight of 16 kDa. It differs from the human leptin sequence by one additional amino acid (methionine) located at the amino-terminal end. BLA 125390 is an application for the treatment of metabolic disorders associated with lipodystrophy. Metreleptin has also been studied for the treatment of obesity

under different INDs. A Risk Evaluation and Mitigation Strategy is proposed by the Sponsor so that metreleptin will only be prescribed by certified physicians and dispensed by specially certified pharmacies. BLA 125390 includes long-term exposure of metreleptin in patients with lipodystrophy (n=72) with up to 11 years of exposure.

The following nonclinical and clinical data has been provided to the BLA:

NON-CLINICAL INFORMATION

The cardiovascular response to subcutaneously (SC) administered metreleptin was assessed in a GLP safety pharmacology study (Study 93063) in conscious male Beagle dogs following single doses of 0, 5, or 25 mg/kg (Serial 0000, [Section 2.6.2.4.2](#) and [2.6.6.3.9](#)). No effects were observed on systemic blood pressure, heart rate, electrocardiogram (ECG) (6-lead) tracings, contractility indices, pulmonary artery pressure, cardiac output, total peripheral resistance, or stroke volume. The mean peak serum concentration (C_{max}) for metreleptin after a 25 mg/kg SC dose was approximately 5700 ng/mL, which is higher than the exposure observed in humans. In clinical study FHA101, the observed median C_{max} after at least 3 months of metreleptin treatment in lipodystrophy patients was 366 ng/mL. The maximum observed leptin level at a single time point in one patient was 3722 ng/mL.

The effects of metreleptin on the cardiovascular system were also studied in unanesthetized, unrestrained male rats (Study GAN00109). In this GLP study, animals were given a single subcutaneous administration of 3, 10, or 30 mg/kg metreleptin. No obvious effect was observed on resting blood pressure and heart rate over the 24-hour observation period.

In a chronic repeated-dose GLP toxicity study in male and female Beagle dogs, metreleptin was administered at dose levels up to 5 mg/kg/day by SC injection for 1-, 3-, and 6-month treatment periods, followed by 1-, 4-, and 1-month recovery periods, respectively (Study WIL-120039). ECG evaluations showed no specific treatment related electrocardiographic changes at Weeks 3, 7, 11, and 23 of the dosing phase. Additionally, there were no significant ECG findings at the Week 7 evaluation of the first recovery phase animals, the Weeks 23 and 27 evaluations of the second recovery phase dogs, and the Week 27 evaluation of the third recovery phase animals.

Reviewer's comments: Metreleptin tested negative for ECG effects in conscious, instrumented dogs given a single dose (up to 25 mg/kg, SC; human equivalent dose of 12.5 mg/kg). This dose is 75 times the maximum clinical dose of 10 mg/kg/day (0.167 mg/kg/day for a 60 kg human). Peak serum drug levels in animals were many fold higher than median drug levels in humans, and similar to or higher than the highest exposure seen in a single patient. There was also no signal for ECG effects in chronic toxicology studies in animals given doses higher than those proposed for humans. A brief literature review in Pubmed did not reveal any ECG effects of leptin. It seems unlikely that acute administration of metreleptin will affect QT interval in humans at the proposed doses.

CLINICAL INFORMATION

ECGs were collected as part of routine safety monitoring in Study DFA102, which investigated the combination of pramlintide/metreleptin for the treatment of obesity.

This study was not designed as a rigorous thorough QTc study. The ECG data from

DFA102 are included in Serial 0017, Section 5.3.5.4, DFA102 CSR, [Section 14.6](#).

These data show there were no clinically significant changes or trends in ECG intervals or rhythm, including QT/QTc interval, in any treatment group during the study. In addition, there were no adverse events of arrhythmia or conduction-related events. Limitations to these ECG data include the following: 1) ECGs were not collected as replicates at the 4 protocol-specified time points over the 26-week study duration (only a single ECG was done at each of the specified time points); 2) ECG measurements were not core lab adjudicated but rather reported according to automated machine readings; and 3) matching pharmacokinetic assessments were not performed at the same visit as the ECG collections.

DFA102 Supporting Data Summary 4.14.2 (Page 13 of 15)
12-Lead Electrocardiogram Parameters and Changes from Screening
Population: Intent-to-Treat (N = 608)

Parameter	Placebo-P +	Pramlintide 360 +	Placebo-P +	Pramlintide 180 +	Pramlintide 180 +	Pramlintide 360 +	Pramlintide 360 +	Pramlintide 360 +	All Subjects (N = 608)
Visit	Placebo-M (N = 75)	Placebo-M (N = 77)	Metreleptin 5.0 (N = 72)	Metreleptin 2.5 (N = 75)	Metreleptin 5.0 (N = 78)	Metreleptin 1.25 (N = 78)	Metreleptin 2.5 (N = 78)	Metreleptin 5.0 (N = 75)	
Statistics									
QTcF Interval (msec)									
Visit 2 (Screening)									
n	75	77	72	75	77	78	78	74	606
Mean (SD)	408.7 (23.90)	406.3 (22.64)	407.4 (21.45)	412.6 (20.85)	407.1 (20.95)	410.2 (19.70)	405.8 (19.78)	408.3 (21.69)	408.3 (21.38)
SE	2.76	2.58	2.53	2.41	2.39	2.23	2.24	2.52	0.87
Median	409.0	405.0	405.5	412.0	406.0	409.0	405.5	408.5	407.0
Min, Max	351, 462	347, 477	358, 463	360, 455	362, 483	366, 463	340, 457	348, 463	340, 483
Visit 5 (Day 1)									
n	74	77	72	74	78	77	78	74	604
Mean (SD)	413.1 (23.99)	408.4 (22.18)	412.4 (20.92)	417.7 (19.36)	411.7 (21.59)	412.8 (20.58)	409.7 (18.80)	408.4 (20.71)	411.7 (21.13)
SE	2.79	2.53	2.47	2.25	2.45	2.35	2.13	2.41	0.86
Median	412.0	410.0	410.5	417.0	413.0	414.0	411.0	408.0	412.0
Min, Max	365, 495	364, 471	361, 483	359, 461	361, 495	356, 457	350, 457	355, 452	350, 495
Change from Screening									
n	74	77	72	74	77	77	78	73	602
Mean (SD)	4.3 (17.87)	2.1 (18.02)	5.0 (16.14)	5.3 (15.75)	4.8 (14.90)	2.4 (13.99)	3.9 (12.76)	0.5 (16.14)	3.5 (15.75)
SE	2.08	2.05	1.90	1.83	1.70	1.59	1.44	1.89	0.64
Median	4.0	5.0	3.5	3.0	5.0	2.0	5.0	-1.0	3.0
Min, Max	-54, 50	-49, 52	-20, 93	-31, 43	-29, 38	-40, 38	-28, 57	-37, 43	-54, 93
QTcF Interval (msec)									
Visit 6 (Week 1)									
n	74	75	69	69	76	76	77	74	590
Mean (SD)	411.4 (22.84)	411.2 (23.44)	410.2 (21.08)	416.0 (21.27)	407.3 (20.14)	410.5 (22.00)	408.8 (18.58)	410.1 (20.91)	410.6 (21.32)
SE	2.65	2.71	2.54	2.56	2.31	2.52	2.12	2.43	0.88
Median	410.5	409.0	410.0	413.0	406.5	411.0	409.0	411.0	411.0
Min, Max	366, 475	341, 492	353, 454	360, 467	357, 468	361, 461	349, 448	372, 452	341, 492
Change from Screening									
n	74	75	69	69	75	76	77	73	588
Mean (SD)	2.9 (15.40)	5.0 (13.99)	3.1 (13.18)	4.3 (13.59)	0.1 (15.43)	0.0 (14.80)	3.2 (15.02)	2.5 (14.35)	2.6 (14.52)
SE	1.79	1.62	1.59	1.64	1.78	1.70	1.71	1.68	0.60
Median	4.0	4.0	3.0	4.0	2.0	0.5	4.0	2.0	3.0
Min, Max	-35, 42	-28, 41	-29, 39	-21, 40	-56, 36	-40, 38	-47, 35	-31, 37	-56, 42
Visit 10 (Week 12)									
n	54	63	50	60	57	52	58	51	445
Mean (SD)	411.8 (23.56)	411.0 (23.34)	409.3 (24.25)	413.5 (19.36)	405.1 (18.94)	410.0 (24.25)	407.8 (20.84)	408.7 (21.12)	409.7 (21.95)
SE	3.21	2.94	3.43	2.50	2.51	3.36	2.74	2.96	1.04
Median	414.0	408.0	411.0	413.0	404.0	411.0	411.5	409.0	410.0
Min, Max	367, 466	354, 492	360, 473	380, 461	361, 442	350, 460	327, 448	363, 463	327, 492

Reviewer's comments: Single 12-lead ECGs were collected at screening (visit 2), day 1 (visit 5), visit 6 (week 1) visit 10 (week 12) and visit 14 (week 28), without time-matched PK samples. ECGs were read on-site by automatic machine reading. Data were expressed as normal and

abnormal (shift from screening) and mean change from screening. Changes in QTcF from screening values in QTcF did not exceed +5 ms. No outlier analysis for QTcF was reported.

There are no reports of sudden cardiac death, ventricular arrhythmias or any clinically relevant ECG changes.

Thank you for requesting our input into the development of this product under BLA 125390. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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

/s/

MONICA L FISZMAN
06/19/2013

JOHN E KOERNER
06/19/2013

KEVIN M KRUDYS
06/19/2013

NORMAN L STOCKBRIDGE
06/19/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 125390

Application Type: New BLA

Name of Drug: Myalept (metreleptin for injection)

Applicant: Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb)

Submission Date: March 27, 2013

Receipt Date: March 27, 2013

1.0 Regulatory History and Applicant's Main Proposals

(Note, this background information and regulatory history summary were taken from the Clinical filing review, written by the Medical Officer, Julie Golden. Additional details are available there.)

Background:

Lipodystrophy is a group of very rare disorders (approximately 1350 cases reported in the literature¹), that is characterized by generalized or partial loss of adipose tissue, leading to the inability to store energy in the form of triglyceride (TG) in physiologic adipose tissue sites. Consequently, patients with lipodystrophy develop ectopic deposition of TG in non-adipose tissues such as liver and muscle, leading to insulin resistance, diabetes, hypertriglyceridemia (causing pancreatitis), and steatohepatitis. Because of the loss of adipose tissue, circulating concentrations of the adipocyte-secreted hormone leptin are very low. Leptin, the product of the *ob* gene, plays a central role in the neurohormonal regulation of energy homeostasis and fat and glucose metabolism. The relative leptin deficiency observed in this disease state contributes to hyperphagia, which exacerbates the metabolic abnormalities as patients ingest more fat than they are able to dispose. Current available therapies for lipodystrophy include diet modification and pharmacologic intervention with oral anti-hyperglycemic agents, insulin, and/or lipid-lowering agents.

Metreleptin, a recombinant analog of human leptin, is a 147-amino acid polypeptide that differs from the human leptin sequence by one additional amino acid, methionine, located at the amino-terminal end. Metreleptin is being supplied as a sterile lyophilized cake and is reconstituted with bacteriostatic water for injection (BWFJ) with 0.9% benzyl alcohol. It is administered as a subcutaneous injection.

The proposed indication as follows: *Metreleptin is a recombinant analog of human leptin indicated for treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy.* The proposed limitations of use include: (1) *Metreleptin is not indicated for use in patients with HIV-related lipodystrophy,* and (2) *Metreleptin is not for use in patients with diabetes mellitus and/or hypertriglyceridemia without concurrent evidence of inherited or acquired lipodystrophy.*

¹ Garg A. Lipodystrophies: Genetic and Acquired Body Fat Disorders. J Clin Endocrinol Metab. 2011; 96(11):3313-3325.

RPM PLR Format Review of the Prescribing Information

The regulatory history for this drug is long and complex.

Regulatory History

Date	Activity
29 Mar 1996	IND 50259 submitted by Amgen
05 Jun 2000	IND 60534 submitted by Phillip Gorden from NIH to study metreleptin for lipodystrophy
16 May 2001	<p>Amgen EOP2 meeting with the Agency (IND 50259)</p> <ul style="list-style-type: none"> • The Division agreed that study 991265 (8-month initial trial in 9 patients) was sufficient to use as the single pivotal trial in a leptin NDA • The Division suggested that the NDA could be strengthened by following patients during a drug withdrawal and re-treatment period • Concern about off-label use was raised; there was discussion about whether this could be addressed through restricted distribution • The sponsor noted that dose and schedule were developed to achieve replacement levels of leptin, but that TG and glucose levels, rather than leptin levels, were used to titrate the drug • The Division indicated that dosing rationale should be included in the NDA • The Division agreed that sufficient data exist from studies 991265 and 970161 [study in primary leptin deficiency] to support use in pediatric patients • The Division concurred that the safety package consisting of the obesity and diabetes trials conducted with metreleptin would provide sufficient safety data to support the NDA, and that these data could be submitted as an ISS without individual study reports • The Division stated that the indication should identify the disease population and benefits expected with the drug • FDA could not state what the review status (i.e., priority vs. standard) would be at this time • The preclinical program is adequate for the narrow indication/population
22 Aug 2001	Amgen was granted orphan designation of metreleptin for the treatment of metabolic disorders secondary to lipodystrophy (OD 01-1467)
06 Sep 2001	Amgen was granted fast track designation of metreleptin for use as hormone replacement in the treatment of congenital leptin deficiency
22 Oct 2001	Amgen was granted fast track designation of metreleptin for the treatment of metabolic disorders associated with lipodystrophy
03 Mar 2006	Amylin assumed sponsorship of metreleptin (IND 50259) from Amgen Amylin assumed ownership of Amgen's metreleptin inventory manufactured at 2 sites (Thousand Oaks and Lake Centre) and Amgen's master and working cell banks
17 Oct 2007	Type C meeting convened to confirm Amylin's interpretation of Amgen's EOP2 meeting in 2001 and to obtain DMEP's guidance related to updated clinical and nonclinical data for lipodystrophy <ul style="list-style-type: none"> • Clinical package of 29 patients from NIH trials sufficient • Non-clinical package sufficient • HIV-related lipodystrophy not within the scope of the proposed indication
19 May 2008	Treatment IND 101824 filed as means to expand access to metreleptin for patients with metabolic disorders associated with lipodystrophy until submission of the NDA Sandoz GmbH is proposed as an additional drug substance manufacturer for the treatment IND
08 Jun 2008	FDA authorized the "Treatment IND May Proceed", but only using Amgen drug substance for clinical use FDA indicated that additional work needed to be performed in order to establish comparability between Sandoz and Amgen drug substance, including a 28-day bridging toxicology study
22 Oct 2009	Request for comments: Amylin proposed filing the lipodystrophy NDA with Amgen drug substance because of its long history of clinical use without apparent safety concerns and continuing stability and based on the large quantity of Amgen drug substance available to supply metreleptin for this small orphan population for the foreseeable future

RPM PLR Format Review of the Prescribing Information

Date	Activity
10 Dec 2009	FDA response indicating lack of concurrence that comparability had been fully established between Amgen and Sandoz metreleptin material by the CMC characterization information provided. FDA recommended against an NDA filing with Amgen drug substance, despite its use to supply the ongoing treatment protocol in lipodystrophy. The lack of a site for pre-approval inspection categorized the Amgen drug substance as out of compliance with Agency policy.
08 Feb 2010	Amylin communicated an intention to file the metreleptin for lipodystrophy NDA with Sandoz material To expedite availability of this orphan designated drug, Amylin submits “Request for Submission of Portions of an Application” (i.e., rolling review)
02 Apr 2010	Amylin requested a teleconference with the chemistry reviewer to clarify the scope of the Agency’s information requests to facilitate transparency and ensure submission of the appropriate information and data
09 Apr 2010	Agency issued advice/information request for a briefing book and meeting to discuss the development proposal and the following specific issues: <ul style="list-style-type: none"> • Amylin’s plans for sourcing drug substance and drug product • Possible alternative scenarios if drug substance from the proposed new drug manufacturer, Sandoz GmbH, cannot be qualified as comparable to material manufactured by Amgen • The need for additional clinical and nonclinical information if the Sandoz material is not comparable • Amylin’s plans for use of Amgen material and Sandoz drug substance within a single NDA • Details on the status and projected timeline for each portion of the lipodystrophy NDA
30 Jul 2010	Agency’s acceptance of rolling submission timeline and plans
13 Oct 2010	Letter states that per the Patient Protection and Affordable Care Act the Agency now believed that the appropriate marketing application for metreleptin is a BLA
18 Oct 2010	Agency’s acceptance of chemical comparability of the Sandoz material
22 Oct 2010	Amylin submitted a request for Agency’s comments regarding Amylin’s proposed filing strategy for the CMC portion of the rolling BLA submission, a strategy that would allow compliance with the agreed upon rolling submission schedule
16 Nov 2010	Results of the 1-month toxicology study in mice adequately bridge the Sandoz-sourced metreleptin to the non-clinical data available for the Amgen sourced metreleptin. The non-clinical data support initiation of clinical studies with the Sandoz-sourced metreleptin. Amylin was asked by FDA to collect anti-leptin antibody data on patients transitioned to as well as those naïve to Sandoz metreleptin and include that information in the BLA safety update.
15 Dec 2010	Clinical and non-clinical modules submitted along with draft product label
May 2011	Meeting with Amylin to discuss 2 patients in the obesity program (IND 50259) with neutralizing antibodies to leptin and excessive weight gain
01 Apr 2012	Submission of Module 3 including data to establish comparability between Sandoz DS made at 2 different fermentation scales. The submission also included: <ul style="list-style-type: none"> • Clinical Addendum to provide clinical experience with Sandoz DS focusing on Amylin’s assessment of the immunogenicity of metreleptin manufactured at Sandoz in comparison with metreleptin manufactured at Amgen • Proposed RMP • Updated draft labeling
30 May 2012	Discuss the completeness of the BLA As studies were still ongoing and enrolling subjects, the Agency conveyed that there were additional evaluable data from subjects who had enrolled in these studies after the datacuts of the original Dec 2010 submission and that such data should be included in the BLA at the time of filing
June 2012	Amylin submitted non-clinical and CMC information amendments to IND 101824, in order to begin dosing patients using metreleptin manufactured at Sandoz at the 1000L scale
11 Jul 2012	Amylin and Agency had a teleconference to agree on the information/data to complete the BLA <ul style="list-style-type: none"> • Agency specifically requested additional efficacy and safety analyses as well as a comprehensive

RPM PLR Format Review of the Prescribing Information

Date	Activity
	assessment of immunogenicity (lipodystrophy and obesity)
22 Jul 2012	FDA requested additional analyses and specific format for data presentation for Summary of Clinical Safety update, Summary of Clinical Efficacy update, and Clinical Addendum
Aug 2012	FDA informed of a 3rd patient in the obesity program (IND 50259) with neutralizing Abs to leptin and excessive weight gain
23 Oct 2012	Agency recommended Amylin request a pre-BLA meeting prior to submission as outlined under PDUFA V's "The Program"
17 Dec 2012	Pre-BLA meeting: <ul style="list-style-type: none"> • Agreements confirmed with regard to outstanding clinical documents/data to complete the BLA filing • Non-clinical information was also confirmed • RMP adequate to mitigate for risks now • A potential exists for a REMS request during review as noted in the preliminary response from FDA • Clarification was received for the 2013 manufacturing campaign
2 Jan 2013	The Agency requested additional information to be submitted with the final section of the BLA in order to facilitate the OSI development of clinical investigator and sponsor/monitor/contract research organization inspection assignments
Jan 2013	FDA informed of 3rd patient in the lipodystrophy program (IND 60534) diagnosed with lymphoma
27 Feb 2013	FDA requested breakdown of clinical data from 11 Jul 2011 cutoff (N = 100) and Jan 2013 cutoff (N = 125) by sex and lipodystrophy subtypes [for oncology consultant]
	FDA requested estimated date for submission of the last BLA module

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: Applicant includes "XX" for month of approval. They will be asked to remove this.

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A** 12. All text must be **bolded**.
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- N/A** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

PATRICIA J MADARA
06/06/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125390	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Myalept Established/Proper Name: metreleptin Dosage Form: lyophilized powder for reconstitution for subcutaneous injection Strengths: (b) (4)mg/ml reconstituted		
Applicant: Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb) Agent for Applicant (if applicable):		
Date of Application: March 27, 2013 Date of Receipt: March 27, 2013 Date clock started after UN:		
PDUFA Goal Date: March 27, 2014		Action Goal Date (if different):
Filing Date: May 26, 2013 (Sunday)		Date of Filing Meeting: April 30, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): treatment of diabetes and / or hypertriglyceridemia in patients with lipodystrophy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> XX Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	XX			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	XX			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		XX		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			Orphan indication

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>XX</p>	<p>BLA</p>																
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>XX</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			XX	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			XX	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?			XX	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) XX All electronic <input type="checkbox"/> Mixed (paper/electronic) XXCTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	XX			
Index: Does the submission contain an accurate comprehensive index?	XX			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	XX			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

XX legible XX English (or translated into English) XX pagination XX navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			XX	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	XX			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	XX			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			XX	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	XX			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	XX			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	XX			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			XX	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			XX	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		XX		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		XX		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	XX			Reviewed – found acceptable
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	XX			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	XX Carton labels XX Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	XX			
Is the PI submitted in PLR format? ⁴	XX			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			XX	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	XX			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	XX			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	XX			
OTC Labeling	XX Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	XX			
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): May 16, 2001	XX			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 17, 2012	XX			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		XX		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 30, 2013

BLA #: 125390

PROPRIETARY NAME: Myalept

ESTABLISHED/PROPER NAME: metreleptin

DOSAGE FORM/STRENGTH: lyophilized powder for reconstitution for subcutaneous injection

APPLICANT: Amylin Pharmaceuticals, LLC (a subsidiary of BMS)

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy.

BACKGROUND: Lipodystrophy is a group of very rare disorders (approximately 1350 cases reported in the literature⁵), that is characterized by generalized or partial loss of adipose tissue, leading to the inability to store energy in the form of triglyceride (TG) in physiologic adipose tissue sites. Consequently, patients with lipodystrophy develop ectopic deposition of TG in non-adipose tissues such as liver and muscle, leading to insulin resistance, diabetes, hypertriglyceridemia (causing pancreatitis), and steatohepatitis.

Because of the loss of adipose tissue, circulating concentrations of the adipocyte-secreted hormone leptin are very low. Leptin, the product of the *ob* gene, plays a central role in the neurohormonal regulation of energy homeostasis and fat and glucose metabolism. The relative leptin deficiency observed in this disease state contributes to hyperphagia, which exacerbates the metabolic abnormalities as patients ingest more fat than they are able to dispose. Current available therapies for lipodystrophy include diet modification and pharmacologic intervention with oral anti-hyperglycemic agents, insulin, and/or lipid-lowering agents.

Metreleptin, a recombinant analog of human leptin, is a 147-amino acid polypeptide that differs from the human leptin sequence by one additional amino acid, methionine, located at the amino-terminal end. Metreleptin is being supplied as a sterile lyophilized cake and is reconstituted with bacteriostatic water for injection (BWFI) with 0.9% benzyl alcohol. It is administered as a subcutaneous injection.

⁵ Garg A. Lipodystrophies: Genetic and Acquired Body Fat Disorders. J Clin Endocrinol Metab. 2011; 96(11):3313-3325.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Patricia Madara	Y
	CPMS/TL:	Mehreen Hai	Y
Cross-Discipline Team Leader (CDTL)	Eric Colman, M.D.		Y
Clinical	Reviewer:	Julie Golden, M.D.	Y
	TL:	Eric Colman, M.D.	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NN	
	TL:	NN	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NN	
	TL:	NN	

Clinical Pharmacology	Reviewer:	Jaya Vaidyanathan	Y
	TL:	Immo Zadezensky	Y
Biostatistics	Reviewer:	Bradley McEvoy,	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Federica Basso	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	NN	
	TL:	NN	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Laura Salazar Fontana	Y
	TL:	Susan Kirschner	N
Product Quality (CMC)	Reviewer:	Laura Salazar Fontana	Y
	TL:	Susan Kirschner	N
Quality Microbiology (<i>for sterile products</i>) Handled by OBP	Reviewer:	NN	
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Kala Suvarna	Y
	TL:	Patricia Hughes	N
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Suzanne Berkman Robotom,	Y
	TL:	Cynthia LaCivita,	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		N
	TL:		N

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	NN	N
	TL:	NN	N
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p>XX Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p>XX YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>XX FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<p>XX YES</p> <p><input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>XX YES Date if known: 12/11/13</p> <p><input type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<p>XX Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p>XX Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p>XX Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: already inspected</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments: not mentioned</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	N/A
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	XX YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	XX YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Curtis Rosebraugh, M.D., MPH; Director, ODE II</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 7/1/13</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: All dates may change if a major amendment submitted</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
	The application is unsuitable for filing. Explain why:
XX	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> XX No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review XX Priority Review
ACTIONS ITEMS	
XX	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
NA	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
NA	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
XX	BLA/BLA supplements: If filed, send 60-day filing letter

XX	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
NN	Send review issues/no review issues by day 74
XX	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
XX	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
XX	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

PATRICIA J MADARA
06/06/2013

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF HEMATOLOGY PRODUCTS

DATE: March 4, 2013

FROM: Karen McGinn, MSN, CRNP

SUBJECT: Consult for DMEP

TO: Mary Roberts, M.D. and Julie Golden, M.D.

THROUGH: R. Angelo de Claro, M.D., Clinical Team Leader (Acting)
Edvardas Kaminskas, M.D., Deputy Division Director

Background:

DMEP is reviewing metreleptin, an analog of human leptin, for the treatment of metabolic complications of lipodystrophy, a rare disorder of leptin deficiency and loss of adipose tissue. Amylin Pharmaceuticals, Inc. has submitted BLA 125390 (IND 101824) for the use of metreleptin to treat diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy. The pivotal clinical trial was conducted by the National Cancer Institute (NCI) in 125 patients with lipodystrophy. Two adult patients in the trial developed peripheral T-Cell lymphoma; however both patients had abnormal bone marrows and symptoms of myelosuppression prior to starting metreleptin. In addition, a 13 year old girl developed systemic ALCL while on the trial. DMEP consulted DHP with the following questions:

1. What is the expected prevalence of non Hodgkin lymphoma in the general population and in populations of patients with autoimmune disorders?
 - a. Would DHP consider 3 cases of NHL in approximately 125 patients with lipodystrophy consistent with the expected rate of occurrence?
2. Are there certain disease conditions or medications that are known to make patients more susceptible to NHL or leukemias? If so, please elaborate.
 - a. Is it biologically plausible that leptin might impact a patient's susceptibility to NHL or other malignancies?
 - b. If there is a risk that leptin is contributing to the appearance of NHL, would this risk apply to all lipodystrophy patients taking metreleptin or are there certain risk factors (such as the type of lipodystrophy—acquired versus congenital) that might predispose a patient taking metreleptin to NHL?
3. This application is likely to be presented at an AC this year. DMEP would like DHP's recommendations of potential AC members with the appropriate expertise to address these issues. DMEP has considered the authors of a recent NEJM paper on JAKs and STATs in Immunity, Immunodeficiency, and Cancer as potential candidates. Do the DHP reviewers have any insight into whether these authors would be appropriate to serve at this AC meeting?

Review of Cases of T-Cell Lymphoma in Patients With Lipodystrophy Taking Metreleptin

Case #1—59 year old woman from Spain with acquired generalized lipodystrophy that had developed over the prior 10 years was seen at the NIH in May 2008. Past medical history included neutropenia in December 2007 for which she was briefly treated with G-CSF and her neutrophil count normalized. The neutropenia recurred in January 2008, and G-CSF was restarted. A bone marrow biopsy was performed in [REDACTED] (b) (6), and the slides were brought to NIH where NIH pathologists diagnosed hypercellular bone marrow with marked atypical T-cell lymphocytosis and myeloid maturation with left shift. At the baseline visit WBC and ANC counts were normal and she had an elevated lymphocyte count of 4200/ μ l (on G-CSF). She started metreleptin on June 4, 2008, and returned to Spain. In [REDACTED] (b) (6) the patient's husband informed the NIH that she had undergone a mastectomy for intraductal carcinoma. In January 2009 the patient developed arm and leg nodules and was diagnosed with peripheral T-cell lymphoma. She subsequently started chemotherapy, discontinued metreleptin, and did not return to the NIH for follow-up.

Case #2—68 year old man with acquired generalized lipodystrophy, diabetes, severe insulin resistance and hypertriglyceridemia was seen at the NIH in May 2002. The lipodystrophy was first noticed in 1997. Past medical history included abnormal liver function tests, hepatosplenomegaly, and chronic idiopathic neutropenia since 1997. A bone marrow biopsy in 1998 was non-diagnostic, but a bone marrow biopsy in May 2002 revealed a markedly hypercellular marrow with erythroid predominance and reactive lymphoid nodules. Peripheral blood smear showed moderate leucopenia; mild, normochromic, normocytic anemia and mild thrombocytopenia. The patient had been prescribed erythropoietin since 2001. During the baseline examination at NIH the patient was noted to have diffuse lymphadenopathy and 1-2 small skin lesions on his leg. He was started on metreleptin and returned to his local hematologist who prescribed a trial of G-CSF of unspecified duration for leucopenia. At a 4 month follow-up visit at the NIH, a liver biopsy was negative for steatohepatitis, an abdominal ultrasound showed splenomegaly, and the lymphadenopathy persisted. At the 8 month follow-up visit, the splenomegaly was unchanged, but the patient reported progression of the skin lesions on his leg with increased size and number of the lesions. Skin biopsy revealed peripheral T-cell lymphoma. Metreleptin therapy was discontinued at that time. Bone marrow biopsy one month later showed hypercellular bone marrow with trilineage hematopoiesis, erythroid hyperplasia, and atypical lymphoid infiltrate suggestive of bone marrow involvement. Also, clonal rearrangement of the T-cell receptor gamma chain was detected in the peripheral blood.

Case #3—13 year old girl with acquired lipodystrophy was taking metreleptin from February 22, 2012 until December 11, 2012. She had noticed a lump under her right breast [REDACTED] (b) (6). Ultrasound of the mass was consistent with a lymph node (3.1 x 1.3 x 2.8 cm), and she was prescribed Augmentin. The mass remained stable or slightly enlarged after one week of Augmentin, and subsequent biopsy of the mass showed anaplastic large cell lymphoma.

Summary of Case Studies

The correlation between metreleptin and the development of T-cell lymphoma in the first two patients is confounded by symptoms of myelosuppression, the use of another cytokine (G-CSF), and abnormal bone marrow biopsies prior to initiation of metreleptin therapy. In addition, the second patient was taking erythropoietin, and had lymphadenopathy, hepatosplenomegaly, and skin lesions before starting metreleptin. Information about the 13 year old girl is incomplete at this time.

Response to Question 1:

On January 1, 2009 the prevalence of NHL in the United States was 484,336 persons (252,111 males and 232,225 females). In 2012 in the U.S., 70,130 men and women were diagnosed with NHL. The median age at diagnosis with NHL is 66 years, and the incidence of NHL increases with increasing age. NHL predominates in males with an incidence of 23.8 per 100,000. The incidence for NHL in females is 16.3 per 100,000.¹ The incidence for T-cell lymphoma in the US is 2.3 per 100,000 men and 1.4 per 100,000 women.¹

- a. The incidence for NHL in patients with lipodystrophy treated with metreleptin in Trials 991265 and 20010769 is 1 of 17 enrolled male patients or 5.9% and 2 of 108 female patients or 1.9%. These translate to 5900 per 100,000 in males (a 248-fold increase over the incidence in the general population) and 1900 per 100,000 in females (a 117-fold increase). In addition, all 3 patients in the trial developed T-cell lymphoma which is much rarer. The incidence rates for T-cell lymphoma in the U.S. for males is 2.3 per 100,000 and for females is 1.4 per 100,000.¹ In the trials the incidence of T-cell lymphoma was 5.8% for males (a 2565-fold increase) and 1.9% for females (a 1357-fold increase). An alternate approach would be the use of odds ratios to summarize the results of case-control studies.

However, whether the increased risk of NHL (or T-cell lymphoma) is related to the underlying condition (lipodystrophy) or the treatment (metreleptin) is unknown. Review of published literature identified a few isolated case reports of concurrent diagnoses of lipodystrophy and lymphoma. However, we were unable to locate a case series of patients with lipodystrophy without metreleptin treatment to evaluate the risk of development of lymphoma in patients with non-HIV lipodystrophy. Finally, please take into consideration that the small population (N=125) in the above clinical trials would lead to wide confidence intervals in the above estimates.

Response to Question 2:

Conditions that are associated with an increased risk for NHL are the following:²

- Congenital (primary) immunodeficiency—25% of patients will develop tumors, 50% of which will be NHL³
- Acquired immunodeficiency syndrome (AIDS)—60-100-fold higher risk for developing NHL⁴
- Autoimmune disorders
 - Sjögrens syndrome/sicca syndrome—40 to 44-fold increased risk for NHL
 - Rheumatoid arthritis^{5,6}
 - conventional antirheumatic treatment--standardized incidence rate (SIR) of 2.5 (95% CI, 0.7-9.0)
 - cytotoxic treatment—SIR of 5.1 (95% CI, 0.9-28.6)

¹ Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2009, National Cancer Institute. Bethesda, MD.

² Müller AM, Ihorst G, Mertelsmann R et al. Epidemiology of non-Hodgkin lymphoma: trends, geographical distribution and etiology. *Ann Hematol* 2005; 84:1-12.

³ Filipovich AH, Mathur A, Kamat D et al. Primary immunodeficiencies: genetic risk factors for lymphoma. *Ca Research* 1992; 52: 5465-7.

⁴ Grulich AE, Wan X, Law MG et al. B-cell stimulation and prolonged immunodeficiency are risk factors for non-Hodgkin lymphoma in people with AIDS. *AIDS* 2000; 14: 133-40.

⁵ Zintzaras E, Voulgarelis M, Moutsopoulos M. The risk of lymphoma development in autoimmune disease. *Arch Int Med* 2005; 165: 2337-44.

⁶ Smedby KE et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *Jour NCI* 2006;

- treatment with a biologic agent—SIR of 11.5 (95% CI, 3.7-26.9)
 - Celiac disease—9-fold increased risk for NHL²
 - Infections²
 - HTLV-1—Increases lifetime risk of developing adult T-cell Lymphoma (ATL) to 6.6% in males and 2.1% in females—Associated with gastric NHLs
 - EBV—Major co-factor in many B-cell lymphoproliferative disorders
 - *Helicobacter pylori*
 - Hepatitis C virus—Odds ratio of 6.2 for developing B-cell NHL and 16.4 for developing T-cell NHL
 - Occupational Exposures
 - Pesticides—2-8-fold increased risk for NHL
 - Ultraviolet radiation
 - Drugs
 - Immunosuppressive drugs
 - after organ transplantation—6-fold increased risk for NHL²
 - after stem cell transplantation—risk of NHL of 1-25%⁷
 - Tumor necrosis factor alpha (TNF α) inhibitors
 - Adalimumab (Humira)—Lymphoma and other malignancies including hepatosplenic T-cell lymphoma in children and adolescents
 - Certolizumab (Cimzia)—Lymphoma and other malignancies in children and adolescents
 - Etanercept (Enbrel)—Lymphoma and other malignancies in children and adolescents
 - Golimumab (Simponi)—Lymphoma and other malignancies in children and adolescents
 - Infliximab (Remicade)—Lymphoma and other malignancies in children and adolescents including hepatosplenic T-cell lymphoma mostly in adolescent young males with Crohn’s disease or ulcerative colitis
- a. It is biologically plausible that metreleptin, a leptin analog, impacts susceptibility to NHL and other malignancies. It is a cytokine that uses the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway for signal induction. Leptin binding activates JAKs, which in turn phosphorylates cytokine receptors which allows selective binding of the STAT family.^{8,15} Dysregulation of STAT proteins contributes to the pathogenesis of various types of lymphoid malignancies. Increased activity of STAT3 was reported in T-cell large granular lymphocytic leukemia^{9,10} Constitutive activation of STAT3 and STAT5 was also found to be an important event in the pathogenesis of anaplastic large cell lymphoma, T-cell angioimmunoblastic lymphoma and Sezary syndrome^{11,12} Leptin exerts proliferative and

⁷ Kuehnle I, Huls MH, Lin Z et al. CD20 monoclonal antibody (Rituximab) for therapy of Epstein Barr virus lymphoma after hematopoietic stem cell transplant. *Blood* 2000; 95: 1502-5.

⁸ Meier C, Hoeller S, Bourgan C et al. Recurrent numerical aberrations of JAK2 and deregulation of the JAK2-STAT cascade in lymphomas. *Modern Pathology* 2009; 22:476-89.

⁹ Schade AE, Wlodarski MW, Maciejewski JP: Pathophysiology defined by altered signal transduction pathways: the role of JAK-STAT and PI3K signaling in leukemic large granular lymphocytes. *Cell Cycle* 2006; 5:2571-2574

¹⁰ Furqan M, Mukhi N, Lee B et al. Dyregulation of JAK-STAT pathway in hematologic malignancies and JAK inhibitors for clinical application. *Biomarker Research* 2013; 1:1-5.

¹¹ Meier C, Hoeller S, Bourgan C, et al. Recurrent numerical aberrations of JAK2 and deregulation of the JAK2-STAT cascade in lymphomas. *Modern pathology* 2009; 22:476-487.

¹² Zhang Q, Nowak I, Vonderheid EC, Rook AH, Kadin ME, Nowell PC, Shaw LM, Wasik MA: Activation of Jak/STAT proteins involved in signal transduction pathway mediated by receptor for

antiapoptotic activities in a variety of cell types, including T lymphocytes, leukemia cells, and hematopoietic progenitors.¹³ Leptin also affects cytokine production, the activation of monocytes/macrophages, wound healing, angiogenesis, and hematopoiesis. In vivo, leptin regulates inflammation, playing an inhibitory role on monocyte/ macrophage-mediated responses while exerting a permissive role on lymphocyte-mediated inflammation. Leptin either induces or increases cell proliferation of different cell types, including T lymphocytes, CD34+ cells, leukemia cells, and endothelial cells. Leptin also acts as an inhibitor of glucocorticoid-induced apoptosis in T lymphocytes and of apoptosis induced by cytokine withdrawal in leukemia cells.¹⁴

- b. A literature search yielded no information about trials of leptin with the objective of discriminating the response of patients with acquired lipodystrophy versus those with congenital lipodystrophy.

Response to Question 3:

The authors of the JAK-STAT article in NEJM are pre-eminently qualified to participate on your Advisory Committee. (b) (4)

[Redacted]

[Redacted]

[Redacted]

interleukin 2 in malignant T lymphocytes derived from cutaneous anaplastic large T-cell lymphoma and Sezary syndrome. Proc Natl Acad Sci 1996; 93:9148-9153.

¹¹ Fernandez-Riejos P, Najib S, Santos-Alvarez J et al. Role of leptin in the activation of immune cells. Mediators of Inflammation 2010;2010: 1-8.

¹² Zhang Q, Nowak I, Vonderheid EC, Rook AH, Kadin ME, Nowell PC, Shaw LM, Wasik MA: Activation of Jak/STAT proteins involved in signal transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from cutaneous anaplastic large T-cell lymphoma and Sezary syndrome. Proc Natl Acad Sci 1996; 93:9148-9153.

¹³ Zhang Q, Nowak I, Vonderheid EC, Rook AH, Kadin ME, Nowell PC, Shaw LM, Wasik MA: Activation of Jak/STAT proteins involved in signal transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from cutaneous anaplastic large T-cell lymphoma and¹²

¹⁴Fantuzzi G and Faggioni R. Leptin in the regulation of immunity, inflammation, and hematopoiesis. Jour Leukocyte Biol 2000; 68: 437-46.

¹⁵O'Shea J, Holland S and Staudt L. JAKs and STATs in immunity, immunodeficiency, and Cancer. NEJM 2013;368:161-170.

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(b) (4)

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/s/

KAREN M MCGINN
03/05/2013

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03/05/2013

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