CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125390Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: BLA 125390 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DMEP PDUFA Goal Date: 2/24/14 Stamp Date: 3/27/2013

Proprietary Name: Myalept

Established/Generic Name: metreleptin

Dosage Form: for subcutaneous injection

Applicant/Sponsor: Amylin Pharmaceuticals,LLC; (a wholly owned subsidiary of Bristol Myers Squibb

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy (1).

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

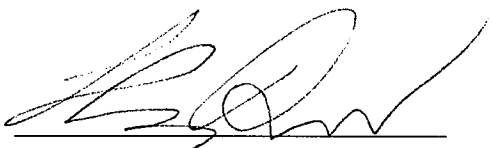
PATRICIA J MADARA
02/17/2014

1.3.3 Debarment Certification

Metreleptin BLA STN125390

In compliance with the Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §335a(k), as amended by the Generic Drug Enforcement Act of 1992, we, Amylin Pharmaceuticals, Inc., state the following with respect to this Biologics License Application.

Amylin Pharmaceuticals, Inc. 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.



12/15/2010

Lloyd A. Rowland
Vice President
Chief Compliance Officer

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125390	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Myalept Established/Proper Name: metreleptin Dosage Form: subcutaneous injection		Applicant: Amylin Pharmaceuticals, LLC Agent for Applicant (if applicable):
RPM: Patricia Madara		Division: DMEP

NDAs and NDA Efficacy Supplements:

NDA Application Type: X 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(For additional information regarding 505(b)(2)s, please refer to http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 2/24/2014	X AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard **X** Priority
Chemical classification (new NDAs only):

XX Fast Track
XX Rolling Review
XX Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: **XX** MedGuide
XX Communication Plan
XX ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	XX Yes, dates 21Nov13, 07Feb14
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes **X** No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	**XX** Yes ☐ No
• Press Office notified of action (by OEP)	**XX** Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None **XX** HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	**XX** No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	**XX** Included
Documentation of consent/non-consent by officers/employees	**XX** Included (not yet complete)
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AP 24Feb14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Proposed by FDA 2/24/14
• Original applicant-proposed labeling	**XX**
• Example of class labeling, if applicable	**N/A**

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	**XX** Medication Guide ☐ Patient Package Insert **XX** Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	XX 2/24/14
• Original applicant-proposed labeling	**XX**
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	2/17/14
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Letter, name acceptable 7/26/13 Review, name acceptable 7/26/13 Letter, name acceptable7/05/2012 Review, name acceptable 6/27/12
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM **XX** DMEPA 11/26/13 **XX** DMPP/PLT+OPDP2/5/14 **XX** DRISK see risk management section ☐ SEALD NN **N/A** CSS **XX** Other reviews PMHS 2/10/14(2)
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	Micro/4-30-13; Nonclinical/5-15-13; Clinical/5-2-13; OBP/5-6-13; Biometrics/5-9-13; RPM/6-6-13 ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes **XX** No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC NN If PeRC review not necessary, explain: orphan indication • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	**XX** Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	**XX** Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	**XX**
❖ Internal memoranda, telecons, etc.	XX
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	**XX** No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	**XX** N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 12/17/2012
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 5/16/2001
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	MCC 9/30/2013 LCM 11/20/2013
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	December 11, 2013
• 48-hour alert or minutes, if available *(do not include transcript)*	minutes
Decisional and Summary Memos	
Office Director Decisional Memo *(indicate date for each review)*	☐ None 2/24/14
Division Director Summary Review *(indicate date for each review)*	☐ None 2/24/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None deputy dd is CDTL
PMR/PMC Development Templates *(indicate total number)*	☐ None 15
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	CDTL, dDD 2/24/14
• Clinical review(s) *(indicate date for each review)*	11/18/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	**XX** None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical review 11/18/13 Page 23, clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DGIEP 11/15/13; QT-IRT 6/19/13; DAARP 2/21/14; DHP 3/5/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	**XX** Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	3/27/13 ☐ REMS memo 2/24/14 DRISK: 11/26/13, 2/5+14/+19+24+25/14 DEPI 9/30/13
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 12/24/13
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	**XX** None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	**XX** None
Statistical Team Leader Review(s) *(indicate date for each review)*	XX None
Statistical Review(s) *(indicate date for each review)*	☐ None 11/25/13; 2/21/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	**XX** None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	**XX** None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/15/13
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	**XX** None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	**XX** None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 12/6/13
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11/6/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	**XX** None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**XX** No carc
❖ ECAC/CAC report/memo of meeting	**XX** None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	**XX** None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	**XX** None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	**XX** None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/20/13;2/14/14; 2/20/14
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 10/18/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None DB VI 10/15/13
❖ Environmental Assessment (check one) (original and supplemental applications)	
XX Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Pages 6 – 7 of Quality Review; 12/19/13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
XX BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: 2/11/14 XX Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

From:	Madara, Patricia
To:	"Patel, Kinnari"
Subject:	RE: BLA 125390 (metreleptin for injection) Labeling agreement: PI, MG, IFU, C+C labels
Date:	Monday, February 24, 2014 7:31:00 PM
Importance:	High

BLA 125390

Dear Dr. Patel;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection), (b) (4) mg/mL.

We note your agreement to the revised package insert, medication guide and instructions for use, sent to you on February 23, 2014 and your concurrence with additional minor revisions to the package insert sent to you on February 24, 2014.

In addition we note your revised container and carton labels submitted by email on February 23, 2014. We agree with your revisions.

We also note your agreement to our revisions to the following REMS documents, sent to you by email on February 24, 2014:

1. The REMS document
2. REMS Web screenshot

We agree with the revisions you made to the following REMS documents and submitted via email on February 24, 2014:

1. Prescriber enrollment form
2. Prescription Authorization Form
3. REMS Supporting document

Finally we agree with your revised Prescriber Training Module, submitted via email on February 24, 2014.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Patel, Kinnari [mailto:Kinnari.Patel@bms.com]
Sent: Sunday, February 23, 2014 4:12 PM

To: Madara, Patricia
Subject: RE: BLA 125390 (metreleptin for injection) Labeling agreement: PI, MG, IFU, C+C labels

Hi Pat,

After reviewing, we accept all track changes proposed by the Agency in the Package Insert, Medication Guide and Instructions for Use. Please accept your recommended revisions to these documents and consider it final.

With this, all labels should be considered final and agreed upon.

Thank you!!

Kinnari

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Sunday, February 23, 2014 2:29 PM
To: Patel, Kinnari
Subject: BLA 125390 (metreleptin for injection) Labeling agreement: PI, MG, IFU, C+C labels
Importance: High

BLA 125390

Dear Dr. Patel;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection), 5 mg/mL.

In addition, we reference your emails (containing revised labeling) received on February 21 (PI, MG and IFU) and 23 (containers and cartons).

We have reviewed the following items and have some very minor revisions and comments. It is important that you respond via email that you accept the changes and DO NOT send any revised labeling back to FDA

Package Insert (enclosed with the following revisions)

- 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 bold type. This has been included (not in track changes.)

- The revision date at the end of highlights replaces the “revision” or “issued” date at the end of the FPI and should not appear in both places. (This has been removed in track changes strike out.)

- (b) (4)

- Please confirm the Highlights is ½ page or less without the boxed warning.

Medication Guide (enclosed with the following revision)

- [redacted] (b) (4)

Please note:
The label of each container (or package if the container is too small) of drug product for which a MG is required must contain a prominent and conspicuous statement instructing the dispenser to provide a MG to each patient and shall state how the MG is provided (21 CFR 208.24). Suggested bolded text is **"ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."** Since the Myalept carton is too small, this should be included on appropriate packaging used to ship the drug to the pharmacy.

Instructions for Use (enclosed with minor revisions)

- Under step 3, Option 2:

  Option 2: Using a vial of mixed MYALEPT:

  Note: For newborns or [redacted] (b) (4) infants using MYALEPT, throw away any unused mixed [redacted] (b) (4) MYALEPT right away. Do not store it for reuse.

- For the answer to question 14

  The standard supplies needed to inject MYALEPT include needles, syringes, liquid for mixing and a disposal container. Your healthcare provider will give you a prescription **for these supplies** which can be filled by a retail or hospital pharmacy, or the specialty pharmacy who distributes MYALEPT.

  "for these supplies" was added in track changes

- [redacted] (b) (4)

- Remember to include the appropriate page numbers throughout the document when printing the actual booklet

Container and Carton Labels:

- We reference your draft labels submitted by email on February 23, 2014. We find them acceptable. The container and carton labels will be considered the final, agreed-upon labels.

Please confirm receipt and acceptance.

Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Patel, Kinnari
To: Madara, Patricia
Subject: RE: BLA 125390 (metreleptin for injection) Labeling agreement: PI
Date: Monday, February 24, 2014 5:13:54 PM

Dear Pat,

Confirm the receipt and accepting FDA recommended changes below.

Thank you,

Kinnari

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Monday, February 24, 2014 4:45 PM
To: Patel, Kinnari
Subject: BLA 125390 (metreleptin for injection) Labeling agreement: PI
Importance: High

BLA 125390

Dear Dr. Patel;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection), 5 mg/mL.

We continue to review the package insert for Myalept and request concurrence that you find the following revisions acceptable. Most are very minor typographical errors but there is also a sentence revision for clarity.

1. Boxed Warning (FPI Only), first paragraph, penultimate sentence. We will revise to: "Test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of MYALEPT efficacy during treatment." (This improves alignment of the PI and REMS.)

2. Section 2.5, 2nd sentence: "lipid-lowering" should be hyphenated

3. Section 4.2, first sentence: We will delete the word (b) (4) to read, "MYALEPT is contraindicated in patients with prior severe hypersensitivity reactions to metreleptin or to any of the product components."

4. Section 5.1, penultimate sentence will be revised to read: "Test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of MYALEPT efficacy during treatment."

nd

5. Section 5.2, 2 paragraph, last sentence. We will insert a comma after "with autoimmune disorders" to read: "Acquired lipodystrophies are associated with autoimmune disorders, and autoimmune disorders are associated with . . ."

6. Section 5.3, we will edit 1st sentence to read: "MYALEPT is available only through a restricted distribution program under a REMS, called the MYALEPT REMS Program, because of the risks associated with the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT and the risk for lymphoma *[see Warnings and Precautions (5.1, 5.2)]*.

7. Section 5.4, the first word should be changed from "Dosages" to "Dosage"

8. Section 6.2, 4th sentence, "was" will be changed to "were" to read, "…and/or loss of MYALEPT efficacy were observed in 6% …"

9. Section 6.2, penultimate section of 1st paragraph should read same as the revision in boxed warning & Section 5.1: "Test for … severe infections or show signs suspicious for loss of MYALEPT efficacy during treatment." (as above)

10. Section 14.1, Treatment Duration and Dosage in the Study. "e.g." should be "i.e." in the parentheses following "The weighted average daily dose…" This will be changed.

Please let me know these revisions are acceptable. Please confirm receipt.
Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Patel, Kinnari
To: Madara, Patricia
Subject: RE: metreleptin BLA - REMS Documents
Date: Monday, February 24, 2014 2:36:15 PM
Attachments: bms986109-rems-prescriber training module-tracked-- 24 Feb 2014.pdf
bms986109-rems-prescriber training module-clean- 24 Feb 2014.pdf

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Dear Pat,

Please see attached REMS Training Module and Training Module tracked documents revised based on feedback from the FDA.

Regarding changes proposed in your email below, we accept. With this, you have all of the REMS documents.

Please confirm receipt of this email.

Thank you,
Kinnari

Kinnari Patel, PharmD, M.B.A.
US Regulatory Strategist, Metabolics

Global Regulatory Sciences
Bristol-Myers Squibb www.bms.com
Route 206 & Province Line Road, (b) (6)
Princeton, NJ 08543
(609) 252-3706, cell (b) (6), fax (609) 252-7781
kinnari.patel@bms.com

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Monday, February 24, 2014 1:56 PM
To: Patel, Kinnari
Subject: RE: metreleptin BLA - REMS Documents
Importance: High

Hi Kinnari;

We have reviewed the REMS documents you submitted and are making the following very minor edits. Please state you concur with our revisions wo sending any documents back to us.

Here are our edits:

- **REMS Document** – the numbering under ETASU 2 is incorrect. We corrected it in the attached document.
- **Prescriber Enrollment Form** – no edits.
- **Prescription Authorization Form** – no edits.
- **Website** – We will delete pages (b) (4)

(b) (4)

- **REM Supporting Document** – no edits

Please let me know these are acceptable. Thanks. Pat

From: Patel, Kinnari [mailto:Kinnari.Patel@bms.com]
Sent: Monday, February 24, 2014 12:15 PM
To: Madara, Patricia
Subject: metreleptin BLA - REMS Documents

Dear Pat,

Please see attached REMS documents revised based on feedback from the FDA and discussion with you today. Note, the REMS Training Module is still pending and will be available in around 1:30 pm.

This includes:

1. REMS doc
2. REMS doc tracked
3. REMS support
4. REMS support tracked
5. Web
6. Web tracked
7. Enrollment form
8. Enrollment form tracked
9. Rx Auth form
10. Rx Auth form tracked

Pending Final batch:

1. Training Mod
2. Training Mod tracked

As FDA has already approved the Information sheet, it is not being included with this email.

Please confirm receipt of this email.

Thank you,
Kinnari

Kinnari Patel, PharmD, M.B.A.
US Regulatory Strategist, Metabolics

Global Regulatory Sciences

Bristol-Myers Squibb www.bms.com
Route 206 & Province Line Road, Rm (b) (6)
Princeton, NJ 08543
(609) 252-3706, cell (b) (6), fax (609) 252-7781
kinnari.patel@bms.com

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/s/

PATRICIA J MADARA
02/24/2014

From: Maslov, Yelena
To: Colman, Eric C
Cc: Madara, Patricia
Subject: RE: Metreleptin HF study
Date: Monday, February 24, 2014 3:30:43 PM

Yes

From: Colman, Eric C
Sent: Monday, February 24, 2014 2:52 PM
To: Maslov, Yelena
Cc: Madara, Patricia
Subject: FW: Metreleptin HF study

Lena, see below - would you agree that the sponsor has submitted sufficient evidence to support approval and use as directed in the final labeling? Eric

From: Nguyen, Quynh Nhu
Sent: Monday, February 24, 2014 2:33 PM
To: Colman, Eric C; Madara, Patricia
Cc: Kaye, Ron D.
Subject: RE: Metreleptin HF study

Hi,

I spoke with Pat Madara. Please see our review comment below. We hope it is helpful in case you need input from CDRH HF perspective. Let me know if you need a finalized memo.

The Sponsor indicated in part of their response that the product is not a combination product, and they did not conduct the human factors study in full accordance with the CDRH HF guidance document. As a result, they did not collect subjective data, i.e. interviewed data from test participants on all incomplete injections and analysis of the data to determine the root cause of these incomplete injections. Therefore, we would find that the study report to be deficient, and we cannot complete our review.

Q-

From: Love, Patricia
Sent: Monday, February 24, 2014 1:55 PM
To: Colman, Eric C; Nguyen, Quynh Nhu; Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Cc: Parks, Mary H; Stradley, Sara; Nikhar, Bindi
Subject: RE: Metreleptin HF study

Eric and Quynh,

A human factors consult can be requested for CDRH's expertise regardless of product classification. In this case the HF study involved user interaction with devices.
Thank you,
Patricia

From: Colman, Eric C
Sent: Monday, February 24, 2014 1:32 PM
To: Nguyen, Quynh Nhu; Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Cc: Parks, Mary H; Stradley, Sara; Love, Patricia; Nikhar, Bindi
Subject: RE: Metreleptin HF study

Okay – thanks for the follow up.

From: Nguyen, Quynh Nhu
Sent: Monday, February 24, 2014 1:26 PM
To: Colman, Eric C; Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Cc: Parks, Mary H; Stradley, Sara; Love, Patricia; Nikhar, Bindi
Subject: RE: Metreleptin HF study

Hi Eric,

I just spoke to Pat Madara due to a Sponsor's response indicating that this product is not a combination product. She confirmed that that determination has been made just a few days ago. As a result, a final human factors review from CDRH HF team is no longer necessary.

Please let me know if you have any further questions.
Q-

From: Colman, Eric C
Sent: Monday, February 24, 2014 1:11 PM
To: Nguyen, Quynh Nhu; Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Cc: Parks, Mary H; Stradley, Sara
Subject: RE: Metreleptin HF study

Hi – just following up on the status of your review.

From: Nguyen, Quynh Nhu
Sent: Friday, February 21, 2014 2:56 PM
To: Colman, Eric C; Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Cc: Parks, Mary H; Stradley, Sara
Subject: RE: Metreleptin HF study

We should be able to complete our review by noon on Monday.

From: Colman, Eric C
Sent: Friday, February 21, 2014 2:49 PM
To: Nguyen, Quynh Nhu; Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Cc: Parks, Mary H; Stradley, Sara
Subject: RE: Metreleptin HF study

We are working with a PDUFA goal date of this Monday for approval of metreleptin.

From: Nguyen, Quynh Nhu
Sent: Friday, February 21, 2014 2:45 PM
To: Colman, Eric C; Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Subject: RE: Metreleptin HF study

I am still reviewing the response, and can not confirm that at this time.

Pat, please issue a supplemental InterCenter Consult request to review the new information contained in the response. Please include the due date that you wish to receive our consult review. Thanks.

From: Colman, Eric C
Sent: Friday, February 21, 2014 2:43 PM
To: Madara, Patricia; Maslov, Yelena; Kaye, Ron D.
Cc: Nguyen, Quynh Nhu
Subject: RE: Metreleptin HF study

Thanks, Pat. Would be helpful if CDRH confirmed that they don't have any unresolved issues.

From: Madara, Patricia
Sent: Friday, February 21, 2014 2:41 PM
To: Maslov, Yelena; Colman, Eric C
Cc: Nguyen, Quynh Nhu
Subject: RE: Metreleptin HF study

CDRH did have some info requests for the company. The company responded by email and officially to the BLA. The responses were forwarded to CDRH with a request for comment.

I did not hear anything and assumed all responses were acceptable.

From: Maslov, Yelena
Sent: Friday, February 21, 2014 2:37 PM
To: Colman, Eric C
Cc: Madara, Patricia
Subject: RE: Metreleptin HF study

Hi Eric,

You might be talking about CDRH and Quynh Nhu Nguyen. DMEPA found the HF study results acceptable and had no other issues. Labeling has been negotiated. I attached our review for our convenience.

Thanks,
Lena

From: Colman, Eric C
Sent: Friday, February 21, 2014 1:41 PM
To: Maslov, Yelena
Cc: Madara, Patricia
Subject: Metreleptin HF study

Lena,

Have you received all the information you need to complete a final review of the HF study? I see emails from late Jan about the need for additional responses from the company but don't know if you've done a more recent review.

Thanks,

Eric

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/s/

PATRICIA J MADARA
02/24/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 (metreleptin) REMS Prescriber training Module
Date:	Tuesday, February 18, 2014 10:02:00 PM
Attachments:	FDA to BMS_18Feb14_rems-prescriber-training-module-script revised.doc
Importance:	High

BLA 125390 **ADVICE / INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). The Division of Risk Management (DRISK) in the Office of Medication Error Prevention and Risk Management has reviewed your proposed REMS materials and has the following comments:

You have now received comments on all the REMS materials (REMS document, prescriber enrollment form, prescription authorization form and assessment). The Prescriber Training Module is attached here.

Revise the materials to reflect agreed upon labeling.

We request that you re-submit the REMS materials via email to facilitate our timely review.

All final REMS materials can be submitted via the gateway once they have been fully agreed upon by the Agency.

1. Prescriber Training Module

The Prescriber Training Module reflects the FDA version of the prescribing information sent to you on Monday, February 17, 2014. Please provide a mock-up pdf of the revised prescriber training module (along with the Introductory Information Sheet and Website, Prescriber Enrollment Form, and Prescription Authorization Form) and a Word version (track changes with your edits and clean).

Please submit the Word version as soon as possible (along with complete REMS). We understand the pdf may take additional time. The PDFs may be submitted later.

See attached revised Prescriber Training Module.

2. REMS Supporting document

The REMS Supporting Document must be consistent with all changes made to the REMS Document and Assessment Plan. Please revise accordingly and resubmit (Word version) for review.

3. General Comments

Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

I will try to schedule a tcon, if needed for Thursday, February 20th.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
02/19/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	Will provide info as it arrives.
Date:	Tuesday, February 18, 2014 5:22:00 PM
Attachments:	SRPI.pdf FDA to BMS_18Feb14_medguide.docx
Importance:	High

Kinnari;

1. Attaching the Med Guide with our revisions. Revisions still in track changes. I hope everything is acceptable. If not, only keep those items with issues in track changes.

2. Attaching something called the Selected Requirements of Prescribing Information (SRPI). You can use it as a guidance to format your label. Do not send it back but use to ensure your final label is in the correct format.

3. Regarding the revised container and carton labels (latest) sent to us, both OBP and DMEPA agree that the statement on the side is confusing. The (b) (4) should be removed to improve clarity.

   solution contains:
   • Metreleptin (b) (4)
   -5 mg/mL)

   It should just be 5 mg/mL, (b) (4)
   This is confusing

4. I still expect to get the REMS today/tonight. Will send as soon as it arrives. However, I will be away from the computer from 7:30 – 9:30.

5. Is the PI coming back to us today?

6. Keeping both tcons on the calendar for now.

Thanks for your help.
Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/19/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 metreleptin - prescribing information
Date:	Monday, February 17, 2014 9:54:00 AM
Attachments:	FDA to BMS_17Feb14_metreleptin_PI.docx FDA to BMS_17Feb14_NEJM.pdf
Importance:	High

Hi Kinnari;

Hope you had a good weekend. Here is the prescribing information. The review team has worked on it all weekend. If you feel strongly there is something you feel should be changed, please revise in track changes and include your rationale. The labeling tcon is scheduled for Wednesday at noon.

Please return to us with your revisions as soon as possible. **Please confirm receipt.** Thanks for your help.

Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
02/19/2014

From: Madara, Patricia
To: Patel, Kinnari (Kinnari.Patel@bms.com)
Subject: BLA 125390 metreleptin container and carton labels - a revision required
Date: Friday, February 14, 2014 5:26:00 PM
Importance: High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We have reviewed your draft container and carton labels submitted informally, via email on February 12, 2014.

We find the revised labels acceptable except for the following.

- **You incorrectly** (b) (4) **Thus, revise the expression of strength on your container label and carton as follows:**

  11.3 mg per vial.

- **If you still wish to keep 5 mg per mL on the labels and labeling, you can place it underneath the strength of the product and state "after reconstitution with 2.2 mL of diluent". For example,**

  5 mg/mL after reconstitution with 2.2 mL of diluent

Please revise the labels and resubmit via email for final review. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/19/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 REMS materials and PMRs/PMCs - urgent agreement needed.
Date:	Friday, February 14, 2014 10:45:00 AM
Attachments:	FDA to BMS_14Feb14_Metreleptin REMS.doc FDA to BMS_14Feb14_Myalept REMS Program_Introduction.doc FDA to BMS_14Feb14_rems-web-page-script.doc FDA to BMS_14Feb14_Metreleptin PMR and PMC milestone dates_rev req.docx
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We have the following urgent requests

1. We have reviewed the postmarketing requirements (PMRs) and postmarketing commitments (PMCs) list you submitted by email and require a few additions and revisions . See the attached document with track changes.

   Note the changes we propose must be included in the letter being sent for clearance in a couple of hours. Hopefully you can provide the number of lots required (PMR#7) and the date (PMC#8) in a very short time.

2. We are attaching the revised REMS doc, REMS Program Introduction, and REMS web page. Please let me know if you suggest any revisions.

Please submit this information officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/19/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 - MedGuide and IFU
Date:	Wednesday, February 12, 2014 1:40:00 PM
Attachments:	FDA to BMS_12Feb14__medguide+IFU.docx
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). Your medication guide and instructions for use have been reviewed by the Patient Labeling Team from the Division of Medical Policy Programs (DMPP). Please see the attached document and the comments below:

1. DMPP often makes significant revisions to the format during their review of patient labeling. Therefore, it is important that you use the version of the patient labeling that is attached to this email as the base document for making subsequent changes.

2. Using the attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

3. Please review and submit revisions, if any, along with your rationale. We may have additional, minor revisions after review by management.

Please confirm receipt.
Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/19/2014

From: Madara, Patricia
To: Patel, Kinnari (Kinnari.Patel@bms.com)
Cc: Hai, Mehreen
Subject: BLA 125390 Request for Information
Date: Wednesday, February 12, 2014 12:31:00 AM
Importance: High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). The Office of Combination Products has reviewed your application and has the following comments and requests for additional information

1. [redacted] (b) (4)

2. In reference to BMS responses of January 24, 2014, the articles you propose to have [redacted] (b) (4)

3. In comparing the BLA IFU and the [redacted] (b) (4)

4. Accordingly, if you wish to proceed with this approach, the following information should be provided to the BLA:

   a. Submit Form 356h to identify the [redacted] (b) (4) and complete all items.
   b. Identify the source of the sterile water (WFI and BWFI) and any FDA approved NDA or ANDA number for them.

You may submit this information via email but also submit it to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/18/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Cc:	Hai, Mehreen
Subject:	Misinformation regarding protocol submission date for PMRs and container and carton labeling.
Date:	Wednesday, February 12, 2014 5:31:00 PM
Importance:	High

Hi Kinnari;

PMRs

Apologies. PMRs# 2+3 and 6+7 will not require a specific protocol submission date. If feasible, a study completion date should be included for these PMRs and the final study report submission date is mandatory.

For all other PMRs, all three dates should be specified in the month / year format.

Mehreen can correct me if I got something wrong. It has been a long day.

Carton and Container Labels

I forwarded your comments regarding the container and carton label revisions to DMEPA and they have responded that they must see and review the actual labels incorporating the changes you described in the email, even though you are agreeing to our recommendations. However, DMEPA did note that your proposal to display the Myalept proprietary name in all lowercase letters **is acceptable.** So you can include that change in the labels you submit.

Please submit the labeling informally, via email, as soon as possible.

Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/18/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 (metreleptin) Request for Information
Date:	Thursday, February 06, 2014 9:26:00 PM
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have the following comments and request for information.

1. The proposed metreleptin label states "Contact Bristol Myers-Squibb at 1-xxx-xxx-xxxx for neutralizing antibody testing of clinical samples." We would like to better understand the neutralizing antibody testing process.

2. Please explain the process a practitioner will need to go through to submit and obtain results regarding neutralizing antibody testing. As part of describing the process, include how the sample is obtained, who it is sent to (and how), how long the testing takes, when a prescriber could expect to receive the result, interpreting the results, and how it is paid for/billed.

Please respond by COB Monday (2/10) or sooner. You may submit this information informally via email but also send it officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/18/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 some revised REMS Materials
Date:	Wednesday, February 05, 2014 12:54:00 PM
Attachments:	FDA to BMS_5Feb14_REMS comments.doc FDA to BMS_5Feb14_rems-prescriber-enrollment-form-script.doc FDA to BMS_5Feb14_rems-rx-authorization-form-script.doc
Importance:	High

Hi Kinnari;

As mentioned previously, we are sending the REMS materials as they become available. Please review our comments and revisions. Additional REMS materials to follow.

Please note that I will be sending our revisions to the Instructions for Use and also additional revisions to the Medication Guide shortly.

If you wish to propose changes to our edits, I am thinking that we may be able to reach agreement via email for many pieces of the labeling and, thus, would not need to discuss everything at a tcon.

Please confirm receipt.
Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/18/2014

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 (metreleptin) - Information Request
Date:	Tuesday, February 04, 2014 6:11:00 PM
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). The Center for Devices and Radiological Health (CDRH) has reviewed your human factors / usability report. They have the following requests for information, clarification and comment.

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.

You may submit this information via email but also send your responses officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
02/17/2014

From: Madara, Patricia
To: Patel, Kinnari (Kinnari.Patel@bms.com)
Subject: BLA 125390 Urgent request for information
Date: Tuesday, January 14, 2014 3:31:00 PM
Importance: High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have the following urgent requests for information.

1. **Provide the** (b) (4)

2. **Please provide your "Supplier Controls Procedures" document or tell us if you don't have one.**

3. **Please provide your "Quality Agreement" with the specialty pharmacy.**

4. **Provide the name that will be on the labels affixed to the boxes that are shipped to patients.**

Please provide this information as rapidly as possible. We will determine the need for a teleconference after reviewing your responses. Submit this information via email but also submit it to your BLA.

Please confirm receipt of this email.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
01/14/2014

From: Madara, Patricia
To: Patel_Kinnari (Kinnari.Patel@bms.com)
Subject: BLA 125390 Myalept - (metreleptin for injection) - request for information
Date: Monday, December 23, 2013 4:30:00 PM
Importance: High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection).

I had emailed you earlier to request some information regarding the (b) (4) with Myalept. Here is a more formal request for information from the Center for Devices and Radiological Health:

1. (b) (4)
2. (b) (4)
3. (b) (4)
   -
4. All device constituent associated documents should be located in Section 3.2.P.7 - Container Closure System. These should include information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations.

5. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.

6. Suggestions regarding the types of documents to submit for review can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

7. To facilitate the review process, include an Application Roadmap, identifying documents addressing 21 CFR part 820 regulations, and the manufacturing of the finished combination product.
8.

Please submit this information officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
12/23/2013

From: Madara, Patricia
To: Patel, Kinnari (Kinnari.Patel@bms.com)
Subject: BLA 125390 (metreleptin) - Request for Information
Date: Tuesday, December 03, 2013 4:39:00 PM
Importance: High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have the following comments and requests for information.

1. **The Amendment 125390/0.37 response to Question 1a states that studies to assess minimum detectable container closure leak size will be submitted in a post-marketing annual report. Please submit these studies during the current review cycle rather than in an annual report. If submission during the review cycle is not possible, please submit a post-marketing commitment for study performance.**

2. **The DMFs referenced for the stoppers ((b) (4)) only provide information regarding the stopper formulation. For microbiology quality assessment the Agency seeks a Letter of Authorization to review DMF (b) (4) including the validation of stopper (b) (4). Please submit a Letter of Authorization permitting Agency review of DMF (b) (4)**

3. **Insufficient details were provided in the Amendment 125390/0.37 response to Question 15 regarding shipping validation. Please submit:**
   a. **A description of the load configurations for minimums loads 1, 2, and 3, and maximum loads 1, 2, and 3.**
   b. **The number and placement positions of temperature probes in the validation loads.**
   c. **The capacity, dimensions, construction materials, and temperature regulation mechanism of the (b) (4) container.**
   d. **The procedures used to simulate summer and winter shipping conditions.**
   e. **The allowable time and temperature limits for temperature excursions.**
   f. **The maximum time allowed for overnight parcel service/morning delivery.**

4. **During stability testing the container closure test provides for a better assessment of microbiology quality than the sterility test. For the post-marketing stability protocol presented in Table 2 of BLA Module 3.2.P.8.2.2, it is recommended that you implement container closure**

integrity testing at annual intervals and at expiry for stability samples stored at 5oC/ambient RH storage conditions, and at the 0 and 6 month intervals using 25oC/60% RH conditions.

Please submit this information officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
12/03/2013

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/s/

PATRICIA J MADARA
12/20/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 - request for information
Date:	Tuesday, November 19, 2013 10:28:00 PM
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have the following request for additional information:

- **Please provide any available follow-up on live births that occurred in mothers treated with metreleptin, including information regarding drug exposure (including through breast milk) in the child, antibody status in the mother, antibody development in the child, and any health issues in the child.**

You may submit this information via email but also submit it to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
11/19/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 (metreleptin) Request for Information #3 for 11/8/13
Date:	Friday, November 08, 2013 6:12:00 PM
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have the following comments and requests for information.

Clinical

1. **In your response dated 06/19/2013 to FDA Question 1 (05/24/2013), you state the following under section 1.4.2, renal adverse events: Of the renal adverse events, there were 17 reports of creatine phosphokinase elevated in metreleptin-treated subjects and 6 in placebo-treated subjects. Is creatine phosphokinase accurate, or did you mean creatinine? If there was an imbalance in CPK (we note that proportions of patients weren't provided), were there any cases of myopathy or rhabdomyolysis? Did patients with lipodystrophy treated with metreleptin experience any elevations in CPK or adverse events that would suggest myopathy?**

2. **Provide an assessment of psychiatric adverse events in the lipodystrophy and obese populations.**

Microbiology

3. **The Metreleptin drug product formulation contains excipients (e.g. polysorbate) that could result in low endotoxin recovery (LER) (see K.L. Williams, Endotoxin Test Concerns of Biologics, American Pharmaceutical Review, October 28, 2013). Please provide results from studies conducted to assess if endotoxin recovery is affected by the polysorbate-containing Metreleptin drug product formulation. Undiluted drug product test samples should be spiked with endotoxin and satisfactory endotoxin recoveries should be demonstrated over time. The studies should be conducted in the same type of containers (e.g., stainless steel formulation tank, glass vial) in which the product and samples are held prior to endotoxin testing.**

Please submit this information officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
11/12/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 (metreleptin)
Date:	Friday, November 08, 2013 1:39:00 PM
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We are continuing to review the BLA and have additional comments and requests for information. I apologize that these were not included in the request sent earlier today.

1 **We have noted numerous hand written changes made to the CRFs from the NIH trial, in some cases dated years later. Clarify why those changes were made, and what the process was for making those changes. Some examples include:**

   a) **Patient 90109, trial 991625 -- AE 1 fever (2002) crossed out in 2006, AE 2 urinary tract infection changed to continuing, AE 3 chronic inflammatory hepatitis (2002) and AE 4 membranoproliferative glomerulonephritis (2002), serious changed from yes to no and related changed from yes to no in 2007, etc**

   b) **Patient 90106, trial 991625 – AE 1 (2000) relationship and severity changed in 2007, etc**

2 **In addition, electronic CRFs appear to all be dated for data entry in 2011 (NIH) or 2010 or later (FHA101). Clarify what happened to the source documents. For example:**

   a) **Patient 90128 had an event of hypoglycemia in 2005, but the AE was initially entered into the eCRF in 2011**

   b) **Patient 648001 had an event of acute pancreatitis in 2009, but the AE was entered into the eCRF in 2011**

You may submit this information via email but also submit it to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
11/08/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 Request for Information
Date:	Friday, November 08, 2013 9:49:00 AM
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have the following comments and requests for information.

- **We have just been made aware of two additional hospitalizations for bacteremia in patient 90164, a 19 yo F with CGL, who was reported to have recently developed category E NAbs, submitted to Dr. Gorden's IND. This brings the total of reports of sepsis in this patient since April 2013 to 5, in addition to references made to an ESBL E. coli infection and C. diff colitis (not reported separately). We have concerns that NAbs to leptin may be contributing to immunosuppression in this patient. Provide your assessment of these AEs, your interpretation of their relationship to NAbs to leptin, and any action that you propose to take as a result.**
- **In addition, please provide an overall assessment of "sepsis", including a review of AEs from patient 90125 (died of septic shock, no ruptured pseudocyst found) and patient 90143 (SAE of sepsis, no source found), and any other cases available.**

Please submit this information officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.
Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
11/08/2013

From: Madara, Patricia
To: Patel, Kinnari (Kinnari.Patel@bms.com)
Subject: BLA 125390 (Myalept, metreleptin for injection)
Date: Tuesday, November 05, 2013 11:56:00 AM

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We are continuing our review of your application and have an additional request for information.

- **You have submitted an SOP titled "SOP-QUC-110 - Locking and Unlocking the Clinical Trial Databases," (Version 04), which was signed off Jan 2012. Please submit all previous versions of this SOP.**

Please submit this information to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

The documents sent in our request for information includes an I am attempting to see if the sponsor's own procedures were followed or not during the time frame of the events.

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/s/

PATRICIA J MADARA
11/05/2013

From: Madara, Patricia
To: Patel, Kinnari (Kinnari.Patel@bms.com)
Subject: BLA 125390 (metreleptin) - Urgent Request for Information
Date: Monday, October 28, 2013 2:28:00 PM
Importance: High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection).

In addition, we reference your document submitted on October 25, 2013, via email, in advance of our teleconference scheduled for October 30, 2013. We have reviewed your "pre-read" document and have the following request for additional information.

1. **Please provide the details of and findings from the sensitivity analysis of missing data referred to in Section 2.2 of the meeting material for the October 30, 2013 teleconference as this information was not included in the BLA submission. In addition, please describe how the derived visits were handled in these analyses. Specifically:**

   a) **How data from a visit that was not mapped to a specific month was handled in the analysis, and**

   b) **How the issue of over-lapping visit windows for 991265 and 20010769 were accommodated in these analyses. For example, the months 8 and 12 visit windows were respectively from 4 to 12 months and 8 to 16 months.**

2. **Please provide this requested information to FDA by October 30, 2013.**

You may submit this information via email but also submit it to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
10/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

MID-CYCLE COMMUNICATION

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Attn: Kinnari Patel, Pharm.D, R.Ph.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin for injection).

We also refer to the teleconference between representatives of your firm and the FDA on September 30, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time:	September 30, 2013; 1PM eastern time
Application Number:	BLA 125390
Product Name:	Myalept (metreleptin)
Indication:	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
Applicant Name:	Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb Company)
Meeting Chair:	Eric Colman, M.D.
Meeting Recorder:	Patricia Madara

FDA Attendees

Office of the Commissioner; Office of Orphan Product Development

John D. Milto, M.D.	Medical Officer

Office of New Drugs; Program for Rare Diseases

Larry J. Bauer	Regulatory Scientist

Office of New Drugs; Office of Drug Evaluation II

Mary H. Parks, M.D.	Deputy Director

Office of New Drugs; Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy Egan, M.D., MPH	Deputy Director for Safety
James P. Smith, M.D., M.S.	Clinical Team Leader
Julie Golden, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Nonclinical Team Leader
Federica Basso, Ph.D.	Pharmacology/Toxicology Reviewer
Julie Van der Waag, MPH	Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Immo Zadezensky, Ph.D.	Clinical Pharmacology Team Leader
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer

Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment; Biotech Manufacturing Assessment Branch

Patricia Hughes, Ph.D.	Team Leader
Kalavati Suvarna, Ph.D.	Quality Microbiology Reviewer
Steven Fong, Ph.D.	Quality Microbiology Reviewer

Office of Pharmaceutical Science, Office of Biotechnology Products, Division of Therapeutic Proteins

Susan Kirshner, Ph.D.	Associate Laboratory Chief
Laura Salazar-Fontana, Ph.D.	Quality Reviewer
Emanuela Lacana, Ph.D.	Quality Reviewer

Office of Biostatistics; Division of Biometrics II

Mark Rothmann, Ph.D.	Team Leader
Bradley McEvoy, Ph.D.	Statistical Reviewer

Office of Surveillance and Epidemiology

Margarita Tossa	Safety Regulatory Project Manager

Office of Medication Error Prevention and Risk Management; Division of Risk Management

Suzanne Robottom, Pharm.D.	Risk Management Analyst

Eastern Rearch Group Attendees

(b) (6)	Independent Assessor

Applicant Attendees

Elisabeth Bjork, M.D.	Head of CV and Metabolism Global Medicine Development, Astrazeneca
Jean Chan, M.D.	Medical Director, BMS
Brenda Cirincione, M.S.	Director, Pharmacometrics, BMS
Fred Fiedorek, M.D.	Senior Vice President, Head of Development - Cardiovascular & Metabolics, BMS
Rob Johnson, Ph.D.	Senior Director, Pharmaceutical R&D, BMS
Sanchali Kasbekar, Pharm.D.	Post-doctoral Fellow, Regulatory Sciences, BMS
Joy Koda, Ph.D.	Senior Director, Medical Development, BMS
Nancy Kribbs, Ph.D.	Director, Global Regulatory Sciences, BMS

Joseph Lamendola, Ph.D.	Vice President, US Regulatory Sciences and Regulatory Policy, BMS
Peter Ohman, M.D.,Ph.D.	Executive Director, Medical Development, Astrazeneca
Jessica Parchman, B.S.	Executive Director Global Quality and Regulatory Compliance, BMS
Kinnari Patel, Pharm.D.	Associate Director, US Regulatory Liaison, BMS
James Pratt, Ph.D.	Associate Director, Biostatistics, BMS
John Roth, Ph.D.	Executive Director, Global Regulatory Sciences - Metabolics, BMS
Denis Roy, Ph.D.	Senior Director, Non-clinical Drug Safety & Comparative Medicine
Cindy Rubin, M.D.	Group Director, Global Clinical Research - Metabolics, BMS
Larry Shen	Vice President, Medical R&D QSMD, BMS
Annie Sturgess, M.S.	Executive Director, CMC Biologics, BMS
Mary Whealy, Ph.D.	Director, Global Regulatory Affairs, Astrazeneca
Mark White, M.D.	Vice President, Product Development, Astrazeneca
Helen Yu, M.D.,Ph.D.	Medical Director, Global Safety, BMS

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

A. Regarding the clinical review, FDA noted the following challenges:

1. Efficacy: Adequate and well-controlled investigations provide the basis for establishing effectiveness for new drugs. In this application the trials are not internally controlled (e.g., no placebo concurrent control), which has led to a challenging review of efficacy. In this setting, we would typically compare the observed results with what would be expected in the absence of treatment (e.g., historical control), but this is problematic for metreleptin because the natural history of this group of diseases is not well described. Furthermore, our review of this application has revealed several issues, such as drug compliance and initiation / adjustments to concomitant medications, with substantial potential to confound the relationship of metreleptin and the outcomes of interest. Our efficacy review is considering whether or not it may be possible to identify particular subgroups for

whom a beneficial effect of metreleptin might be especially convincing. We also note that the proposed indication is very broad.

2. Safety: The challenge in interpreting the adverse events is teasing out the progression of, or association with, the underlying disease from any possible adverse effects caused by the drug. Once again, the lack of a concurrent control is extremely limiting. Safety issues we are particularly focusing on relate to leptin's interaction with the immune system, such as the adverse events of lymphoma, potentially other cancers, and exacerbation of autoimmune diseases, as well as the immunogenicity of metreleptin.

B. The Division of Therapeutic Proteins noted there were concerns with the level of aggregates in the multi-dose vial and with validation of the immunogenicity assays and the neutralizing antibody assays.

C. The Biotech Manufacturing Assessment Branch asked for an update on the status of an information request sent to the company on September 16, 2013. BMS stated they were working on the responses. They would submit responses to approximately half the questions by October 7, 2013. The other information requests from FDA would take additional time.

3.0 INFORMATION REQUESTS

A. Clinical

1. Summarize your assessment of metreleptin efficacy and safety in patients with generalized lipodystrophy versus those with partial lipodystrophy.

   a. For efficacy, in addition to an overall subgroup analysis, separate the subgroup analysis by leptin category status (F $<$ or $\geq$ 4 ng/mL, M $<$ or $\geq$ 2 ng/mL).

   b. Because patients with AGL may be at risk for diseases that could be impacted or exacerbated by metreleptin treatment, such as autoimmune hepatitis or T-cell lymphoma, provide a separate safety assessment of this group of patients.

2. Provide the number of years of lipodystrophy diagnosis prior to enrollment for each patient.

3. The NIH protocol provides advice for dose titration and then drug withdrawal for lack of efficacy. Describe the clinical scenarios for those patients who underwent dosing changes and/or withdrawal for efficacy.

4. Provide any available information regarding caloric intake (patient level and summary data) and symptoms of hyperphagia prior to and during metreleptin treatment.

5. Using the most recent data cut, provide the following data: fasting insulin, c-peptide, measures of insulin sensitivity (OGTT, insulin tolerance test), RMR / REE, hypothalamic-pituitary-gonadal / -thyroid / -adrenal axes, and 24hr urine protein and creatinine. (According to the NIH protocol, these items were collected.)

a. For all available data, summarize results overall and by lipodystrophy subtype and summarize the clinical significance of the observed changes.

6. Provide any available information regarding changes with metreleptin treatment in bone mineral density, bone age, and pathologic bone findings by x-ray in the NIH trials.

7. Provide additional information on the following patients:

a. NIH 90164:

i. Provide follow-up on the 15-day safety report of neutralizing antibodies (IND 50259 serial number 0267), including information on the 2 hospitalizations for sepsis, binding antibody titer, most recent leptin concentration, any follow-up of HbA1c, fasting glucose, and serum TG.

ii. We note there was a suggestion of loss of efficacy in year 2 coinciding with category C NAbs and binding Ab titer 78125 – are there any explanations during that time for the apparent worsening of metabolic control?

b. NIH 90151:

i. Is there any other information known about the event of anoxic encephalopathy that led to this patient's death?

c. NIH 90106:

i. Table 42 from the clinical safety update states that the baseline 24 hr urine protein was 2.6 g, yet the dataset indicates that this value was measured on day 68 (coinciding with an AE of proteinuria on d 65). Did this patient have a true baseline value?

8. For all patients who underwent liver biopsy, provide pathology reports, overall biopsy diagnosis (i.e., definite steatohepatitis, borderline, none, cirrhosis, etc.), and available biopsy scores.

9. Provide data on liver size by MRI for all patients (we have only 90101-29).

10. Provide MRI data of fat %, if done.

11. Provide NAFLD Activity Scores (NAS), with the breakdown of its components for all patients' biopsies (this was done for the 2013 publication [Zadeh])

12. Based on how visit windows for 20010769 were defined, please describe how a visit is mapped to an analysis visit given the overlapping window definitions. For example, consider a patient with one post-baseline measurement at month 10. Because the visit windows are defined as ±4 months for the Month 8 and Month 12 visit, it is unclear whether this patient's visit would be classified as Month 8 or

Month 12. Note that the following rule provided in the SAP does not address this issue: "If there are data from more than one visit available for the same scheduled visit, the clinical laboratory measures collected from the visit with date closest to the scheduled visit date will be used for summary and analysis while data collected from all visits will be listed."

B. Chemistry

Provide this information to the BLA by November 7th, 2013. If you are unable to do so then you should contact the FDA to discuss alternative dates for providing the requested information.

1. Regarding drug substance:

   a. The information you provided indicates that metreleptin drug product is light labile. However, we cannot find information in your submission about how you control light exposure of DS. To address our concern, provide information on how you protect DS from light during storage and handling.

   b. Your manufacturing process includes shipping drug substance, and DS release/stability samples. However, you did not provide shipping stability data, shipping validation data, and the shipping validation protocol used for shipment of metreleptin DS samples. Similarly, you did not provide any of this information for drug product, or drug product release and stability samples. Therefore we cannot evaluate the adequacy of your shipping procedures. Provide shipping stability data, shipping validation data, and shipping validation protocol fr metreleptin DS and DP.

2. Regarding drug product:

   a. You propose that metreleptin can be reconstituted in WFI for single use or in WFI containing 0.9% benzyl alcohol (BWFI) for multiple dose use within 3 days. However, the data provided in table provided in table 29 in section 3.2.P.8.3.6.3.1 indicate that the use of BWFI as diluent results in out of specification results for amounts of total oligomer. Out-of-specification results are not obtained when metreleptin is diluted in WFI. Moreover, you did not provide data from an adequate number of lots to fully understand the impact of BWFI on oligomer content. To address this concern, provide data for total oligomer content for all lots of drug product upon reconstitution with BWFI and throughout the intended storage period at (b) (4). If BWFI reconstituted metreleptin has higher oligomer content than WFI reconstituted metreleptin then BWFI may not be a suitable diluent for metreleptin.

   b. You propose an in process control limit of (b) (4) mg/ml for metreleptin bulk concentration. This limit will allow concentrations during manufacturing to range from (b) (4). Metreleptin release specifications for content are 90-110% of label claim e.g. 11.3 mg/vial to be reconstituted in 2.2 mL of diluent. We are concerned about the suitability of your proposed in process control strategy since

acceptance limits may fail to ensure that metreleptin concentration at release always meet the specification acceptance criteria. Please, address this concern

c. As part of process validation you provided metreleptin concentration for five filled vials taken from the beginning, middle and end of the filling run. This is not acceptable because you did not provide the fill volume or fill weight to demonstrate vial fill uniformity. Provide the following:

   i. Fill volume or weight data obtained for each validation lot to support consistent fill throughout the filling process.

   ii. The average number of vials filled per lot of drug product manufactured at (b) (4)

   iii. The number of vials per lot of drug product manufactured at (b) (4) that will be routinely tested for fill uniformity (metreleptin concentration and fill volume).

d. You described the lots of metreleptin drug product used to support the proposed specifications in Table 1 in section 3.2.P.5.6, Justification of specification. According to that table, process validation lot 090653F, manufactured with the proposed commercial process was used in the clinical setting. However, lot 090653F was manufactured with drug substance lots containing high bioburden in the last steps of the manufacturing process and you committed to use this lot only for validation purposes and not for clinical settings. Clarify whether you used lot 090653F in clinical settings.

e. To establish release specifications you determined the mean (b) (4) of available release and stability data and single point in time retrospective data for all the lots of drug product manufactured at (b) (4). However, some of your proposed acceptance criteria for quantitative assays are wider than the calculated mean (b) (4), and they are not established based on your manufacturing or clinical experience for these specifications. This approach is not acceptable because the blind use of (b) (4) without taking into consideration the criticality of the product attributes with respect to safety and efficacy is not appropriate for establishing acceptance criteria. Revise your proposed acceptance criteria for the following assays to reflect the impact of the attribute on safety and efficacy, and manufacturing experience:

   i. Metreleptin content by UV Spectrophotometry.

   ii. Potency.

   iii. Non dissociable oligomer content.

   iv. Purity and impurities.

f. With regards to purity as measured by RP-HPLC, we note that release specifications are set wider for drug product than for drug substance. This approach is not acceptable since (b) (4)

content. Therefore, the purity specification should be similar too. Revise your specifications to address this concern.

g. Your submission includes drug product stability data for metreleptin stored at the recommended storage, under accelerated, and stress conditions. However, you did not provide drug product stability specifications so we cannot assess the suitability of your stability program. Provide a table containing the DP stability specifications including the quality attribute(s) being tested, methods and the proposed acceptance criteria.

h. You propose to eliminate testing for pH, protein concentration and purity by SDS-PAGE for your DP annual stability testing. These tests, however, are included in the stability testing scheduled for drug product validation lots and we believe that these tests are important for stability indicating attributes. Provide a rationale and a justification for excluding these tests from the annual stability testing program.

3. Regarding potency specification:

a. The proposed specification for both DS and DP is (b) (4) of reference standard by a cell proliferation bioassay (32D OBECA cell model). The proposed specification is not acceptable because assay validation, product characterization, and manufacturing experience indicate that the potency specification acceptance criteria can be significantly tightened. Revise DS and DP potency specification acceptance criteria to reflect your clinical experience, manufacturing experience, and assay validation results.

4. Regarding the container closure system:

a. You provided a list of potential substances that can leach from the container closure system into both the DS and DP that is based on vendors' experience. Moreover, you state that the lack of the impact of these potential leachables on Metreleptin is based on the margin of safety when compared to the maximum acceptable human dose (mg/day) published data. Your approach for assessment of safety of leachables solely is based on the theoretical estimate and therefore it is not acceptable. Provide the experimental results from your extractables and leachable studies to support your theoretical assessment. Also provide an assessment of the impact of extractables and leachables on product quality.

5. Regarding diluent (WFI or BWFI) used in SOP, method validation, and DP stability:

a. You propose to reconstitute the lyophilized drug product (DP) cake with either water for injection (WFI) or bacteriostatic WFI (BWFI) containing 0.9 % of benzyl alcohol. At least one of your revised SOPs (TM-0357r01) indicates the use of Milli-Q-water (REST110005, based on TM-0357) for routine assay performance. Method validation should be conducted with the different diluents used for reconstitution of the product to ensure that the method is suitable for its intended purpose. Provide information on what diluents were used for your drug product release test validation

exercises and available data on the impact of the diluent in product quality attributes.

b. In most of the analytical procedures used to assess critical stability attributes, the DP samples are reconstituted in water (milli-Q, HPLC grade, purified) while BWFI is used for non-critical quality attributes (e.g. appearance, osmolarity). Explain the rationale behind the selection of WFI or BWFI.

Please list your analytical methods and provide the information requested above in a table with the following suggested format:

Method	DP reconstitution diluent (WFI or BWFI)in SOP	Rational	DP reconstitution diluent used in validation exercise	DP reconstitution diluent used in stability samples

6. Regarding your immunogenicity assays:

a. You state that the cut point for your electrochemiluminescence (ECL) assay was confirmed for detection of anti-metreleptin antibodies using sera from the obese population. However, you are assessing for anti-drug antibodies in lypodystrophy patients not obese subjects. As stated in the FDA draft guidance on immunogenicity assay development, assay background and cut point, can differ between populations. Therefore it is necessary to confirm that the cut point is appropriately set in the population targeted for treatment. Please provide data to support the selection of your screening and specificity cut points using sera from the lipodystrophy population that you intend to treat.

b. Samples from your pivotal studies were tested for binding antibodies at two different sites: (b) (4) and Amylin. The assay validation reports from each testing site differ in the calculated assay cut point. Since you intend to report the frequency of anti-metreleptin biding antibodies using data collected using both assays, you should to demonstrate that the method performed equivalently between sites. Provide data to demonstrate that the developed ECL method performed equivalently at Amylin and (b) (4).

c. We are concerned that the titering approach used for the identification of neutralizing antibodies fails to detect low positive samples because your estimated sensitivity for the assay is 5 ug/ml. FDA draft guidance recommends that to detect antibodies that may be clinically meaningful, assay sensitivity should be around 500 ng/ml. During previous interactions with the agency, it was discussed that a ligand

binding method could be developed to address the lack of sensitivity of your cell based assay. Provide any developmental information available on a ligand binding assay that can be used to identify samples positive for the presence of neutralizing antibodies.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

A. The risk management plan you have proposed, which includes a Medication Guide, a REMS with ETASU, enhanced pharmacovigilance, and a voluntary patient registry as a PMR appears reasonable at this time. The decision on the need for a REMS and any FDA revisions to the proposed REMS will be conveyed to you after further internal discussions. It should be noted that if FDA makes the determination that a REMS with ETASU is required, your proposed labeling will need to be updated to provide information regarding the REMS program; this may include the need for a Boxed Warning. Additionally, the adverse events that FDA would require for enhanced pharmacovigilance have not yet been finalized. Once FDA comes to internal agreement, those specifics will be conveyed to you. Finally, whether the registry will be required as a PMR is still under consideration. Consistent with our July 17, 2013 letter, PMRs will be conveyed to you by February 1, 2014.

5.0 ADVISORY COMMITTEE MEETING

A. As previously stated, the Advisory Committee Meeting (AC) is scheduled for December 11, 2013. There are no updates available at this time. The company asked if they could request a separate teleconference to discuss topics related to the AC. FDA told the firm to request this teleconference in writing.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

A. FDA reminded the applicant that the late cycle meeting had been scheduled for November 20, 2013. The briefing document for this meeting would be provided by FDA no later than November 12, 2013.

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/s/

ERIC C COLMAN
10/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

GENERAL ADVICE

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Kinnari Patel, Pharm.D., R.Ph.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for metreleptin. The final reviewable portion was dated and received on March 27, 2013.

We also refer to your March 8, 2012, submission containing a Metreleptin Patient Registry Summary which you propose as part of your risk management plan (Appendix 3).

We have reviewed the referenced material. While a determination has not been made as to whether this study would be required as a postmarketing requirement (PMR) should your application be approved, we are providing some recommendations below for your consideration. At this time we do not require a response to these recommendations; however, if metreleptin receives FDA approval and if the registry is required as a PMR, your proposed protocol should incorporate these recommendations. Additional details regarding PMRs, will be conveyed to you on or before February 1, 2014.

1. We suggest removing HIV-associated lipodystrophy or localized lipodystrophy as registry exclusions.

2. Clarify if the protocol is for U.S. only or if it will apply to other countries should the drug be approved elsewhere.

3. Clarify how prescribers will be identified and trained to administer the informed consent and data collection forms. Develop standard operating procedures that cover enrollment procedures to be conducted by the pharmacy distribution center and by the prescriber.

4. Include plans to collect data on the number and percent of metreleptin *prescribers* (and their specialties) who actively prescribe metreleptin, but refuse registry participation. Compare demographic variables (specialty, location, etc.) of metreleptin prescribers who agree to participate to those who do not.

5. Patients who discontinue metreleptin, but are willing to remain in the registry should be followed to the end of the study, if possible.

6. We encourage having standard operating procedures to try to locate patients lost to follow-up, such as attempting contact by phone, mail, and/or email; by calling at various hours; and by attempting to contact the participant's designated secondary contacts (the primary care physician, next of kin, or other contacts as provided in the participant's consent).

   The following reference may be helpful: Hunt JR & White E. Retaining and tracking cohort study members. *Epid Rev* 1998;20(1):57-70.

   Standard operating procedures should also address procedures to be conducted when the participant's vital status remains unknown and no contacts can be reached. The study can seek to obtain the participant's vital status through vital statistics records (the Social Security Administration in the U.S.) and other sources of information as available and as allowed by each country's regulations (e.g., National Death Index (NDI) in the U.S.).

7. Incorporate a second technique (e.g., a patient treatment diary) to evaluate metreleptin adherence/exposure beyond documenting prescribing information at enrollment and changes made to the patient's treatment since the prior visit.

8. Provide information on how adverse events of special interest (AESI) will be diagnosed and validated.

9. All data elements related to outcomes will need to be incorporated and captured on the standardized data collection forms.

10. Collect information on risk factors for each AESI (as feasible) on the data collection forms.

11. On the data collection forms, prompt clinicians to ask about specific medications that may affect AESI.

12. Include a plan to report registry enrollment to the FDA annually by country.

13. Include a statistical analysis plan.

14. There is no compulsory format or template for a product registry. However, elements that could be considered for inclusion are as follows (order and headings at the investigator's discretion):

    - title page, table of contents, list of abbreviations, and abstract;
    - study objectives, description of drug risks;
    - study methods: design, setting, study time period and schedule, population source, physician and patient recruitment, inclusion/exclusion criteria, data sources, exposure and outcome ascertainment and validation, collection of covariates, follow-up of patients, documentation of patient withdrawal, drug discontinuation and losses to follow-up;

- sample size/power calculations, statistical analyses, data management/security, software, quality control;
- comparison populations for interpreting results;
- managing and reporting of AEs/SAEs, site/clinician training, protocol modification, record retention;
- human subjects protection, informed consent, ethics committee/IRB involvement;
- plans for reporting study results including study strengths and weaknesses; references and appendices.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

AMY G EGAN
10/07/2013

From: Madara, Patricia
To: Patel, Kinnari (Kinnari.Patel@bms.com)
Subject: BLA 125390 Myalept (metreleptin) - Request for information
Date: Wednesday, September 18, 2013 10:34:00 PM
Importance: High

BLA 125390 **INFORMATION REQUESTS**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We are continuing our review of your application and have an additional request for information.

- **In trial DFA104, there is an adverse event of lung adenocarcinoma in patient 109001. The CSR synopsis and AE narrative states that the patient was randomized to P+ML; however, the AE listing from DFA104, as well as the cancer assessment provided in BLA125390 submission 6/24/2013, state that the patient was randomized to placebo. Please clarify the randomization group and the treatment that the patient received during the trial.**

Please submit this information to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
09/18/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 Myalept (metreleptin for injection) - Request for Information
Date:	Monday, September 16, 2013 3:12:00 PM
Attachments:	16Sept13 Request for Information.pdf
Importance:	High

INFORMATION REQUEST

BLA 125390

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have additional requests for information. Please reference the attached PDF document.

Submit your responses officially to the BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

1) Regarding validation of container-closure integrity (CCI):
   a) Module 3.2.P.3.5.5.1 states that CCI was determined by Amylin dye ingress method TM-0372 with container-closure systems immersed in 0.1% methyl orange dye, but details of the method and results were not provided. Submit details of the CCI test method and results, including the number of containers tested, the vacuum and pressure parameters used for challenge, the time of immersion challenge, descriptions for positive and negative controls, validation acceptance criteria, and method sensitivity (minimum detectable leak size).

   b) Submit the production parameter limits for crimper pressure, crimper height, and crimper rotational speed, and data demonstrating that CCI is maintained at the minimum and maximum allowable (worst case) crimper parameter limits.

2) Regarding the Antimicrobial Preservative Effectiveness data presented in Table 12 of Module 3.2.P.2.5:
   a) Submit the number of vials tested for each challenge microorganism.
   b) Submit the procedure for neutralization of the benzyl alcohol preservative in BWFI prior to plating of the challenge microorganisms on colony enumeration plates.

3) Module 3.2.P.3.5.3.2 presented processing hold time results for two lots (090653F and 171003F), and stated that hold times for Metreleptin (b) (4) and formulated bulk Metreleptin drug product would be established when the results for a third lot become available. Clarify when this information will be provided. If the information is available please submit.

4) Submit the alert and action limits for bioburden, endotoxin, and TOC for water for injection (WFI).

5) Regarding (b) (4)
   a) (b) (4)
   b)
   c)
   d) Submit the procedure, acceptance criteria and data for validation of (b) (4) efficacy.

6) Regarding (b) (4) of the Metreleptin 5.0 mL vials in the (b) (4) (b) (4)
   a) Submit 2010 qualification report PQR0691.00-10-01, and 2009 qualification report PQR0691.00-09-01.
   b) Submit the (b) (4) endotoxin-challenged vials used for validation.
   c) Submit the (b) (4) vials used for validation.

7) Regarding (b) (4) of stoppers in (b) (4):
   a) Submit 2010 qualification report PQR0468.EQUIP-10-01, and 2009 qualification report PQR0468.EQUIP-09-01.
   b) Report PQR0468.EQUIP-11-01 only presented (b) (4) Submit a

description of the [redacted]. Illustrations and/or photos of the [redacted] would be helpful.

c) [redacted]

d) Submit the acceptance criteria and three most recent, consecutive data for:
   i) [redacted]
   ii)
   iii)
   iv)

8) Regarding [redacted]
   a) Submit 2010 qualification report PQR0461.EQUIP-10-01, and 2009 qualification report PQR0461.EQUIP-09-01.
   b) [redacted].
   c) Submit the acceptance criteria and three most recent, consecutive data for:
      i) [redacted]
      ii)
      iii)
      iv)

9) Regarding media fill simulation validation:
   a) Submit a summary of the acceptance criteria for fill simulation.
   b) Submit a data summary for all media fill simulations conducted in 2011 and 2012 in support of Metreleptin fill. Your response should include:
      i) Data for at least three successive fills conducted with simulated [redacted].
      ii) The number of vials filled per simulation.
      iii) A comparison of the simulation fill times with the time allowed for Metreleptin fill.
      iv) The size of the vials filled and the fill volume.
      v) The number of vials exhibiting contamination.
      vi) The results for negative controls and growth promotion controls.
      vii) Environmental monitoring results.
   c) Submit the procedures performed in the event of a media fill failure. Your response should include a description of the impact of failure on product release and future product fills.

10) Submit the model number or name, catalog number, and dimensions of the [redacted]

11) Submit the model number or name, catalog number, and dimensions for the [redacted]

12) Submit the catalog number and dimensions for the [redacted] (b) (4)

13) Regarding the studies used to establish the minimum [redacted] (b) (4)

14) Regarding the bacterial retention validation study for the [redacted] (b) (4) presented in Module 3.2.P.3.5.4.1:
    a) [redacted] (b) (4)
    b)
    c)
    d)
    e)

15) Submit the procedures, acceptance criteria, and data for Metreleptin drug product shipping validation.

16) Rabbit pyrogen test data as required in 21CFR610.13(b) was not provided in the submitted BLA. Please submit the data. The rabbit pyrogen test should be performed on three drug product lots as per the requirements of USP <151>, *Pyrogen Test*, to demonstrate that the drug product does not contain pyrogenic substances other than bacterial endotoxin.

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/s/

PATRICIA J MADARA
09/16/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 - Request for Information
Date:	Thursday, September 12, 2013 1:39:00 PM
Importance:	High

INFORMATION REQUEST

BLA 125390

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have an additional request for information.

- **The NIH protocol states: A-100 will be administered twice a day (BID) by subcutaneous injection at doses predicted to achieve 50%, 100% and 200% of normal leptin levels based on a "normal body fat" of 30% in females, and 20% in males. Please clarify what are considered "normal leptin levels" (with any applicable literature references).**

Please submit this information officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
09/12/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Cc:	Madara, Patricia (Patricia.Madara@fda.hhs.gov)
Subject:	BLA 125390 - Requests for information
Date:	Friday, August 30, 2013 1:03:00 PM
Importance:	High

BLA 125390 **INFORMATION REQUESTS**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We are continuing our review of your application and have additional requests for information.

From the Division of Good Manufacturing Practice Assessment

(Please note: We understand you had previously responded to the requests below in your pre-BLA briefing document. However, please also submit the information officially to the appropriate module of the BLA.)

1. Please clarify whether (b) (4) in section 3.2.S.2.2.3.5 of the submission.
2. During the inspection of the drug substance (DS) manufacturing facility, it was noted that changes to the manufacturing process were implemented during manufacture of the 2012 DS lots. Please update the manufacturing process description to include the changes that were implemented. The duration of each process step along with the hold steps should be included.
3. Please provide the revised in-process bioburden and endotoxin alert and action limits for all intermediates based on process capability and data from 2012 lots.
4. Please provide details of the method used for bioburden and endotoxin testing of in-process intermediates and (b) (4). A 10 mL sample should be used for bioburden testing of in-process intermediate to improve sensitivity of the test. The data from 3 lots of in-process intermediates and (b) (4) to support that the bioburden and endotoxin test methods used for in-process intermediates and (b) (4) are suitable for its intended use should be included.
5. The bioburden and/or endotoxin levels increased during the hold study for in-process intermediates at manufacturing scale. Please repeat the hold time study using pre-defined bioburden and endotoxin limits. Please provide the protocol for the hold time study for review prior to execution. The bioburden levels above the pre-set limits should be investigated and organisms identified. The hold time for the process intermediates should be established based on data from the repeat study. The hold times for the process intermediates should not exceed those in the 2012 manufacturing campaign until the hold time study is completed.

6. Please provide details of the worst case (b) (4) and hold conditions and justification for its use to support (b) (4) hold time of 31 days. The data from this study should be submitted to the BLA.
7. Please set the bioburden acceptance criterion for the chromatography post-equilibration (b) (4) to in-process bioburden action limit for the ongoing study on the chromatography (b) (4) re-use.
8. Please adjust the bioburden and endotoxin limits for WFI flush of (b) (4) after the clean-in place step to reflect the WFI bioburden and endotoxin limits. Please also readjust the bioburden limits for the post-equilibration (b) (4) used to monitor effectiveness of sanitization and short term storage of membrane.
9. Please clarify if the shipper (b) (4) used in the Amgen shipping validation studies is used for commercial shipment of metreleptin drug substance from the Sandoz Kundl site to the fill-finish site (b) (4)). The duration and transport method used for commercial shipment should be included.
10. Please provide summary shipment data (temperature, fill volume, duration) for the process validation lots using the (b) (4) shipper.
11. Please provide the protocol and results obtained during the repeat free fall drop testing of shipper per ASTM D 880-92.

From the Division of Biometrics VI

12. Please submit the purity and individual impurity data for metreleptin drug product in SAS or Excel format officially to the BLA. Currently, these data are only available as a PDF file.

Please confirm receipt of this email.

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
08/30/2013

Hennessey, Lyndsay

From: Hennessey, Lyndsay
Sent: Monday, August 19, 2013 5:28 PM
To: 'Patel, Kinnari'
Cc: Madara, Patricia
Subject: BLA 125390 Metreleptin - Quality Information Request

BLA 125390 Quality Information Request

Dear Dr. Patel,

In reference to your BLA Metreleptin STN 125390/0, the Quality reviewers have identified the following in order to complete their review. A written response is requested by September 16, 2013. Please provide a PDF copy of your official submission.

Regarding metreleptin DS (b) (4):

(b) (4)

1. (b) (4)
2.
3.

Regarding the potency assay:

(b) (4)

1. (b) (4)

Regarding identity test and characterization:
You provided immunological assays for identity and characterization of DS but you did not provide specificity of the antibody and origin of the antibody used for these assays.

1. Provide information on the origin, characterization, and specificity of the anti-metreleptin antibody used in the ELISA and Western blot for the DS characterization and comparability study.

Regarding impurities:

You describe the presence of [redacted] of metreleptin. However, you have not provided sufficient details about those impurities for us to evaluate your control strategy. To address this concern please answer the following questions:

1. What is the [redacted]?
2. Do the [redacted].
3. Do [redacted] product have any biological function?

Regarding the physicochemical analysis included in your comparability exercise:

1. You provided characterization data on metreleptin DS stored under oxidizing storage conditions to assess comparability between [redacted]. Please provide SEC data on lots from both scales stored under oxidizing conditions.

2. You set acceptance criteria for impurity peaks by RP-HPLC to [redacted]. Please provide suitable acceptance criteria for each individual impurity peak that are based on manufacturing experience and potential risk to product quality.

3. Your RP-HPLC chromatogram for metreleptin DS show a peak [redacted] that you did not identify. Please provide characterization data on this peak so that we can evaluate your control strategy for impurities by HPLC.

Regarding manufacturing process development:

For commercial manufacture you propose to [redacted] However you only show development data for [redacted]. Furthermore, manufacturing validation data from the [redacted] L scale showed lower yield and purity than that of [redacted] process. We are concerned that you are not operating an optimized process. To address this concern:

1. Provide justification with supporting data for using the [redacted] commercial manufacturing scale.

Regarding Control of materials:

1. You will be using materials [redacted] that can introduce disease risk to humans. You did not provide sufficient documentation that the materials [redacted] are safe for pharmaceutical use. Provide representative CoAs of the raw materials [redacted] used in the manufacturing of metreleptin [redacted]

2. You provided data showing [redacted] Please address this concern and provide data to demonstrate genetic stability of your cell bank.

3. Provide the post approval protocol intended to be used for qualification of new master and working cell banks. In the absence of such a protocol introduction of new master and working cell banks will require a prior approval supplement.

Kindly acknowledge receipt of this request.

Thank you,

Lyndsay Hennessey
Regulatory Health Project Manager
FDA/CDER/OPS/OBP-IO
10903 New Hampshire Ave.
WO Building 21 Room 1523
Silver Spring, Maryland 20993-0002
Lyndsay.Hennessey@fda.hhs.gov
240-402-3746

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/s/

LYNDSAY J HENNESSEY
08/19/2013

From: Madara, Patricia
To: "Patel, Kinnari"
Subject: RE: BLA 125390 (Myalept; metreleptin for injection) - Request for Information
Date: Tuesday, July 30, 2013 5:03:00 PM
Importance: High

Hi Kinnari;

Please see our clarifications, comment and an additional request below. Please confirm receipt. Thanks.
Sincerely;
Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Patel, Kinnari [mailto:Kinnari.Patel@bms.com]
Sent: Monday, July 29, 2013 5:59 PM
To: Madara, Patricia
Subject: RE: BLA 125390 (Myalept; metreleptin for injection) - Request for Information

Dear Pat,

For the FDA request for information below, we would like to gain clarity on following two questions. Your advice/guidance on these would be greatly appreciated as we create the responses.

First Clarification: History of type 2 diabetes

Question 1a: For the requested baseline history of type 2 diabetes, the Sponsor would like to inform the Agency that patients' history was captured as diabetes mellitus or instances of lipoatrophic diabetes. As type 2 diabetes may not have been uniformly captured and specified, the Sponsor would propose to include the available diabetes-related history including information of few patients having type 1 diabetes. Does the Agency agree with this proposal?

FDA Response:

Yes, we agree with this approach.

Second Clarification: Clarify how to tabulate data for the 4 patients with modified first dose date

The 4 patients with a modified first dose date and rationale for using it are in the BLA in 2 places. Most recently, it was supplied in Appendix 7 of the Clinical Safety Update. It was

originally submitted to the BLA in the NIH SAP as part of the 2010 submitted files. Appendix 7 of the Safety Update was a cut-n-paste from the SAP to reduce the need of the reviewer to pull up the SAP if they so desired to understand the 4 cases.

Clarifying question 2: In the request received 26JUL2013, tabular listings for all NIH and FHA patients are requested, displaying efficacy (HbA1c and TG) and corresponding concomitant diabetes and lipid lowering medications at specific visits (NIH: Baseline, Month 4, Month 8, Month 12, Year 3, Year 5 and Year 10; FHA: Baseline, Month 3, Month 9, Month 12, Year 3, Year 5, and Year 10). In the BLA, 4 NIH patients (90105, 90106, 90110, 90128) had their efficacy data summarized using a modified first dose date due to extended "off drug" periods early on when initiated metreleptin therapy. It is the Sponsor's view that this provides an assessment of what metreleptin therapy can provide when taken regularly. In the 26MAY2013 FDA request, it was noted that lab data (including HbA1c and TG) taken within days prior to the first dose was missing for 2 of the 4 patients (90105 and 90106); these data have been subsequently submitted to the BLA. The Sponsor seeks clarity on the FDA Reviewer's preference for the tabular display of data for these 4 patients. Should data be tabulated for these 4 patients according to the true first dose date (recognizing the potential that some of the desired time points to be included that a patient may have been off study drug), or using the modified first dose date (recognizing that there is some prior study drug exposure and thus 'Baseline' would not represent naïve to study drug exposure).

FDA Response:

Please provide the data in the table for those 4 patients using the modified first dose date, but include the "true" baseline (the treatment naïve value). In addition, provide summaries of the results based on the 2 approaches as a footnote to each table.

Additional FDA Request and Comment

We would also like to ask you to add one more item in your tables: metreleptin dose at each visit requested (NIH: Baseline, Month 4, Month 8, Month 12, Year 3, Year 5 and Year 10; FHA: Baseline, Month 3, Month 6, Month 9, Month 12, Year 3, Year 5, and Year 10).

Also, we would like to clarify that HbA1c and TG values and diabetes and lipid concomitant medications for FHA should also correspond with the appropriate visits for that particular protocol (mo 3, 6, 9, and 12) – we apologize for the error on the original request.

Please do let me know if you have any questions.

Kind regards,
Kinnari

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Friday, July 26, 2013 11:17 AM
To: Patel, Kinnari
Subject: BLA 125390 (Myalept; metreleptin for injection) - Request for Information
Importance: High

INFORMATION REQUEST

BLA 125390

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have additional requests for information. Please see the attached PDF document.

You can provide this information informally, via email but also submit if officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
08/01/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125390

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Route 206 & Province Line Road
Princeton, NJ 08543

Attention: Kinnari Patel, PharmD
Associate Director, Metabolics
Global Regulatory & Safety Sciences – US

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Metreleptin. The final reviewable portion was dated and received on March 27, 2013.

We also refer to:

- Your initial proprietary name submission, dated April 10, 2012, for the proposed proprietary name Myalept;
- Our initial correspondence dated July 5, 2012, finding proposed proprietary name, Myalept, conditionally acceptable;

We have completed our re-review of the proposed proprietary name, Myalept, and have concluded that it is acceptable. The proposed proprietary name, Myalept, will be re-reviewed 90 days prior to BLA action date. If **any** of the proposed product characteristics as stated in your March 27, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Patricia Madara at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/26/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 (Myalept; metreleptin for injection) - Request for Information
Date:	Friday, July 26, 2013 11:17:00 AM
Attachments:	26July13_clinical Information Request.pdf
Importance:	High

INFORMATION REQUEST

BLA 125390

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We continue to review your application and have additional requests for information. Please see the attached PDF document.

You can provide this information informally, via email but also submit if officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Information Request

1. Please provide tables for each patient from the NIH trials and FHA101 in a similar format to Tables 1a-13 in Appendix 5 of the Clinical Efficacy Update and include the following information:

    a) Study ID, type of lipodystrophy, age/sex/race, baseline history of type 2 diabetes (y/n), baseline history of pancreatitis (y/n)

    b) Available values of HbA1c (%) and TG (mg/dL) at baseline, month 4, month 8, month 12 (or closest value to mo 12 up until mo 18), year 3, year 5, year 10

    c) Concomitant diabetes and lipid medications (including drug name and dose) at baseline, month 4 (month 3 FHA), month 8 (month 9 FHA), month 12 (or closest value to mo 12 up until mo 18), year 3, year 5, year 10

    d) If results from a particular a study visit aren't available (reported as "NA"), provide reason (e.g., discontinued, treatment ongoing but hasn't yet reached that visit yet, travel considerations, etc.)

    e) Provide comments on compliance (study drug, concomitant medication, diet, etc.) at each visit

    f) Provide any information on dosing gaps

2. Provide datasets used to generate these tables.

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/s/

PATRICIA J MADARA
07/26/2013

From:	Madara, Patricia
To:	Patel, Kinnari (Kinnari.Patel@bms.com)
Subject:	BLA 125390 (metreleptin) request for information
Date:	Monday, July 15, 2013 12:13:00 PM
Importance:	High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We are continuing our review of your application.

In addition, we reference our request for information dated May 24, 2013 and your response to question 10. We have reviewed your proposal and have the following comment and request:

- (b) (4) **As initially requested, please provide an updated laboratory analysis dataset that includes all available data with a new derived visit variable based on the patient's first exposure to metreleptin. Please provide the requested dataset to FDA by 23 July 2013.**

You may provide this information informally, via email but also submit if officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
07/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

EXTENSION USER FEE GOAL DATE

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Kinnari Patel, Pharm.D., R.Ph.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to the final reviewable unit of your Biologics License Application (BLA) dated and received March 27, 2013, submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin for injection).

On June 24, 2013, we received your solicited amendment to this application, which the Division has determined constitutes a major amendment. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 24, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 1, 2014.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JAMES P SMITH
07/17/2013
on behalf of Eric Colman

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, June 13, 2013 2:52 PM
To: Patel, Kinnari
Subject: BLA 125390 (metreleptin) REQUEST FOR INFORMATION
Attachments: 13June13 information request.pdf

Importance: High

BLA 125390 **INFORMATION REQUEST**

Dear Kinnari;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We are continuing our review of your application and have additional requests for information. Please see the attached PDF document.

You may provide this information informally, via email but also submit if officially to your BLA. **Please confirm receipt of this email**.

Thanks for your help.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Please respond to the questions below by June 17, 2013.

1. For Study FHA101, please describe how a patient with a missing value for their derived analysis visit was handled if they had had another measurement that was also within the analysis visit window. For example, the 6 month HbA1c analysis visit value on 12/20/2010 for patient 648011 was missing, but the HbA1c value from a 12/13/2010 visit was not missing. Other instances were identified and are shown in the Table below for the first year for the primary study endpoints. If there are other instances including those that occurred after the first year of follow-up, provide a list of the patients, dates, visits and endpoints for which this occurred. Furthermore, if this handling of missing data is not considered an error or an oversight, provide the rationale for excluding these data from the analysis.

Endpoint	**Patient ID**	**Analysis Visit (mo)**	**Date of analysis visit with *missing* endpoint value**	**Date(s) of visit with *available* endpoint value**
HbA1c	648011	6	12/20/2010	12/13/2010
	677002	6	11/08/2011	10/03/2010, 12/07/2010
FPG	648011	6	12/20/2010	12/13/2010
	677001	9	11/16/2011	1/20/2012
FTG	648011	6	12/20/2010	12/13/2010
	677001	9	11/16/2011	1/20/2012

FPG-fasting plasma glucose; FTG-fasting serum triglycerides

2. It appears that the only SAP included in the submission referencing Study FHA101 was dated 10/27/2010, which was after the first datacut of 06/14/2010. Please clarify whether this SAP was finalized before data were available for any analysis. If the SAP was not finalized prior to the data being available for any analysis, please submit the last available version before the data was accessible. If such a document is not available, please describe why.

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/s/

PATRICIA J MADARA
06/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

FILING COMMUNICATION

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Attention: Kinnari Patel, Pharm.D.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-04000

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin for injection). The final reviewable portion was dated and received on March 27, 2013.

We also refer to your amendments dated April 18, 29, and May 2, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is November 27, 2013.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 24, 2013. In addition, the planned date for our internal mid-cycle review meeting is July 1, 2013.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

1. **From (1) the metreleptin + pramlintide clinical program, and (2) the Amgen trials not included in the Integrated Summary of Safety, provide a safety summary that includes an assessment of:**
   a. **Deaths, serious adverse events, and adverse dropouts**
   b. **Adverse events of special interest**
      i. **Cancer, including hematological malignancies**
      ii. **Renal adverse events**
      iii. **Pancreatitis adverse events**
      iv. **Liver-related adverse events**
      v. **Cardiovascular adverse events, as well as a blood pressure and heart rate assessment**
      vi. **Hypoglycemia**
      vii. **Immunogenicity (if not previously addressed in the Clinical Addendum)**
2. **Provide Case Report Forms for deaths, serious adverse events, and adverse dropouts from the obesity trials (Amgen and Amylin).**
3. **Provide a safety assessment based on all current worldwide knowledge regarding this product, including:**
   a. **Data that supported the recent Japanese approval[1]**
   b. **Compassionate use for primary leptin deficiency and lipodystrophy**
   c. **Investigational use, including non-lipodystrophy and non-obesity indications**
   d. **Literature review, including a review of leptin and cancer risk in humans**
4. **Provide financial disclosures for investigators from the Amgen-sponsored trials.**
5. **Provide an English translation of the Japanese metreleptin for lipodystrophy label.**
6. **Clarify the disposition for patient 90103 from study 991265 (see below for discrepancy) and confirm the accuracy of the recorded disposition for all patients in the NIH and FHA101 trials.**

[1] http://www.shionogi.co.jp/ir_en/news/detail/e_130325.pdf

The following discrepancy was noted:

The clinical efficacy update p 17, states that patient 90103 elected not to enroll into Study 20010769. Furthermore, the clinical safety update p 174, subject disposition by cohort table, records no patients in cohort 1 (patients who initiated treatment in study 991265) who withdrew due to an adverse event.

However, the SAP for study 991265-20010769, section 7.1.5 states:
Patient 90103 would have been consented onto Study 20010769 in Jan 2002 (Month 16 visit), but it was decided to not enroll the patient into the study due to a serious adverse event. The patient was withdrawn from Study 991265 in Jun 2002 and never signed the Informed Consent for Study 20010769 because the patient met an exclusion criterion for the latter study.

Office of Biostatistics; Division of Biometrics II

7. **Although Study 991265 was performed at two sites (NIH and UTSW), the submission appears to only include information and data on patients enrolled at the NIH site. Please specify how many patients were studied at the UTSW site and clarify whether any of the UTSW patients were followed under Protocol 20010769. If data on patients that were initially enrolled at the UTSW site are available, provide analysis datasets that include all data on these patients collected under Protocols 991265 and (if followed under) 20010769. Also, provide relevant documentation for these datasets including define files.**

8. **For each of the 9 patients listed in Table 1 of the NEJM article entitled "Leptin-Replacement Therapy for Lipodystrophy" by Oral et al. (2002, vol 346, pages 570-578), provide the study site where the patient was studied (NIH or UTSW) and their corresponding unique patient identifier from Study 991265.**

9. **There appear to be several discrepancies between the data available for Study 991265 and the data presented in Table 2 of the NEJM article referenced above. For example, for Patient 90101 (which appears to correspond to Patient 1 in the article), her baseline HbA1c value in the manuscript is reported as 8.6, but is listed as 8.0 in the analysis dataset. Another inconsistency identified is the fasting plasma triglyceride values for patient 90102 (which appears to correspond to Patient 2 in the article). In the article, this patient's baseline and month 1 value are 633 and 523, respectively, while in the analysis dataset her baseline value is 523 and her month 1 visit value is 633. Due to these inconsistencies, each value listed in Table 2 of the article needs to be compared with the value in the analysis data. For each discrepancy identified, provide a list that summarizes the discrepancy. Each summary should include the patient ID, the visit numbers where the discrepancy occurred, the endpoint with the discrepancy, the discrepant lab values, the reason for the discrepancy, and the correct value. In addition, provide a revised analysis dataset with the corrected values.**

10. The submission does not appear to include data on several patients before they initiated metreleptin use for the first time. For example, Patient 90106 in Study 991265 initiated treatment on 9/08/2000 but stopped treatment after experiencing an AE. After having a similar treatment-AE episode approximately two weeks later, metreleptin was restarted for a third time on 11/15/2000. For this patient, the baseline data is based on a visit that occurred on 11/13/2000, and *not* before treatment was initiated treatment on 9/08/2000. This issue was also identified to have occurred in Patient 90105 in Study 991265. If this issue occurred in additional patients for any study that was included as part of the submission, please provide their IDs. Furthermore, to allow for a thorough evaluation of the metreleptin submission, all data on all patients need to be provided to FDA. Therefore, provide updated analysis datasets that includes all data on all available measurements. In these datasets, there should be a new derived visit variable defined according to the patients first exposure to metreleptin. If these data are not available, please explain why.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide (MG), and Instructions for Use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert, Medication Guide, and Instructions for Use and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

You submitted establishment information that is not required as part of a BLA for specified products. Please refer to the *Guidance for Industry For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product*

or a Monoclonal Antibody Product for In Vivo Use for the information you should include in your application. We will assess this information during the pre-license inspection of your establishment, but not as part of your application. Its inclusion in the file does not constitute approval.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN
05/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

BLA ACKNOWLEDGEMENT

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Kinnari Patel, Pharm.D, R.Ph.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

We have received your submission described as the "final reviewable unit" of your "rolling review" Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Myalept (metreleptin for injection)

Date of Application: March 27, 2013

Date of Receipt: March 27, 2013

Our Secondary Tracking Number (STN): BLA 125390/0

Proposed Use: indicated for the treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
05/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

ACKNOWLEDGE CORPORATE ADDRESS CHANGE

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Kinnari Patel, Pharm.D., R.Ph.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

We acknowledge receipt of your May 13, 2013, correspondence, notifying the Food and Drug Administration (FDA) that your address has been changed from:

Amylin Pharmaceuticals, LLC
9625 Towne Centre Drive
San Diego, CA 92121

To:

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Route 206 & Province Line Road
Princeton, NJ 08543

for the following Biologics License Application (BLA):

BLA 125390 for Myalept (metreleptin for injection)

We have revised our records to reflect this change.

Please cite the BLA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
05/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

ACKNOWLEDGE CORPORATE NAME/ADDRESS CHANGE

Amylin Pharmaceuticals, LLC
Attn: Kinnari Patel, Pharm.D, R.Ph.
Associate Director, Metabolics
Route 206 & Province Line Road
Princeton, NJ 08543

Dear Dr. Patel:

We acknowledge receipt of your March 5, 2013, correspondence notifying the Food and Drug Administration (FDA) that the corporate name and address has been changed from:

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

To:

Amylin Pharmaceuticals, LLC
9625 Towne Centre Drive
San Diego, CA 92121

for the following Biologics License Application (BLA):

BLA 125390 for Myalept (metreleptin for injection)

We have revised our records to reflect this change.

Please cite the BLA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
05/21/2013

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, April 25, 2013 5:00 PM
To: 'Patel, Kinnari'
Subject: FW: BLA 125390 Myalept (metreleptin for injection) Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis requests for information

Importance: High

Hi Kinnari;

Please see the email below, sent to Amylin last September. Amylin never responded to this info request, stating the information would be included in the final module of the BLA. Can you tell me if your BLA module addresses these questions. If yes, please let me know where the information can be found. If not, can you please respond. You can send informally, by email but also submit officially to the BLA.

Many thanks for your help. Please confirm receipt.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Madara, Patricia
Sent: Monday, September 17, 2012 3:13 PM
To: 'Nguyen, Huy'
Cc: Madara, Patricia
Subject: BLA 125390 Myalept (metreleptin for injection) Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis requests for information
Importance: High

BLA 125390 INFORMATION REQUEST

Amylin Pharmaceuticals, LLC
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for metreleptin. The Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA) is reviewing the labeling and instructions for use submitted for Myalept and has the following requests for additional information and clarification:

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.

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?

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).

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?

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.)

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.

7. In your clinical studies, did patients self-administer the product or was the product administered to them by a healthcare professional?

Please submit your responses officially to your BLA. Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
04/25/2013

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, February 27, 2013 2:15 PM
To: 'kinnari.patel@bms.com'
Subject: Metreleptin - Request for Information
Signed By: patricia.madara@fda.hhs.gov

IND 101824
BLA 125390

INFORMATION REQUEST

Dear Kinnari;

Please refer to your treatment Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin for injection). We have the following requests for additional information:

- **Please provide a breakdown of the number of men and women overall and by lipodystrophy type for the July 11 2011 cutoff (n=100) and January 2013 cut off (n=125) datasets.**
- **Please provide an update on the estimated date for submission of the last module of the Myalept BLA.**

You may provide this information informally, via email. **Please confirm receipt of this email**.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
02/27/2013

Madara, Patricia

From: Madara, Patricia
Sent: Monday, January 28, 2013 11:36 AM
To: 'Nguyen, Huy'
Subject: RE: BLA - information request - to be included with submission of the final section
Importance: High

Hi Huy;

I forwarded your email to the Office of Scientific Investigations and received the following responses:

Regarding your question: *"Will the combined listings for FHA101 as detailed in the table above, be sufficient to meet FDA/OSI's needs?"*

The OSI response: **The combined listings for FHA101 as detailed in the table will be sufficient to meet our needs for site inspection.**

Regarding your comment: *"....since this request was received after the Pre-BLA meeting that took place on December 17, 2012, we respectfully request to be able to submit this information in the 30-day period following submission of the last portion of the BLA...."*

The OSI response: **The timeframe is acceptable.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Nguyen, Huy [mailto:Huy.Nguyen@amylin.com]
Sent: Friday, January 25, 2013 5:25 PM
To: Madara, Patricia
Subject: RE: BLA - information request - to be included with submission of the final section
Importance: High

Hello Pat,

Per your information request sent via email on 2-Jan-2013 regarding the OSI request that site level data be included in the BLA,"OSI Pre-BLA 125390 Request IND 101824", we have a few questions for clarifications. Considering the pending BLA submission in ~ Mar-2013, we are sending these questions via email but are happy to also officially submit them if needed. Also, we would also welcome the opportunity to discuss via TC with the appropriate people at OSI etc to ensure that our proposal provides the needed information to satisfy this request. Our proposal is briefly outlined below:

- **Section I (Request for general study information and specific Clinical Investigator information):**
  We will submit this information in the in the last portion of the BLA

- **Section II (Request for Subject Level Data Listings by Site):**
  We believe that current listings to be included with the last portion of the BLA to be submitted sometime in March 2013, will contain the information that FDA/OSI is requesting, albeit in a slightly different format.

  Background: To help frame the question, it is helpful to know that there are just 2 studies submitted in support of this BLA, which provide efficacy and safety data in the proposed patient population. Both studies are ongoing (open enrollment, open duration). Among these 2 studies, there are 4 sites, with most subjects coming from 2 sites as illustrated in the table below.

Study	Site Information	Disposition
NIH 99-1265/20010769 (N=72 as of 31JUL2012)	Site No. 901 Bethesda, DM	72 enrolled/treated 20 discontinued
FHA101 (N=28 as of 07MAR2012)	Site No. 648 Ann Arbor, MI	25 enrolled/treated 6 discontinued
	Site No. 649 Santa Barbara, CA	1 enrolled/treated 1 discontinued
	Site No. 677 Greenville, NC	2 enrolled/treated 1 discontinued

In the BLA, summaries and patient data listings are provided by study – note we did not integrate data from the NIH and FHA studies. The patient numbering schema in both the NIH and FHA studies are of the form SSSPPP where SSS is a 3-digit site number and PPP is a 3-digit patient ID within each site. All listings are sorted by patient number, which implicitly also sorts by site for the FHA study. The following table identifies the listing number and number of pages in the listing that would contain the different data types. For FHA101, also provided is the page numbers that patients from site 648 comprise within the current combined listings (across sites). As can be seen, although the listings are not broken out by site, patients from site 648 comprise nearly all pages of the listings and are easily found within the combined listing sets.

Best Available Copy

Requested Listing	NH 991265200010769	FHA 101
IL2a (Screen Failure)	Not Available	Not Available
IL2b (Dosing)	App 3.5.1 (45 pages)	App 3.5.1, 3.5.2 (7 pages; Site 648 pages 1-6)
IL2c (Disposition)	App 3.1.1, 3.1.2 (4 pages)	App 3.1 (6 pages; Site 648 pages 1-5)
IL2d (Evaluability)	Not Applicable	Not Applicable
IL2e (Eligibility)	Not Available	App 3.3.1 (8 pages; Site 648 pages 1-8)
IL2f (AEs, SAEs, Deaths)	AEs: App 3.2.2 (32 pages) SAEs: App 3.2.4.3 (5 pages) Deaths: App 3.2.4.6 (1 page)	AEs, SAEs, Deaths: App 3.7.2 (49 pages; Site 648 pages 1-44)
IL2g (Deviations)	Not Available	App 3.3.2 (2 pages; Site 648 pages 1-2)
IL2h (Efficacy)	App. 3.8.1, 3.8.2, 3.9.1, 3.9.2, 3.10.1, 3.10.2, 3.16.1, 3.16.2, 3.17.1, 3.17.2 (223 pages)	App 3.9.2 (44 pages; Site 648 pages 1-41)
IL2i (ConMeds)	App 3.7.2 (153 pages)	App. 3.8.2 (109 pages; Site 648 pages 1-109)
IL2j (Laboratory/Vitals)	Labs: App 3.25.1, 3.25.2, 3.26.1, 3.26.2, 3.27.1, 3.27.2, 3.28.1, 3.28.2 (960 pages) Vitals: 3.29.1, 3.29.2 (28 pages)	Labs: App. 3.9.2 (44 pages; Site 648 pages 1-41) App. 3.9.3 (26 pages; Site 648 pages 1-26) App. 3.9.4 (4 pages; Site 648 pages 1-4) Vitals: App 3.10 (32 pages; Site 648 pages 1-32)

Will the combined listings for FHA101 as detailed in the table above, be sufficient to meet FDA/OSI's needs?

- **Section III (Request for Site Level Dataset):** Considering the data submitted in support of this application is derived from 2 studies with a total of 4 sites (w/ the majority of subjects coming from 2 sites), and that FDA indicated this is optional, we do not plan to provide a site level dataset.

Lastly, since this request was received after the Pre-BLA meeting that took place on December 17, 2012, we respectfully request to be able to submit this information in the 30-day period following submission of the last portion of the BLA, in accordance with the provision stipulated by PDUFA V.

Thanks and best regards,

Huy Nguyen

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Wednesday, January 02, 2013 6:03 AM
To: Nguyen, Huy
Subject: BLA - information request - to be included with submission of the final section
Importance: High

BLA 125390 **ADVICE / INFORMATION REQUEST**

Amylin Pharmaceuticals, LLC
9360 Towne Centre Drive

San Diego, CA 92121

Hi Huy;

Welcome back. Hope you had a wonderful holiday. Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for MYALEPT (metreleptin for injection).

I have attached a PDF document containing advice and requests for additional information to be submitted with the final section of your BLA. The purpose of the information is to help facilitate the Office of Scientific Investigations (OSI) development of clinical investigator and sponsor/monitor/CRO inspection assignments.

Please note that although the information would be extremely helpful in our site selection process, Part III is voluntary and optional as part of an OSI pilot program, with no penalty for not participating in this request.

OSI has staff that can assist you with any technical questions that may come up regarding these requests.

Please contact me if you have any questions. Please confirm receipt of this email

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
01/29/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101824

MEETING MINUTES

Amylin Pharmaceuticals, LLC
Attention: Orville Kolterman, M.D.
Sr. Vice President, Chief Medical Officer
9360 Towne Centre Drive
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Myalept (metreleptin).

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2012. The purpose of the meeting was to discuss submission of a BLA for Myalept.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	PreBLA
Meeting Date and Time:	December 17, 2012, 3:00 PM eastern time
Meeting Location:	White Oak Campus, Building 22
Application Number:	IND 101824
Product Name:	Myalept (metreleptin for injection)
Indication:	Treatment of metabolic abnormalities associated with lipodystrophy, including insulin resistance, type 2 diabetes, and hypertriglyceridemia
Sponsor/Applicant Name:	Amylin Pharmaceuticals BristolMyersSquibb Astrazeneca
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Patricia Madara, M.S.

FDA ATTENDEES

Office of the Commisssioner; Office of Orphan Product Development

Jeff Fritsch	Director, Regulatory Affairs

Office of New Drugs; Program for Rare Diseases

Kathryn O'Connell, M.D., Ph.D.	Medical Officer

Office of New Drugs; Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D.	Director
Amy Egan, M.D., MPH	Deputy Director for Safety
Julie Golden, M.D.	Medical Officer
Mary Roberts, M.D.	Medical Officer
Federica Basso, Ph.D.	Pharmacology/Toxicology Reviewer
Pamela Lucarelli	Acting Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer

Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment

Patricia Hughes, Ph.D.	Team Leader
Steven Fong, Ph.D.	Quality Microbiology Reviewer

Office of Pharmaceutical Science, Office of Biotechnology Products, Division of Therapeutic Proteins

Susan Kirshner, Ph.D.	Associate Laboratory Chief
Laura Salazar-Fontana, Ph.D.	Quality Reviewer
Cecilia Tami, Ph.D.	Quality Reviewer
Montserrat Puig, Ph.D.	Quality Reviewer

Office of Biostatistics; Division of Biometrics II

J. Todd Sahlroot, Ph.D.	Deputy Division Director and Team Leader
Janice Derr, Ph.D.	Statistical Reviewer

Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis

Yelena Maslov, Pharm.D.	Team Leader
Kevin Wright, Pharm.D.	Safety Evaluator

Office of Surveillance and Epidemiology/Division of Epidemiology I

Patricia Bright, MSPH., Ph.D.	Epidemiologist

Office of Scientific Investigations; Division of Good Clinical Practice Compliance

Cynthia Kleppinger, M.D.	Senior Medical Officer

Office of Planning and Analysis; Planning and Evaluation Staff

Kimberly Taylor	Research Analyst

EASTERN RESEARCH GROUP ATTENDEES

(b) (6)	Independent Assessor

Amylin Pharmaceuticals / BristolMyersSquibb / Astra Aenecao Attendees

Jean Chan, M.D.	Medical Director, Amylin
Wade DeMond	Director, Regulatory CMC, Amylin
Carla Hekman-Bicsak, Ph.D.	Associate Director, Pharmaceutical R&D, Amylin
Amy Jennings, Ph.D.	Director, US Regulatory Affairs, BMS
Rob Johnson, Ph.D.	Director, Pharmaceutical R&D, Amylin
Joy Koda, Ph.D.	Senior Director, Medical Development, Amylin
Orville Kolterman, M.D.	Senior Vice President, Chief Medical Officer, Amylin
Huy Nguyen	Associate Director, Regulatory Affairs, Amylin
Mark Rosolowsky, Ph.D.	Vice President, Regulatory CMC - BMS
Denis Roy, Ph.D.	Senior Director, Non-clinical Drug Safety & Comparative Medicine, Amylin
Mary Whealy	Director, Global Regulatory Affairs, Astrazeneca
Mark White, M.D.	Vice President, Product Development, Astrazeneca
Carla Hekman-Bicsak, PhD	Associate Director, Pharmaceutical R&D, Amylin
James McDermott, PhD	Executive Director, Product Development, Astrazeneca
James Pratt, PhD	Associate Director, Biostatistics, Amylin
Karen Lutz, PhD	Director, Medical Research, Amylin
Peter Öhman, MD PhD	Executive Director, Medical Development, Astrazenca
Helen Yu, MD PhD	Medical Director, Global Safety, Amylin

Background

Metreleptin is a recombinant methionyl-human leptin, produced in E. coli. The recombinant protein has 147 amino acid residues, including the amino-terminal methionine that is not native to the human leptin protein.

Amylin Pharmaceuticals is developing metreleptin for treatment of lipodystrophy (IND 101824). Lipodystrophy is a rare disease that may be inherited or acquired. It is characterized by metabolic abnormalities, including insulin resistance, type 2 diabetes, hypertriglyceridemia, and steatohepatitis. There is currently no approved treatment for lipodystrophy. Therefore, metreleptin has received Orphan Drug designation for treatment of lipodystrophy. Amylin has already submitted sections of a BLA (125390) for use of metreleptin for treatment of diabetes mellitus and/or hypertriglyceridemia in patients with lipodystrophy.

Recently, Amylin was notified that the BLA 125390 for Myalept (metreleptin for injection) would be reviewed according to the provisions negotiated under PDUFA V and "The Program" for new molecular entities (NMEs). The company was encouraged to request a preBLA meeting. The official request was received on November 9, 2012.

At the meeting, Amylin presented slides that included their questions from the briefing document, FDA's preliminary comments and Amylin's responses to Agency questions. In addition, Amylin included data and questions related to FDA's information requests, sent to the company on November 27 and December 2, 2012. Amylin responded to these requests via email on December 8, 2012.

Questions from the briefing document and the Agency's pre-meeting responses follow in normal font. Items discussed at the meeting are in **bold** font. In addition, reference is made to Amylin's slides at the end of the document.

Questions to FDA:

Format and Content of BLA

1. Does the Agency concur that the remaining submission planned as outlined in Section 7 is sufficient to support the filing and potential approval of the metreleptin BLA?

FDA Pre-meeting Response

Chemistry, Manufacturing, and Controls

Please ensure that you have provided the CMC information requested by the Agency via e-mail on November 27, 2012.

Clinical

We concur, based on agreed-upon data and analyses to be submitted as discussed in Appendix 6 of your briefing package. Make sure that the TOC in Appendix 10 aligns and is consistent with these agreements. For example, in the efficacy update it is not clear where subgroup analyses or concomitant medications for the NIH trial will be presented. In addition, the primary efficacy analyses for FHA101 should, to the extent possible, mirror those conducted in NIH patients (e.g., efficacy data in the overall patient population, etc.). In the safety update it is not clear where safety analyses of the pediatric population will be presented.

Please confirm if part of your safety analysis includes a subgroup analysis by lipodystrophy type.

Meeting Discussion

The sponsor noted that all information requested by the clinical review team as outlined in Appendix 6 of the briefing document will be included in the final section of the BLA.

Specifically, the company noted that efficacy analyses for FHA101 will mirror those conducted for the NIH study. A pediatric subgroup analysis will be included, in addition to a subgroup analysis by lipodystrophy type. (See sponsor slide #3)

The clinical team confirmed that the sponsor's proposal was adequate.

2. Does the Agency confirm previously agreed proposed content and format of the 120-day safety update to focus on SAEs and AEs of interest?

FDA Pre-meeting Response

In addition to SAEs and AEs of interest, previously agreed upon, the 120 day safety update should include withdrawals due to an adverse event.

We have the following questions regarding the 120 day safety update.

Will the 120 safety update include information from both the NIH 20010769 and FHA101 studies?

Please confirm the dates the 120 safety update will encompass for the NIH 20010769 and FHA101 studies.

Are new patients enrolled after the July11, 2011 (NIH) and March 7, 2012 (FHA101) data cut-offs included in the 120 day safety update? If so, how many new patients are included?

Meeting Discussion

The sponsor agreed that the 120-day safety update will include all previously agreed upon SAEs, AEs of interest and withdrawals due to AEs and will include patients from both the NIH and FHA101 studies.

The sponsor provided a slide (see sponsor slide #5) which outlined the dates the 120 day safety update would cover. They reported that a total of 25 new patients would be included in the 120 safety update (18 from the NIH study and 7 from the FHA101 study). The sponsor emphasized that the new patients will provide limited safety information as 10 of the 18 new patients enrolled in the NIH study have not returned for follow up visits and the 7 new patients enrolled in the FHA study have follow up information covering only two to three months of treatment.

The company noted that the clinical addendum in the final submission would include an analysis of immunogenicity for both the obesity and lipodystrophy programs.

3. With metreleptin being a new medicinal entity, does the Agency intend to convene an advisory committee meeting to review this program prior to approval? If so, when does the Agency expect this meeting to occur?

FDA Pre-meeting Response

The need for an advisory committee meeting will be determined upon receipt of the application. If a meeting is determined to be useful, we will try to schedule it approximately 5½-6 months/8½-9 months after initial receipt of the complete application.

Meeting Discussion

No additional discussion.

4. Since the "rolling BLA" for metreleptin began under PDUFA IV, would the application, once deemed to be complete for filing purposes, be subject to a 6-month/10-month review cycle according to PDUFA IV or an 8-month/12-month review cycle under PDUFA V?

FDA Pre-meeting Response

As a new biologic, the application will be part of The Program and, therefore, be reviewed on a 8-month/12-month clock.

Meeting Discussion

No additional discussion.

Risk Management Plan

5. Does the Agency have any preliminary comments at this time on the proposed RMP and our rationale for why a REMs is not needed?

FDA Pre-meeting Response

Your proposed pharmacovigilance plan appears adequate at this time. We will continue to assess the need for a REMS throughout the review cycle. If during the course of the review, we determine that a REMS is necessary to ensure that the benefits of metreleptin exceed the risks, we will notify you of such a determination and the basis for it.

Meeting Discussion

Amylin acknowledged that the need for a REMS was a review issue. It was noted that under PDUFA V, submission of a REMS can constitute a major amendment. Amylin requested that they be notified as early in the review process as possible if FDA determined that a REMS for metreleptin was necessary.

Chemistry, Manufacturing, and Controls

6. Does the Agency agree that the additional data completes the DS process validation and that appending this information to the BLA Module 3 is the appropriate mechanism for submission? Background information to support this question can be found in Section 6.4.

FDA Pre-meeting Response

Please ensure that you have provided the CMC information requested by the Agency via e-mail on November 27, 2012.

Meeting Discussion

The sponsor presented slides containing FDA information requests sent on November 27 and December 2, 2012. They also showed slides containing their proposed response to request #5 (not previously submitted to FDA) and asked the Agency if the planned response was adequate. (See sponsor slide #10)

FDA commented that they could not definitively respond to the questions at this meeting. It was noted that a response at this time was premature and the adequacy of the responses would be a review issue.

Amylin asked about the best way to get their protocol for the in-process hold time study approved and FDA responded that the protocol should be submitted to the IND for faster feedback. However, it should also be submitted to the BLA.

FDA noted that it was impossible to determine if any submission to the BLA would be considered a major amendment until after it had been received.

Amylin also mentioned that they would be manufacturing drug product in (b) (4) as originally noted.

Amylin presented a slide outlining their response to question #4 in FDA's information request sent on November 27, 2012 (see slide #12). This response had not been previously submitted to or reviewed by the Agency.

FDA commented that acceptability of the proposed plan would be a review issue. Amylin presented a slide outlining their response to question #8 in FDA's information request sent on November 27, 2012 (see slide #14). This response had not been previously submitted to or reviewed by the Agency.

FDA commented that the new procedures should lead to better control. The Agency noted it was up to the sponsor to make sure suitable controls were in place.

7. Amylin also intends to provide additional DS stability data as part of the proposed CMC amendment. Amylin believes the DS stability program is appropriate to support assignment of the recommended storage condition (b) (4) and retest period (b) (4)) for commercial DS. Does the Agency concur? Background information to support this question can be found in Section 6.5.

FDA Pre-meeting Response

a) FDA agrees that the proposed stability package can be filed. The adequacy of the information to support your storage condition and dating period is a review issue.

b) The FDA does not allow retesting for commercial DS regulated as a biologic. We don't understand the need for retesting in lieu of using a stability protocol to establish your dating period.

Meeting Discussion

No additional discussion.

8. Amylin also intends to provide additional drug product stability data as part of the proposed CMC amendment. Amylin believes the drug product stability program is appropriate to

support assignment of the recommended storage condition (2-8□C) and expiration dating period (b) (4) for commercial drug product. Does the Agency concur? Background information to support this question can be found in Section 6.6.

FDA Pre-meeting Response

FDA agrees that the proposed stability package can be filed. The adequacy of the information to support your storage condition and dating period is a review issue.

Meeting Discussion

No additional discussion.

9. Per previous agreement with the Agency, Amylin plans to update the pending BLA submission during review with metreleptin drug substance and drug product stability data no later than 3 months prior to the action date. Does the Agency agree? Background information to support this question can be found in Section 6.7.

FDA Pre-meeting Response

No, per PDUFA V, FDA will not accept unsolicited updates beyond 30 days after the original BLA. We will request additional stability data if needed.

Meeting Discussion

No additional discussion.

Additional Comments from DMEPA:

Please provide the answers to the following questions at the time of the BLA submission:

1. DMEPA requests that the Applicant indicate their 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.
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?
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).

Meeting Discussion

Amylin noted that the multi-use vial used in clinical trials is the configuration proposed for product launch. The company asked for clarification regarding what information was required by the Agency (i.e. was any information required other than pharmacovigilance and medication error data from the clinical trials)

FDA responded that they were primarily interested in medication errors associated with drug preparation and administration.

In response to a question from FDA, the company confirmed that no syringe would be packaged with the multi use vial.

4. In your clinical studies, did patients self-administer the product or was the product administered to them by a healthcare professional?
5. 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?
6. 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.)
7. 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. Thus, please ensure to 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.

Additional Regulatory Comments

1. As stated in our November 15, 2012, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

2. Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

3. In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

4. Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the

meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

5. Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

Additional Meeting Discussion

As requested at the Type A teleconference held on December 5, 2012, the sponsor provided an update on drug substance and drug product to be used for the commercial launch of Myalept.

The company noted they would launch using drug product (DP) produced during the product validation run (b) (4). This DP would be produced using drug substance (DS) generated by Sandoz (b) (4). (b) (4)

Stability data for the BLA would come from product validation runs #1 and #2 and from another drug lot (b) (4)

FDA advised the sponsor to inform FDA where, within the BLA, the drug product validation data would be found. The company noted it would probably be included in the batch release data.

Amylin noted that they hoped to file for the complete BLA in March 2013.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

1. **The content of a complete application was discussed. The Agency pointed out that it was impossible to determine if a submission to the BLA was a major amendment until it had been received. The clinical information the company planned to submit appeared to contain all the data requested by the Agency.**

2. **All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application**

3. **A preliminary discussion on the need for a REMS was held and it was concluded that the proposed pharmacovigilance plan appeared adequate at this time. FDA would continue to assess the need for a REMS throughout the review cycle. If, during the course of the review, it was determined that a REMS was necessary to ensure that the benefits of metreleptin exceed the risks, FDA would notify the company of such a determination and the basis for it. Amylin acknowledged that the need for a REMS was a review issue. It was noted that under PDUFA V, submission of a REMS constitutes a major amendment.**

4. **Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.**

Post Meeting Comment

1. **All laboratory data in final individual study reports, integrated summaries, and datasets, including those data presented in the form of tables and graphs, supporting an application should be in U.S. (conventional) units.**

Attachment: Sponsor slides

22 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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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
01/14/2013

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, January 02, 2013 9:03 AM
To: 'Nguyen, Huy'
Subject: BLA - information request - to be included with submission of the final section
Importance: High
Attachments: OSI_Pre-BLA 125390 Request IND 101824 .pdf

BLA 125390 **ADVICE / INFORMATION REQUEST**

Amylin Pharmaceuticals, LLC
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Welcome back. Hope you had a wonderful holiday. Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for MYALEPT (metreleptin for injection).

I have attached a PDF document containing advice and requests for additional information to be submitted with the final section of your BLA. The purpose of the information is to help facilitate the Office of Scientific Investigations (OSI) development of clinical investigator and sponsor/monitor/CRO inspection assignments.

Please note that although the information would be extremely helpful in our site selection process, Part III is voluntary and optional as part of an OSI pilot program, with no penalty for not participating in this request.

OSI has staff that can assist you with any technical questions that may come up regarding these requests.

Please contact me if you have any questions. Please confirm receipt of this email

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested, as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original BLA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original BLA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site, if appropriate
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the BLA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

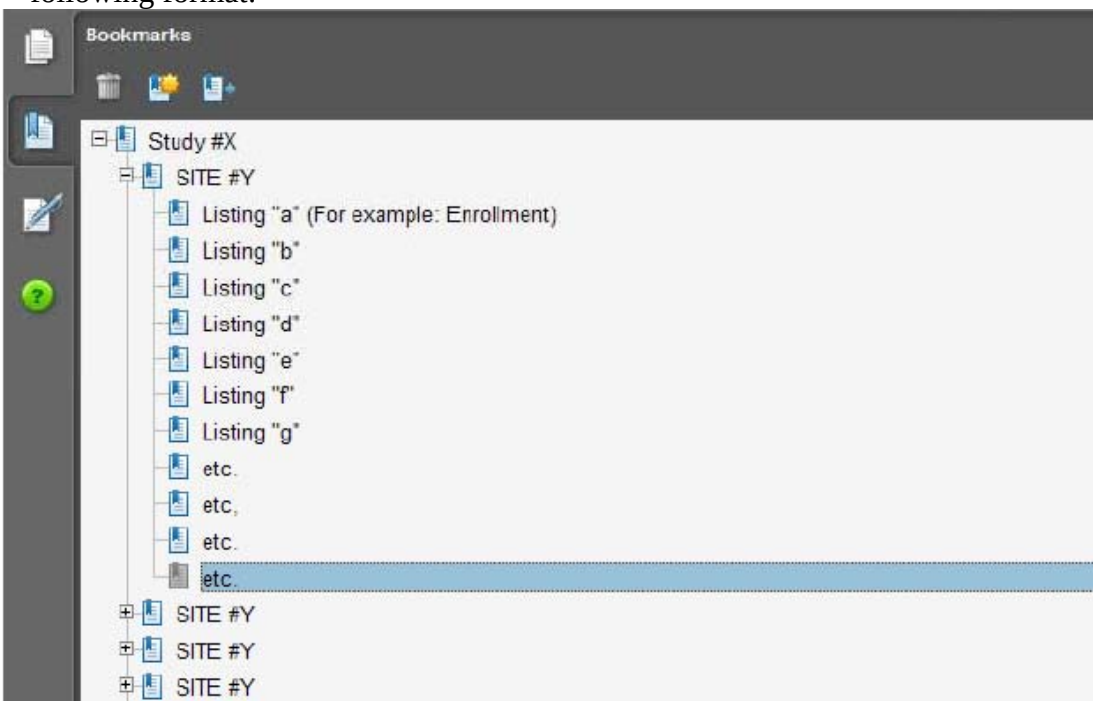
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the BLA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

OSI Pre-BLA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@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/

PATRICIA J MADARA
01/02/2013

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, November 27, 2012 10:06 AM
To: 'Nguyen, Huy'
Importance: High
Attachments: 27Nov12_email_OC_BMAB_IR_ BLA 125390.pdf

BLA 125390 **INFORMATION REQUEST**

Amylin Pharmaceuticals, LLC
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for MYALEPT (metreleptin for injection).

We have attached a PDF document containing requests for additional information. We are requesting this information to aid in our preparation for your preBLA meeting scheduled for December 17, 2012. These data are not required for the Type A meeting on December 5, 2012.

Please contact me if you have any questions.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

STN 125390 Metreleptin from Amylin Pharmaceuticals, LLC.

Information request dated 11/26/2012.

1. Please clarify whether [redacted] section 3.2.S.2.2.3.5 of the submission.

2. During the inspection of the drug substance (DS) manufacturing facility, it was noted that changes to the manufacturing process were implemented during manufacture of the 2012 DS lots. Please update the manufacturing process description to include the changes that were implemented. The duration of each process step along with the hold steps should be included.

3. Please provide the revised in-process bioburden and endotoxin alert and action limits for all [redacted] based on process capability and data from 2012 lots.

4. Please provide details of the method used for bioburden and endotoxin testing of in-process [redacted] are suitable for its intended use should be included.

5. The bioburden and/or endotoxin levels increased during the [redacted] at manufacturing scale. Please repeat the [redacted] using pre-defined bioburden and endotoxin limits. Please provide the protocol for the [redacted] for review prior to execution. The bioburden levels above the pre-set limits should be investigated and organisms identified. The [redacted] should be established based on data from the repeat study. The [redacted] should not exceed those in the 2012 manufacturing campaign until the [redacted] is completed.

6. Please provide details of the worst case [redacted] conditions and justification for its use to support [redacted]. The data from this study should be submitted to the BLA.

7. Please set the bioburden acceptance criterion for the [redacted] t for the ongoing study on the [redacted].

8. Please adjust the bioburden and endotoxin limits for [redacted]

9. Please clarify if the [redacted] (b) (4) . The duration and transport method used for commercial shipment should be included.

10. Please provide summary shipment data (temperature, fill volume, duration) for the process validation lots using the [redacted] (b) (4).

11. Please provide the protocol and results obtained during the [redacted] (b) (4) testing [redacted] (b) (4)

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
11/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 050259
BLA 125390

ADVICE/INFORMATION REQUEST

Amylin Pharmaceuticals, LLC
Attention: Orville Kolterman, M.D.
Sr. Vice President, Chief Medical Officer
9360 Towne Centre Drive
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and to your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act for Myalept (metreleptin).

We also refer to your amendments dated April 3, 2012 (to BLA 125390) and June 21, 2012 (to IND 050259), containing data comparing metreleptin drug substance manufactured by Sandoz at the (b) (4). In addition, we reference the Prior Approval Inspection conducted at Sandoz in August 2012.

We have reviewed the information referenced above and have the following comments and recommendations:

1. As a result of our review of your comparability data and the findings from the Prior Approval Inspection, we conclude that metreleptin manufactured at the (b) (4) (b) (4) during the campaign that produced the validation lots and GMP lot B039242 is not safe to use in the clinic due to the high bioburden load in the final (b) (4)

2. Review of the process validation data submitted as part of the original metreleptin BLA (BLA 125390) and the information gathered during the corresponding Prior Approval Inspection show high levels of bioburden in all drug substance (DS) lots manufactured during the campaign mentioned above. The presence of bacterial proteins can impact the quality, stability and the safety of biologics.

3. To use (b) (4) material produced during the new (b) (4) 2012 manufacturing campaign in the clinic, you will need to provide the Agency with the corresponding in-process and release data test bioburden results for those lots.

As sponsor of IND 050259, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
10/17/2012

Madara, Patricia

From: Madara, Patricia
Sent: Monday, September 17, 2012 3:13 PM
To: 'Nguyen, Huy'
Cc: Madara, Patricia
Subject: BLA 125390 Myalept (metreleptin for injection) Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis requests for information

Importance: High

BLA 125390 INFORMATION REQUEST

Amylin Pharmaceuticals, LLC
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for metreleptin. The Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA) is reviewing the labeling and instructions for use submitted for Myalept and has the following requests for additional information and clarification:

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.

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?

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).

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?

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.)

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.

7. In your clinical studies, did patients self-administer the product or was the product administered to them by a healthcare professional?

Please submit your responses officially to your BLA. Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
09/17/2012

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, September 04, 2012 1:08 PM
To: 'Nguyen, Huy'
Subject: RE: FDA's Advice regarding contents of the Clinical Updates documents
Importance: High
Attachments: 4Sept12_FDA Response to Amylin email comments_27Aug12.pdf

Hi Huy;

I apologize for the delay. We have reviewed your responses, received via email on 27August12. Please see the attached PDF document with our comments and request in track changes. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Nguyen, Huy [mailto:Huy.Nguyen@amylin.com]
Sent: Monday, August 27, 2012 3:15 AM
To: Madara, Patricia
Cc: Hai, Mehreen
Subject: RE: FDA's Advice regarding contents of the Clinical Updates documents

Hello Pat,

We have reviewed the Agency's additional advice, received August 15, regarding the clinical information required for BLA 125390. Attached here with is a document containing Amylin's response to these additional advice/comments received from the Agency. We will also submit a copy of the attached document to the BLA for official records. We hope that the Agency will find these responses and proposals (along with those previously discussed/proposed in the August 07 submission) acceptable, thus enabling Amylin and BMS to begin working on these documents for submission to BLA 1125390.

Thanks and best regards,

Huy Nguyen

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]

Sent: Wednesday, August 15, 2012 1:03 PM
To: Nguyen, Huy
Subject:
Importance: High

BLA 125390 **ADVICE**

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for MYALEPT (metreleptin for injection).

In addition, reference your amendment dated August 7, 2012, containing a response to FDA's advice, sent on July 22, 2012, providing comments regarding the clinical information we require for your BLA to be considered complete. We have attached a PDF document containing additional advice based on the August 7, 2012 submission. Our comments are provided as "balloons" in the right-hand margin of the document.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Efficacy and Safety

- Comment A1 [Country of origin]: Can the NIH/FHA investigators at least give some idea if patients they are treating are from the US or other countries?

  Sponsor's Response: This data has not been captured in the study database prepared to support the application. In response to this request, the Sponsor has confirmed with the investigators at NIH that this information on country of origin for each NIH patient can be provided in a standalone MS Excel file. For FHA101, a similar spreadsheet can be provided (It should be noted that all patients from FHA101 are from the US.) These additional data from both studies will not reside in the respective databases but rather the respective MS Excel files will be included in Module 1.11.4. The Sponsor will not be able to source verify the data since the data will not be in the database.
  Is this approach acceptable to the Agency?

Yes.

- Comment A2 [Efficacy by relevant background medications (insulin, metformin, TZDs, sulfonylureas, fibrates, statins]: Also, if not already planned, you should provide a summary of changes (increases/decreases in dose, stopping/starting) anti-diabetes meds (esp. insulin) an drugs for hyperTG.

  Sponsor's Response: The Sponsor plans to provide an overall summary of number of patients with changes (increase, decrease, stopping, starting) in relevant diabetes and lipid medications.
  Is this approach acceptable to the Agency?

Yes.

- Comment A3 [Efficacy by metreleptin dose]: Also, BID vs QD

  Sponsor's Response: The sponsor plans to summarize key efficacy endpoints through the first year on treatment for the QD only, the BID only, and the QD/BID combination subgroups, based on dosing frequency in the first year on treatment.
  Is this approach acceptable to the Agency?

Yes.

- Comment A4 [Categorical analysis of efficacy parameters – Proportion reaching A1c targets at any time point in first year]: Also, 2 consecutive values and at the end of 1 year

Sponsor's Response: The Sponsor plans to summarize the proportion of patients achieving A1c targets for any 2 consecutive values within the first year of treatment and as well as summarize the proportion of patients achieving A1c targets at the end of 1 year of treatment. It should be noted that not all patients have values at 4, 8, and 12 months of treatment; analysis will be performed with any 2 consecutive post-baseline values within the first year of treatment. The timing of data collection following the first year is highly variable; thus, continuing these analyses beyond the initial 12 months of treatment appears to have limited value.
Is this approach acceptable to the Agency?

Yes.

- Comment A5 [Categorical analysis of efficacy parameters – Proportion reaching TG targets of ≤ 150 mg/dL, ≤ 200 mg/dL, ≤ 350 mg/dL at any time point in the first year]: Would also recommend: the median value for the cohort, 500 mg/dL (considered "severe" hyperTG in drug labels), and a value at which patients lower their risk of pancreatitis.

Sponsor's Response: The Sponsor plans to include TG targets of 500 mg/dL and 1000 mg/dL for this analysis. The median baseline value for the cohort is 359 mg/dL, which is very close to the previously planned analysis target of 350 mg/dL.
Is this approach acceptable to the Agency?

Yes.

- Comment A6 [Categorical analysis of efficacy parameters – Proportion reaching TG targets of ≤ 150 mg/dL, ≤ 200 mg/dL, ≤ 350 mg/dL at any time point in the first year]: Also, 2 consecutive values and at the end of 1 year.

Sponsor's Response: The Sponsor plans to summarize the proportion of patients achieving the specified TG targets listed above as well as percent change (decrease) of ≥20%, ≥30%, ≥50% for any 2 consecutive values within the first year of treatment and at the end of 1 year of treatment. As above, it should be noted that not all patients may have values at 4, 8, and 12 months of treatment; analysis will be performed with any 2 consecutive post-baseline values within the first year of treatment.
Is this approach acceptable to the Agency?

Yes.

- Comment A7 [Categorical analysis of efficacy parameters – Proportion reaching TG percent change of ≥20%, ≥30%, ≥50% at any time point in the first year for those with baseline values >150 mg/dL, > 200 mg/dL, >350 mg/dL]: See comment above re: TG cut-offs

Sponsor's Response: The Sponsor will also perform this analysis (proportion reaching TG percent change [decrease] of ≥20%, ≥30%, ≥50%) for those with baseline TG values of >500 mg/dL and those with baseline TG values of >1000 mg/dL.
Is this approach acceptable to the Agency?

Yes.

- Comment A8 [Categorical analysis of efficacy parameters – Composite summaries]: What cut-offs do you propose? At any time point? At 1 year?

  Sponsor's Response: The Sponsor plans to perform the composite analyses for A1c and/or TG targets using an A1c cut-off of ≤7% and TG cut-off of ≤500 mg/dL at any time point in the first year as well as for any 2 consecutive values within the first year of treatment and at the end of 1 year of treatment.
  Is this approach acceptable to the Agency?

Yes.

- Comment A9 [Safety analysis for pediatric patients – Growth]: Please provide the growth charts of these pediatric patients populated with their longitudinal height data.

  Sponsor's Response: The Sponsor is planning to provide growth charts (height, weight, BMI) for pediatric patients. Additionally, Tanner Scores, where available, would also be included with growth charts for each patient (see below for an example of how these data would be presented)

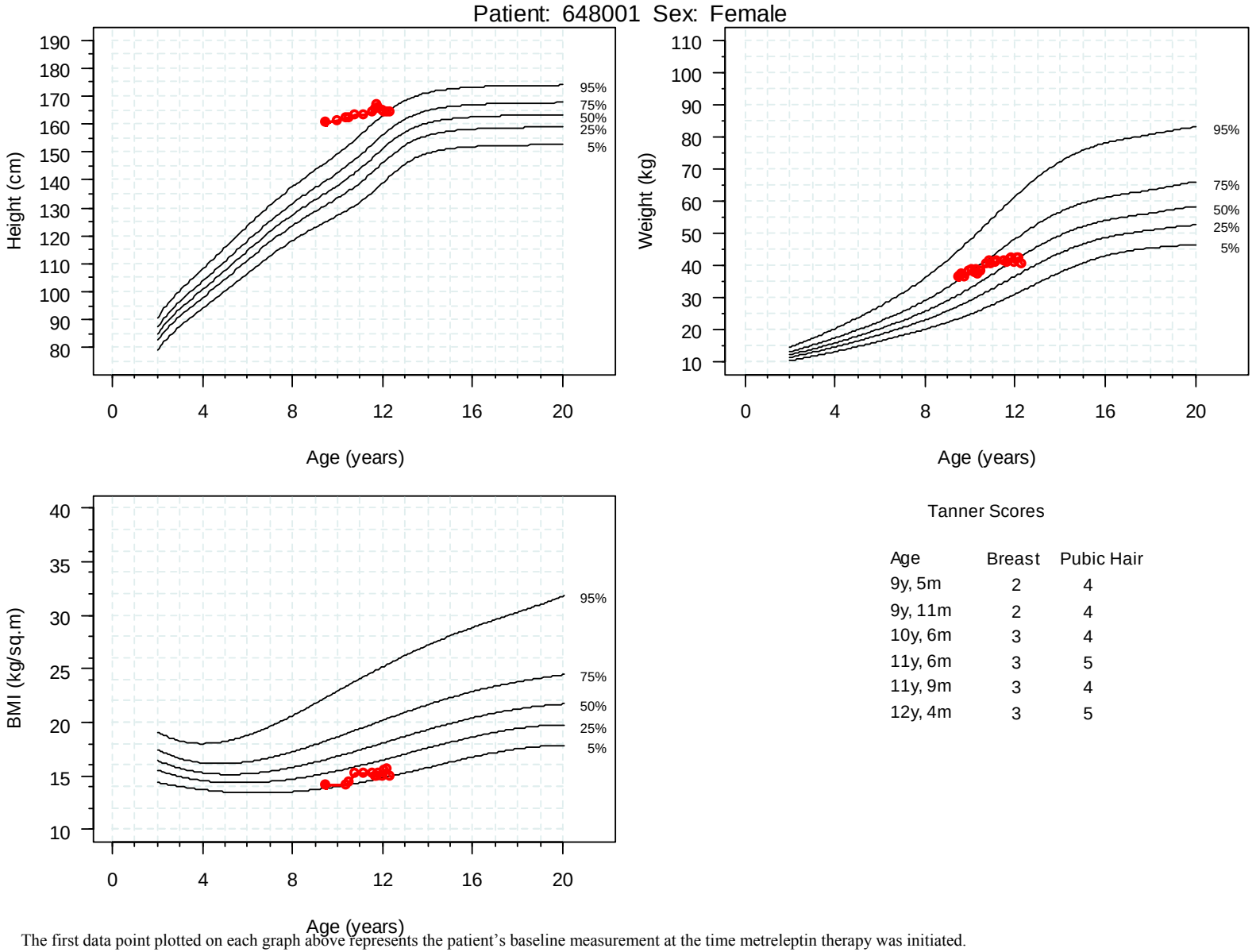
- Comment A10 [Safety analysis for pediatric patients – Pubertal status]: Did the NIH collect this information? Can this information be obtained from the NIH for an analysis?

  Sponsor's Response: Following receipt of this request, the Sponsor has discussed the issue with the NIH investigators. This data may not have been collected in a standardized manner; however, the investigators at NIH have agreed to perform chart reviews and extract pubertal status assessments (Tanner Scores) on pediatric patients where available and provide this information in a MS Excel file. Thus, these data will not reside in the study database but rather included in Module 1.11.4 as a MS Excel file provided by the investigators. Additionally, Tanner scores, where available, would also be included with growth charts for these patients per the example below. The Sponsor will not be able to source verify the data since the data will not be in the database.
  Is this approach acceptable to the Agency?

FDA Response: This approach is acceptable with the following modification. Please include a table of the numerical measurements of height, weight, BMI, and Tanner staging and the corresponding dates on the same page as the growth charts.

Please confirm that these growth charts are the same as the 2000 CDC growth charts.

Date	Height	Weight	BMI	Tanner stage		
				Breast (girls)	**Testicle size (boys)**	**Pubic hair**



Tanner Scores

Age	Breast	Pubic Hair
9y, 5m	2	4
9y, 11m	2	4
10y, 6m	3	4
11y, 6m	3	5
11y, 9m	3	4
12y, 4m	3	5

The first data point plotted on each graph above represents the patient's baseline measurement at the time metreleptin therapy was initiated.

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/s/

PATRICIA J MADARA
09/04/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, August 15, 2012 4:03 PM
To: 'Nguyen, Huy'
Importance: High
Attachments: 7Aug12_response-efficacy-safetyfrom FDA.pdf

BLA 125390 **ADVICE**

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for MYALEPT (metreleptin for injection).

In addition, reference your amendment dated August 7, 2012, containing a response to FDA's advice, sent on July 22, 2012, providing comments regarding the clinical information we require for your BLA to be considered complete. We have attached a PDF document containing additional advice based on the August 7, 2012 submission. Our comments are provided as "balloons" in the right-hand margin of the document.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
08/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

MEETING MINUTES

Amylin Pharmaceuticals, Inc.
Attention: Orville Kolterman, M.D.
Sr. Vice President, Chief Medical Officer
9360 Towne Centre Drive
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your rolling Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for metreleptin for injection.

We also refer to the teleconference between representatives of your firm and the FDA on July 11, 2012. The purpose of the meeting was to discuss the data FDA requires in order to file your BLA.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Attachment 1: proposed table of contents for BLA response
Attachment 2: proposed table of contents for efficacy update report
Attachment 3: 11July12 email from Amylin

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	July 11, 2012
Meeting Location:	teleconference
Application Number:	BLA 125390
Product Name:	Myalept (metreleptin for injection)
Indication:	treatment of lipodystrophy
Sponsor/Applicant Name:	Amylin Pharmaceuticals
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Patricia Madara

CDER Attendees

Office of New Drugs; Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D.	Director
Julie Golden, M.D.	Medical Officer
Mary Roberts, M.D.	Medical Officer
Federica Basso, Ph.D.	Pharmacology/Toxicology Reviewer
Mehreen Hai, Ph.D.	Acting Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Translational Sciences; Office of Biometrics; Division of Biometrics II

Janice Derr, Ph.D.	Statistical Reviewer

Office of Pharmaceutical Science; Office of Biotechnology Products; Division of Therapeutic Proteins

Susan Kirshner, Ph.D.	Associate Laboratory Chief
Emanuela Lacana, Ph.D.	Supervisory Biologist
Laura Salazar-Fontana, Ph.D.	Primary Quality Reviewer
Cecilia Tami, Ph.D.	Quality Reviewer
Montserrat Puig, Ph.D.	Quality Reviewer

Office of Surveillance and Epidemiology

Margarita Tossa, M.S.	Safety Regulatory Project Manager

Office of Compliance; Office of Manufacturing and Product Quality; Division of Biotech Manufacturing Assessment Branch

Kalavati Suvarna, Ph.D.	Quality Microbiology Reviewer

Amylin Attendees

Orville Kolterman, M.D.	SVP & Chief Medical Officer
Jean Chan, M.D.	Director, Medical Development
Chris Weyer, M.D.	SVP, Research and Development
Sean Zhao, MD, Ph.D.	VP, Global Safety
Joe Heilig, Ph.D.	Sr. Director, Bioanalytical Chemistry
Joy Koda, Ph.D.	Sr. Director, Medical Development
Karen Lutz, Ph.D.	Director, Medical Research
Jim Pratt	Associate Director, Biostatistics
David Lokensgard, Ph.D.	Principle Fellow Scientist, Pharmaceutical Research and Development
Carla Hekman Bicsak, Ph.D.	Associate Director, Pharmaceutical Research and Development
Huy Nguyen	Associate Director, Regulatory Affairs

Bristol Myers Squibb (BMS) Attendee

John Roth, PhD	Executive Director, Regulatory Science

Background

Amylin Pharmaceuticals was granted a rolling review status for BLA 125390 (previously considered an NDA) on July 30, 2010. The first portion of the application, consisting of clinical and nonclinical modules, was submitted on December 15, 2010.

The "final" portion of the rolling BLA was submitted on April 2, 2012, containing the Quality module and additional clinical information. The FDA held a filing meeting on May 16, 2012. On May 17, 2012, the clinical reviewers, Drs. Golden and Roberts, held a brief, informal teleconference with Amylin to obtain clarification regarding submission of clinical data. Subsequently, FDA requested another brief teleconference with the company to inform the applicant that the Agency did not consider the BLA complete. Therefore it would not be filed until additional information was received.

A teleconference was held on July 11, 2012 in order to further discuss the clinical data required for the application to be considered complete. In addition, a short discussion related to the inspection of manufacturing facilities was held.

Also note that Amylin submitted, via email, CMC immunogenicity related information on July 11, 2012. This information was briefly discussed.

Discussion Regarding Clinical Data

The FDA clinical reviewers began by referencing the proposed table of contents (TOC) submitted by Amylin on July 08, 2012, via email. FDA suggested discussing the general requirements related to submission of clinical data at the current teleconference and following up with more details by email (see attachments).

First, FDA asked Amylin to confirm that their "update" would include all information related to the new patients and updated data for patients previously submitted to the BLA.

The company confirmed that the submission would include efficacy and safety data for all newly enrolled patients and all new adverse events for patients enrolled prior to the last data cut-off. Efficacy data would be included for all 72 patients treated with metreleptin. The data cut-off would be more recent.

Post meeting request: please clarify for our records the new data cut-offs (NIH study and FHA101) that will be used in the BLA submission.

FDA stated that the sponsor should conduct a comprehensive assessment of all adverse events.

Amylin confirmed that data would be refreshed to include all patients and all events. An integrative overview of adverse events would be provided and narrative text would focus on newly enrolled patients. The text would follow the same structure as previously submitted and would include data summaries.

FDA commented that the text should not just focus on newly enrolled patients, it should be a comprehensive discussion of the safety findings in all patients exposed to metreleptin. In addition, the text should be reflected in the tables.

Amylin agreed to this structure.

FDA asked for confirmation that the new clinical efficacy document would be an integrated assessment of old and new data. Amylin agreed, and stated it would focus on key efficacy endpoints.

Regarding the adverse event data set, FDA asked if all patients would be included in the new document or if the reviewers would need to merge the old and new data sets. Amylin confirmed that they would be submitting one cumulative data set.

Regarding the clinical addendum, FDA stated that this document should be broadened to include a full immunogenicity assessment of metreleptin. A comparison between Amgen and Sandoz drug and immunogenicity assessments for both the obesity and lipodystrophy programs should be included. In addition, relevant literature should be reviewed and discussed. Any discussion of antibody data in the clinical summaries should cross-reference the clinical addendum.

The company stated that it would be updated to the extent possible and would replace the previous clinical addendum with the new one. They would focus on the transition from Amgen to Sandoz metreleptin. They understood that the Agency wanted to see data from both the obesity and lipodystrophy programs. Amylin noted that the Amgen monotherapy antibody data was 10 years old and was collected using a different methodology. Analysis of this data would not be comparable to Amylin's results.

FDA emphasized that the Agency wanted this document to give a full understanding of the immunogenicity of metreleptin and how it may impact its safety and efficacy. Amylin can propose how they will analyze and present the data .

Amylin stated that they would map out the data the company can provide. Amylin noted that the vast majority of patients develop binding antibodies. They will highlight those patients who have high titers. Regarding the Amgen data, it is archival information that Amylin did not generate. The assay used was very insensitive.

FDA understood this position but did want an assessment from Amylin for overall safety and efficacy.

Finally, FDA asked the sponsor to analyze the pediatric population separately for safety and efficacy.

Amylin agreed, and noted they have conducted analyses based on age and gender. FDA confirmed that the pediatric population was all patients under 18 years old.

Post-meeting comment: We note that you have presented data for patients under 12 years old separately in some efficacy analyses. We encourage you to continue to evaluate this subset of patients where relevant.

Discussion with Office of Compliance (OC) regarding Inspection

The Office of Compliance acknowledged Amylin's e-mail dated July 10, 2012 informing the Agency of a change in manufacturing schedule. In the e-mail, Amylin stated that Sandoz (drug substance manufacturing site) would be shut down between (b) (4) for maintenance. FDA asked whether the whole facility was in shutdown or if only specific areas/buildings used for metreleptin manufacturing were undergoing maintenance. FDA noted that Sandoz would not be in operations for a major portion of the planned inspection dates.

Amylin stated that they had very little influence over the dates available for manufacturing. They had accepted the dates proposed by Sandoz based on the need to provide additional information to FDA before the Agency would consider the application complete. A portion of the manufacturing operations will be available for inspection but (b) (4) operations would start early (b) (4) Amylin suggested that FDA inspectors could extend their trip in order to see the (b) (4) process. The next planned (b) (4) is scheduled to occur during the first (b) (4) The (b) (4) procedure scheduled for 2013 was for previously manufactured material. Amylin stated that it will be possible for FDA to see the (b) (4) suite but not the

process itself. There is no flexibility to return to the original dates since Sandoz is currently in shut-down mode.

OC stated that the inspection dates would be discussed internally based on the revised manufacturing schedule provided in the July 10, 2012 e-mail. FDA asked Amylin to contact the Agency prior to changing manufacturing schedules that impact any planned inspection dates.

Discussion Regarding Submission Timing

FDA commented that after submission of the new clinical information, only the standard 120-day safety update would be required. Amylin noted they could provide an update on all adverse events of interest after the cut-off date.

Amylin stated they could provide datasets and documents by the end of July 2012, however, they could not commit to that timeframe for submission of the immunogenicity data.

FDA noted that July 30, 2012, was no longer a critical time point for submission of clinical data. Rather, it was most important that the clinical amendment be complete.

Discussion with Office of Biotechnology Products

The Division of Therapeutic Proteins (DTP), Office of Biotechnology Products (OBP) referenced the email received from Amylin on July 11, 2012, containing a response to an information request sent by FDA on July 6, 2012. DTP noted that after reviewing the information, they could not identify the specific protocol to which data were referenced. DTP requested that Amylin identify the study in which each subject was enrolled when samples were drawn. In addition, DTP noted that the identification numbers for standard operating procedures (SOPs) could not be found.

Amylin responded that the SOPs were proprietary information and may not be provided by the laboratories conducting the assays. The company indicated they would try to provide this information and the SOPs would be available on inspection.

The teleconference ended.

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Madara, Patricia

From: Nguyen, Huy [Huy.Nguyen@amylin.com]
Sent: Wednesday, July 11, 2012 2:31 AM
To: Madara, Patricia
Cc: Hai, Mehreen
Subject: RE: BLA 125390 - request for information for July 11th teleconference
Importance: High
Attachments: Response to 06Jul12 FDA Request for Info_Final .docx; xls-antibody-NIH-10JUL2012.xls; xls-antibody-FHA101-10JUL12.xls; emfalert.txt

Hello Pat,

Follows is Amylin's response to the Agency's request for information. Each of FDA' question is being repeated here for your convenience:

1. **Please provide a table linking each individual clinical trial (NIH 991265, 20010769, Treatment IND FHA101 and additional patients treated after July 31st, 2009 cutoff date) with:**

- **treatment frequency and dosage.**
- **Metreleptin DP lot numbers used. Also, please indicate if and where in the electronic submission you have included the release data for the selected lots.**
- **Identification numbers of the screening, confirmatory and neutralization assays used in the assessment of anti-leptin binding and neutralizing antibodies for each trial together with corresponding SOPs.**

Amylin's response

Please refer to the attached table for information requested.

Additional patients treated after the July 31, 2009 cut-off date were enrolled in either NIH study 20010769 or Treatment IND FHA101. The information requested for these clinical trials is summarized in the table attached.

Bioanalytical reports (with their listed REST documents) contain the assay results requested above.

- Release data for the selected lots of DP used (referenced in the attached table) can be found in BLA 125390, Serial 0003, in Module 3.2.P.5.4, Batch Analysis (Metreleptin, Injection) (b) (4). Table 1 lists the Drug Product lots used in the clinical studies. Release data is provided in Tables 5-9.

2. **Please clearly point to the location of the validation reports for the immunogenicity assays (binding, confirmatory and neutralizing) that were used to test patient samples from clinical studies NIH991265, NIH 20010769, treatment IND FHA01 and additional patients dosed after the cutoff date of July 31st, 2010.**

Amylin's response

- For NIH Study 991265, Amgen assay methods, Validation Reports REST100236 and REST100239 can be found in BLA125390 Serial 0000, Module 5.3.1.4; Amylin assay methods, Validation Report REST070493R1, can be found in

BLA125390 Serial 0003, Module 5.3.1.4

- For NIH Study 20010769 (FHA906), Amgen assay methods, Validation Reports REST100241 and REST100239 can be found in BLA125390 Serial 0000, Module 5.3.1.4; Amylin assay methods, Validation Report REST070493R1 can be found in BLA125390 Serial 0003, Module 5.3.1.4
- For Amylin Study FHA101, Amylin assay methods, Validation Reports REST110276 and REST110170 can be found in BLA125390 Serial 0003, Module 5.3.1.4

3. **Please provide an excel document containing the patient ID number, type of lipodystrophy (acquired generalized, congenital generalized, acquired partial and familial partial), binding antibody titer and absence/presence of neutralizing antibodies for analysis.**

Amylin's response

Requested information is provided in 2 separate excel files, 1 for NIH studies 991265/20010769 (which were integrated for analysis) and 1 for Treatment IND FHA101.

Thanks,

Huy Nguyen

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Friday, July 06, 2012 5:05 PM
To: Nguyen, Huy
Cc: Longer, Mark
Subject: BLA 125390 - request for information for July 11th teleconference
Importance: High

BLA 125390 INFORMATION REQUEST

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for metreleptin. We are reviewing the chemistry module of the BLA and have the following requests for information:

CMC Immunogenicity-related questions:

Please provide a table linking each individual clinical trial (NIH 991265, 20010769, Treatment IND FHA101 and additional patients treated after July 31st, 2009 cutoff date) with:
treatment frequency and dosage.
Metreleptin DP lot numbers used. Also, please indicate if and where in the electronic submission you have included the release data for the selected lots.
Identification numbers of the screening, confirmatory and neutralization assays used in the assessment of anti-leptin binding and neutralizing antibodies for each trial together with corresponding SOPs.

Please clearly point to the location of the validation reports for the immunogenicity assays (binding, confirmatory and neutralizing) that were used to test patient samples from clinical studies NIH991265, NIH 20010769, treatment IND FHA01 and additional patients dosed after the cutoff date of July 31st, 2010.

Please provide an excel document containing the patient ID number, type of lipodystrophy (acquired generalized, congenital generalized, acquired partial and familial partial), binding antibody titer and absence/presence of neutralizing antibodies for analysis.

Huy, I know you are just returning to the office however, to the extent possible, please provide information prior to our teleconference scheduled for July 11, 2012.

nks for your help. **Please confirm receipt of this email.**

:erely;

Madara
ulatory Project Manager
ision of Metabolism and Endocrinology Products
ce of Drug Evaluation II
ter for Drug Evaluation and Research
03 New Hampshire Avenue
er Spring, MD 20993-0002
ne: 301-796-1249

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/s/

PATRICIA J MADARA
08/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

MEETING MINUTES

Amylin Pharmaceuticals, Inc.
Attention: Orville Kolterman, M.D.
Sr. Vice President, Chief Medical Officer
9360 Towne Centre Drive
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your "rolling" Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for metreleptin for injection.

We also refer to the teleconference between representatives of your firm and the FDA on May 30, 2012. The purpose of the meeting was to discuss the data FDA would require in order to file your BLA.

A copy of the official minutes of the telecom is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: May 30, 2012
Meeting Location: teleconference

Application Number: BLA 125390
Product Name: Myalept (metreleptin for injection)
Indication: **[**Insert indication]
Sponsor/Applicant Name: Amylin Pharmaceuticals

Meeting Chair: Mary H. Parks, M.D.
Meeting Recorder: Patricia Madara

CDER Attendees

Office of New Drugs; Office of Drug Evaluation II

Lee Ripper	Associate Director for Regulatory Affairs

Office of New Drugs; Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D.	Director
Mary Roberts, M.D.	Medical Officer
Patricia Madara, M.S.	Regulatory Project Manager

Office of Pharmaceutical Science; Office of Biotechnology Products; Division of Therapeutic Proteins

Laura Salazar-Fontana, Ph.D.	Quality Reviewer

Amylin Attendees

Orville Kolterman, M.D.	SVP & Chief Medical Officer
Jean Chan, M.D.	Director, Medical Development
Huy Nguyen	Associate Director, Regulatory Affairs

Background

Development of metreleptin (recombinant-methionyl human leptin) began in 1996, under IND 50,259, as a treatment for multiple indications. On August 22, 2001, the drug was granted orphan status for two indications: 1) treatment of metabolic disorders secondary to lipodystrophy and 2) treatment of leptin deficiency secondary to generalized lipodystrophy and partial familial lipodystrophy. Lipodystrophy is a rare disease that may be inherited or acquired. It is characterized by metabolic abnormalities, including insulin resistance, type 2 diabetes, hypertriglyceridemia, and steatohepatitis. There is currently no approved treatment for lipodystrophy.

On October 17, 2007, a guidance meeting was held to discuss submission of an NDA for metreleptin for treatment of lipodystrophy. Treatment IND 101824 was opened on May 19, 2008 to provide a mechanism whereby metreleptin could be provided to all patients who meet select criteria for lipodystrophy until metreleptin became an approved therapy.

On October 12, 2010 FDA notified Amylin that, in light of section 7002(e) of the Patient Protection and Affordable Care Act (Public Law No. 111-148), the appropriate marketing application for this proposed biological product would be a Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act. It should be noted that Amylin was granted a rolling review status for this BLA (previously considered an NDA) on July 30, 2010. The first portion of the application (BLA 125390), consisting of clinical and nonclinical modules, was submitted on December 15, 2010.

The "final" portion of the rolling BLA was submitted on April 2, 2012, containing the Quality module and additional clinical information. The FDA held a filing meeting on May 16, 2012. On May 17, 2012, the clinical reviewers, Drs. Golden and Roberts, held a brief, informal teleconference with Amylin to obtain clarification regarding submission of clinical data. Subsequently, FDA requested another brief teleconference with the company to discuss the data required in order to consider the application complete.

Discussion

FDA began by noting that the cut off date for clinical data was July 2009. Since that time, the number of lipodystrophy patients treated with metreleptin has increased significantly. FDA understands that some years ago, the Agency had agreed that data from a smaller number of patients (N=29) would be acceptable for submission of a BLA. However, at this time, the Division believes the data from the new patients is critical to conducting a complete, thorough review of metreleptin safety and efficacy.

Amylin noted that there were 17 new patients enrolled in the NIH studies and 18 new subjects in Amylin's treatment IND. Amylin stated that the information from new patients represented a small dataset and the safety profile of metreleptin had not changed with inclusion of these individuals.

FDA commented that, although the "N" of new patients was small, the total number of patients in the metreleptin lipodystrophy clinical development program was small and therefore each individual patient contributes a significant portion of the efficacy and safety data . Furthermore, it was the Division's role to determine, upon review of the additional data, if the overall efficacy and safety profile of metreleptin had been unaltered with the inclusion of new patients.

Amylin stated they were planning to include safety information from the 35 new patients in the 120-day safety update but efficacy information would not be included. Obtaining efficacy data from patients enrolled in the NIH trials may be difficult.

FDA acknowledged this difficulty but requested the submission of efficacy data from the 18 new patients enrolled in the treatment IND. This information was very relevant and important to a though review of the BLA.

In addition, submission of the immunogenicity datasets, as SAS transport files, for both the lipodystrophy and obesity programs were critical for the BLA review.

In summary, this rolling BLA would not be considered "complete" at this time and the PDUFA "clock" would not be started. The application would remain in a "rolling review" status and would not be considered "refuse-to-file."

Another teleconference would be planned to discuss the requirements for a complete clinical module in greater detail and the meeting ended

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/s/

PATRICIA J MADARA
07/31/2012

Madara, Patricia

From:	Madara, Patricia
Sent:	Sunday, July 22, 2012 5:26 PM
To:	'Nguyen, Huy'
Subject:	BLA 125390 (metreleptin) - additional requests for information
Importance:	High
Attachments:	BLA 125390 eff_saf request 7_20_12.doc; Proposed TOC for Clinical Addendum Update 18Jul2012_comments 7_20.docx

BLA 125390 **ADVICE**

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for MYALEPT (metreleptin for injection).

In addition, reference our July 11, 2012, teleconference held to discuss the clinical information required for your BLA to be considered complete. As mentioned at the meeting, we are providing additional details. Please see the attached list of requests for safety and efficacy data and our comments inserted into your proposed table of contents (TOC).

Please note that after receiving this information, we will still need to review the application before determining if it is complete.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Efficacy

- As per the 7/11 teleconference, efficacy data update will include the original patients, with data updated/refreshed at the new data cut, as well as data from newly enrolled patients
- As discussed at the 7/11 teleconference, refer to other sections of the BLA where appropriate for items not addressed in the efficacy update (e.g., Summary of Clinical Efficacy)
- Include the following in an easy-to-find chart or listing by patient: age; sex; race; country; type of lipodystrophy (including description of fat distribution/body composition, if available); height/weight/BMI; years of diagnosis; co-morbidities (including baseline HbA1c, TG, glucose; history of autoimmune disease; medications); baseline leptin concentration; baseline ALT/AST/liver volume; baseline urinary protein excretion
- To the extent possible, efficacy analyses should be conducted overall and by lipodystrophy type, age, sex, race, country of origin, baseline metabolic abnormalities (including the basis for inclusion: diabetes, elevated insulin, hypertriglyceridemia), relevant background medications (e.g., insulin, metformin, TZDs, fibrates), baseline leptin, leptin antibodies (presence/absence, titers), metreleptin dose, investigator (FHA101)
- Provide mean and categorical (% responders) results for efficacy parameters
- Include any new efficacy data available about starting/stopping metreleptin, with efficacy results presented graphically
- Discuss how compliance with dietary recommendations impacts efficacy
- Include updated line listings and efficacy datasets
- Figures should be updated with new data, including those presenting longitudinal data. Figures in which each patient is plotted separately in a single chart or plot are helpful to get a sense of the efficacy data variability.

Safety

- As per the 7/11 teleconference, safety data update will include the original patients, with data updated/refreshed at the new data cut, as well as data from newly enrolled patients.
- As discussed at the 7/11 t-con, a separate safety analysis should be done of pediatric patients to include standard assessments such as SAE, TEAE, but should also include information, if available, on growth and puberty as well as additional safety analyses requested in the following comments. Provide the rate per patient years in these analyses.
- Provide mean and categorical changes in vital signs for lipodystrophy and obese patients in the ISS (HR 5, ≥10, ≥15, ≥20 bpm at any time or at two consecutive visits, SBP ≥5 mmHg, ≥10 mmHg, ≥15 mmHg, ≥20 mmHg at any time or at two consecutive visits, DBP ≥5 mmHg, ≥10 mmHg, ≥15 mmHg, ≥20 mmHg at any time or at two consecutive visits). Also provide this analysis in subjects with hypertension at baseline. Include the n, %, and rate per PY

- Provide the mean (with standard error bars) change over time in vital signs graphically using the x axis to represent the visits. Provide the n of subjects at each time point. For lipodystrophy and obese ISS.
- Provide mean and categorical changes in clinical laboratory evaluations (for example number and %, and rate per PY of subjects (lipodystrophy and obese ISS) with serum creatinine values increasing by >0.3 mg/dL, shifts in proteinuria >1 g, >2 g from baseline, shifts in white blood cell count using clinically relevant cutoffs, n, %, rate per PY of hemoglobin < 12 g/dL).
- Provide the number and %, and rate per PY of subjects (lipodystrophy and obese ISS) with ALT or AST >3x ULN, 5x ULN, 10 x ULN
- Provide any instances of Hy's Law (see guidance on Drug Induced Liver Injury) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf
- Express extent of exposure in terms of patient-years exposure in the overall group, by sex, by type of lipodystrophy, and by age (<18 yo, ≥18 yo) in the lipodystrophy studies. Please also provide extent of exposure by patient-years in the ISS for the obese trials overall and by sex, hypertension, diabetes.
- Provide the source documents on any pregnancies including newborn examinations occurring in the lipodystrophy or obesity clinical trials
- Perform a search of the obese ISS and lipodystrophy datasets for the following MedDRA SMQ terms related to autoimmune diseases: anaphylactic reaction, angioedema, severe cutaneous reactions and provide the incidence and rates (per patient years) of these events by treatment group
- Provide the rate per patient years with TEAE, SAE, AE leading to withdrawal, other adverse events of interest such as immune related AE, pancreatitis, t-cell lymphoma, hepatitis, proteinuria in obese ISS and lipodystrophy subjects.
- Express the percentage and rate per patient years of patients who experienced hypoglycemia divided by serious and nonserious instances in the obese ISS and lipodystrophy trials
- Submit to the BLA updated narratives incorporating the previous information submitted to Agency regarding the 2 patients with T-cell lymphoma
- Submit to the BLA the completed study reports and associated datasets from the pramlintide + metreleptin program.
- See comments embedded in attached TOC for clinical addendum.

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/s/

PATRICIA J MADARA
07/22/2012

Madara, Patricia

From: Madara, Patricia
Sent: Friday, July 06, 2012 8:05 PM
To: 'Nguyen, Huy'
Cc: 'mark.longer@amylin.com'
Subject: BLA 125390 - request for information for July 11th teleconference

Importance: High

BLA 125390 INFORMATION REQUEST

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for metreleptin. We are reviewing the chemistry module of the BLA and have the following requests for information:

CMC Immunogenicity-related questions:

1. **Please provide a table linking each individual clinical trial (NIH 991265, 20010769, Treatment IND FHA101 and additional patients treated after July 31st, 2009 cutoff date) with:**
   a. **treatment frequency and dosage.**
   b. **Metreleptin DP lot numbers used. Also, please indicate if and where in the electronic submission you have included the release data for the selected lots.**
   c. **Identification numbers of the screening, confirmatory and neutralization assays used in the assessment of anti-leptin binding and neutralizing antibodies for each trial together with corresponding SOPs.**

2. **Please clearly point to the location of the validation reports for the immunogenicity assays (binding, confirmatory and neutralizing) that were used to test patient samples from clinical studies NIH991265, NIH 20010769, treatment IND FHA01 and additional patients dosed after the cutoff date of July 31st, 2010.**

3. **Please provide an excel document containing the patient ID number, type of lipodystrophy (acquired generalized, congenital generalized, acquired partial and familial partial), binding antibody titer and absence/presence of neutralizing antibodies for analysis.**

Huy, I know you are just returning to the office however, to the extent possible, please provide information prior to our teleconference scheduled for July 11, 2012.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
07/06/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125390

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
Suite 110
San Diego, CA 92121-3030

Attention: Orville Kolterman, MD,
Sr. Vice President, Chief Medical Officer

Dear Dr. Kolterman:

Please refer to your original Biologics License Application (BLA) dated and received December 15, 2010, submitted under section 351 of the Public Health Service Act, for Metreleptin, for Injection, 10 mg.

We also refer to your correspondence dated and received April 10, 2012, requesting review of your proposed proprietary name, Myalept. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Myalept, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 10, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Patricia Madara at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/05/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, June 27, 2012 2:58 PM
To: 'Nguyen, Huy'
Subject: RE: Request for Clarification
Importance: High

Hi Huy;

I have forwarded your proposals to the metreleptin review team. We are willing to use the documents sent on June 25th as the basis for an in-depth discussion on July 11th. However, the complete clinical package you describe MUST be received by FDA no later than the morning of July 30, 2012. We must conduct a cursory review in order to determine if your manufacturing site inspection can proceed as planned. Since the foreign site inspection is planned for mid August, July 30th is the very latest date we can receive the clinical package. Indeed, it would be greatly appreciated if you could submit it before July 30th. As emphasized previously, it is important that the data we receive is a complete clinical package, in order for the BLA to be filed and the inspection to proceed as planned.

Assuming you can submit a complete clinical module by July 30th and the manufacturing site inspection proceeds as originally scheduled, we have the following information request:

1. **Please provide the shipping validation study protocol and data to support shipping of drug substance from the Sandoz drug substance manufacturing site located at Kundl, Austria to the (b) (4) drug product manufacturing site located at (b) (4)**

2. **Please provide your microbial control strategy for the drug substance manufacturing steps. A justification for the in-process bioburden limits at the different manufacturing steps should be included.**

3. **Please clarify the steps of the manufacturing process that use (b) (4)**

Please contact me if you have any questions.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Nguyen, Huy [mailto:Huy.Nguyen@amylin.com]

Sent: Tuesday, June 26, 2012 2:05 PM
To: Madara, Patricia
Subject: RE: Request for Clarification

Hello Pat,

If the Agency accepts our proposal, we are currently targeting the middle of August to submit the proposed documents and supporting datasets as outlined in the documents I sent you yesterday.

Thanks,

Huy Nguyen

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Tuesday, June 26, 2012 10:56 AM
To: Nguyen, Huy
Subject: Request for Clarification
Importance: High

Hi Huy;

I am getting ready to forward your proposals to the metreleptin BLA review team. I understand they would serve as a basis for in-depth discussion at the 7/11 tcon. However, it would be much more informative if you could provide the date for submission of this information to FDA.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Nguyen, Huy [mailto:Huy.Nguyen@amylin.com]
Sent: Monday, June 25, 2012 9:25 PM
To: Madara, Patricia
Subject: RE: A follow up to our t-con yesterday morning regarding BLA125390
Importance: High

Hello Pat,

Please accept our sincere gratitude to Dr. Parks for accepting our request to submit "top line results" of the additional clinical information prior to our July 11th teleconference. Amylin understands that submission of this information would be used as a basis for our discussion only and would not constitute a fulfillment of FDA's request for additional data in order to consider the BLA complete for review. Upon further consideration, Amylin believes that it would be better to provide our proposal for the submission format of the additional data that

FDA's request during the May 30th teleconference. In this regard, submission of Amylin's proposal prior to the teleconference would serve to communicate our thinking process to the FDA in a transparent manner, and to provide the Agency with an adequate amount of time in advance of the teleconference to consider our proposal. We could then have an efficient and meaningful dialog at the teleconference and hopefully achieve agreement regarding the format for submission of this additional data. Attached herewith for the Agency's consideration are two MS Word documents:

1. A document outlining the proposed submission in a CTD Table of Content format. This document conveys the number of reports/analyses being proposed for submission and their locations within the CTD structure, indicates whether these reports/analyses are new or revised (as in a replacement of a previous submitted document), and provides the locations of datasets supporting these reports/analyses

2. A document containing the proposed Tables of Content for the actual reports being proposed for submission. These proposed reports would contain safety and efficacy analyses of refreshed data from the additional patients (17 patients for the NIH study and 18 patients for the FHA101 study) who enrolled after the data cuts used to create the December 2010 submission (Serial 0000 of the BLA).

We sincerely hope that the Agency will find our proposal acceptable and will accept our BLA for filing and begin your review process of the application. Additionally, we also hope that the Agency will consider continuing with inspectional activities of the Sandoz facility as previously planned if the Agency finds our proposed submission acceptable.

Sincerely,

Huy Nguyen

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Thursday, June 07, 2012 8:09 AM
To: Nguyen, Huy
Subject: RE: A follow up to our t-con yesterday morning regarding BLA125390
Importance: High

Hi Huy;

I have checked schedules at FDA yet again and July 11th is absolutely the first date available. Also, I have spoken to Dr. Parks and she agrees to submission of those top line results available prior to the 7/11/12 tcon. These would be used to supplement the discussion and would not be viewed as fulfilling our request for additional data. Also, at this tcon, it would be helpful if you could provide a timeframe for submission of the information / datasets requested earlier.

I will send a tentative list of attendees at a later date.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: Nguyen, Huy [mailto:Huy.Nguyen@amylin.com]
Sent: Tuesday, June 05, 2012 1:17 PM
To: Madara, Patricia
Subject: RE: A follow up to our t-con yesterday morning regarding BLA125390

Good morning Pat,

We would like to speak with the Agency a little bit sooner in order to resolve any outstanding issues pertaining to the Metreleptin BLA for filing purposes. However, we understand the challenge with scheduling a meeting for Agency personnel. We will accept the proposed date and time if it is not feasible for FDA to participate in this teleconference sooner.

Please let me know as soon as you can regarding the acceptability for Amylin to provide top line results (summary tables) of our data acquired in preparation of the 120-Day Safety Update submission, in advance of the 7/11 teleconference.

Thanks and best regards,

Huy Nguyen

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Friday, June 01, 2012 6:42 AM
To: Nguyen, Huy
Subject: RE: A follow up to our t-con yesterday morning regarding BLA125390

Hi Huy;

I have not had any response to your suggestions yet. With regard to the next tcon, I have found one date/one time. The difficulty is due to a combination of annual leave and the fact that required OBP reviewers will be away on inspections. Therefore, please let me know the acceptability of Wednesday, July 11th at 1 PM EDT.

Thanks for your help.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Nguyen, Huy [mailto:Huy.Nguyen@amylin.com]
Sent: Thursday, May 31, 2012 1:33 PM
To: Madara, Patricia
Subject: A follow up to our t-con yesterday morning regarding BLA125390

Hello Pat,

During the t-con that took place yesterday morning between Amylin and Agency personnel, the Agency inquired about whether raw datasets (XPT files) were submitted for the Clinical Addendum document in the April 2, 2012 BLA rolling submission (Serial 0003). Amylin indicated that we would verify this for the Agency. We have now been able to confirm that XPT files were not submitted with the Clinical Addendum document. What were submitted with this document were Supporting Data Summaries for this supportive document in the BLA. We do have the raw data for this and will plan to submit them to the Agency.

Additionally, there was a discussion regarding the need to have a follow up meeting between us. I imagine that you are currently trying to ascertain the availability of Agency personnel for this upcoming meeting. Please let me know when you have some proposed dates/times so we can plan for this meeting together. Being that the context of yesterday's meeting was regarding the need for FDA to receive data from additional patients of the NIH and FHA 101 studies to begin the review of BLA125390, we would like to propose for Amylin to send FDA top line results of what we have been able to acquired thus far in our process for preparation of the 120-Day Safety Update submission. These summary tables would offer a more robust view of the safety and efficacy profiles of Metreleptin, based on the what Amylin submitted in Serial 0000 of the rolling BLA submission and the refreshed data comprising of additional patients who have enrolled in these studies since the first data cuts. We believe that these data would be helpful for the upcoming discussion in term of setting the stage for an agreement between us regarding how we could collaborate in enabling the Agency to begin the review of this BLA. Please let me know what format you would like us to submit this information.

Thanks and best regards,

Huy Nguyen

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/s/

PATRICIA J MADARA
06/27/2012

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, May 22, 2012 10:32 AM
To: 'Nguyen, Huy'
Subject: BLA 125390 - request for clarification

Importance: High

BLA 125390 INFORMATION REQUEST

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for MYALEPT (metreleptin for injection).

In addition, we reference our email request for information sent on May 2, 2012 and your response dated May 18, 2012. We have reviewed your amendment and have the following requests for clarification.

- **On May 18, 2012, you submitted CSRs for study Lept-950272 and study Lept-970171.** (b) (4) [redacted]

- **Please clarify:**
  1) Are you planning to send an updated label (b) (4) [redacted]
  2) Are you planning to submit study Lept-970121 (b) (4) [redacted] **)? If you plan to submit study Lept-970121, please provide a timeframe.**

Thanks for your help. You may respond by email but submit all new information officially to the BLA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
05/23/2012

Madara, Patricia

From: Madara, Patricia
Sent: Monday, May 14, 2012 12:01 PM
To: 'Nguyen, Huy'
Cc: Madara, Patricia
Subject: RE: BLA 125390 - Request for Information
Importance: High

Hi Huy;

A couple of questions regarding BLA 125390:

1. Can you provide an estimated timeframe for response to the request below.

2. Can you please clarify if clinical study FHA906 is the same as NIH 991265-20010769.

Thanks for your help. Please confirm receipt.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Nguyen, Huy [mailto:Huy.Nguyen@amylin.com]
Sent: Wednesday, May 02, 2012 3:12 PM
To: Madara, Patricia
Subject: RE: BLA 125390 - Request for Information

Hello Pat,

I acknowledge receipt of the Information Request below.

Best regards,

Huy Nguyen

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Wednesday, May 02, 2012 11:27 AM
To: Nguyen, Huy
Cc: Madara, Patricia

Subject: BLA 125390 - Request for Information
Importance: High

BLA 125390 INFORMATION REQUEST

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Hi Huy;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for metreleptin.

We are beginning to review your BLA and have the following request for additional information or clarification.

Please submit the complete final study reports for any relevant clinical pharmacology studies, especially studies used to support PK information described in the package insert. If these data have been submitted, please provide their location within your application.

nks for your help. This information should be officially submitted to the BLA. **Please confirm receipt of this email.**

:erely;

Madara
ulatory Project Manager
ision of Metabolism and Endocrinology Products
ce of Drug Evaluation II
ter for Drug Evaluation and Research
03 New Hampshire Avenue
er Spring, MD 20993-0002
ne: 301-796-1249

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/s/

PATRICIA J MADARA
05/14/2012

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, April 12, 2012 10:24 AM
To: 'Nguyen, Huy'
Cc: Chiang, Raymond
Subject: BLA 125390 (metreleptin) - questions and requests for information

Importance: High

Hi Huy;

All the disciplines are starting to look thru the metreleptin BLA and I have the following requests for clarification.

1. Did Amylin conduct a Human Factors Study for use of metreleptin. If yes, was it included in your BLA submission. I am thinking that you did not conduct one since we never saw a protocol but please confirm.

2. If possible can you send hard copies of the "Instructions for Use" booklet. You should send them directly to me at the address below. Also, the Patient Labeling Team is wondering if you plan to submit a "more traditional" version of the IFU (i.e. as part of the label).

3. Finally, please note that I will be out of the office next week but will be accessing email. I will be able to respond within a day or two. In case of dire emergency only, you can contact:

Raymond Chiang, MPT, MS, MS
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1940

Please let me know if you have any questions. I will be in the office this Friday. Thanks for your help with these requests.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125390/0

BLA ACKNOWLEDGEMENT
December 30, 2010

Amylin Pharmaceuticals, Inc.
Attention: Orville Kolterman, M.D.
Sr. Vice President, Chief Medical Officer
9360 Towne Centre Drive
San Diego, CA 92121

Dear Dr. Kolterman:

We have received your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: metreleptin

Date of Application: December 15, 2010

Date of Receipt: December 16, 2010

Our Submission Tracking Number (STN): BLA 125390/0

Proposed Use: treatment of inherited or acquired lipodystrophy (not associated with HIV)

We have received your application submitted under Section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 356) for review of an incomplete application for a Fast Track Product. We acknowledge your schedule for submission of the remaining portions of this application. In accordance with provision (c) of the act, our review clock will not start until the date on which you submit the final portion and inform us that your application is complete.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-1249.

Sincerely,

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	June 7, 2010
Meeting Location:	teleconference
Application Number:	IND 101824
Product Name:	Metreleptin
Indication:	Congenital or acquired lipodystrophy, not associated with HIV
Sponsor/Applicant Name:	Amylin Pharmaceuticals, Inc.
Meeting Chair:	Eric Colman, M.D.
Meeting Recorder:	Patricia Madara

FDA Attendees

Office of Drug Evaluation, Immediate Office

Anne Pariser, M.D.	Acting Associate Director for Rare Diseases
Kay Schneider, M.S.	Project Manager

Office of Drug Evaluation II

Leah Ripper	Associate Director for Regulatory Affairs

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Julie Golden, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Nonclinical Pharmacology/Toxicology Team Leader
Enid Galliers	Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Jayabharathi Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment; Division of Pre-Marketing Assessment I

Suong Tran, Ph.D.	CMC Lead, Branch 7
Muthukumar Ramaswamy, Ph.D.	Quality Reviewer, Branch 7

Office of Regulatory Policy; Division of Regulatory Policy I

Janice Weiner, J.D., M.P.H.	Regulatory Counsel

Office of Orphan Products Development

Mathew Thomas, M.D.	Medical Officer

Amylin Pharmaceuticals Attendees

Alix Alderman	Director, Regulatory Affairs
Jean Chan, M.D.	Director, Medical Research
Brenda Cirincione, Ph.D.	Director, Quantitative Pharmacology and ADME
Carole Evans	Director, Regulatory CMC
Julia Feliciano, J.D.	Vice President, Legal Commercial
Carla Hekman, Ph.D.	Associate Director, Pharmaceutical Research & Development
Rob Johnson, Ph.D.	Director, Product Development
Mark Longer, Ph.D.	Senior Director, Regulatory Affairs
Sandra Matsumoto, Ph.D.	Manager, Regulatory Affairs
Christine Mendoza, Ph.D.	Principal Scientist, API Development
Denis Roy, Ph.D.	Senior Director, Nonclinical Drug Safety
Irina Yushmanova, M.D.	Director, Global Safety

Background

Under IND 101824, Amylin Pharmaceuticals is developing metreleptin (recombinant methionyl human leptin) for treatment of lipodystrophy. Lipodystrophy is a rare disease that may be inherited or acquired. It is characterized by metabolic abnormalities, including insulin resistance, type 2 diabetes, hypertriglyceridemia, and steatohepatitis. There is currently no approved treatment for lipodystrophy.

IND 101824 is a treatment IND that provides a mechanism whereby metreleptin is provided to patients who meet select criteria for lipodystrophy.

The sponsor requested this Type C meeting to discuss the possibility of submitting portions of its lipodystrophy application at varying times (i.e., rolling review). The Agency granted the teleconference to obtain more details related to the timing for submission of each portion.

Discussion

The FDA began with an opening comment regarding submission of the application for rolling review. FDA noted that while this course was probably acceptable, the Agency could not provide a definitive response until after an internal meeting scheduled for mid-July.

FDA asked at what point Amylin planned to start using metreleptin manufactured by Sandoz in clinical studies. The sponsor stated that they hoped to begin as soon as Sandoz is qualified as a manufacturing site. Amylin also noted that they had already provided a partial response related to the required CMC data and are currently completing additional chemistry studies and the 28 day toxicology study. In summary, Amylin plans to submit the toxicology report and remaining CMC information by the third quarter of 2010.

FDA asked about the timing of submission of clinical information for patients exposed to Sandoz drug product, including those initially treated with Sandoz material and those transitioned from Amgen material. The sponsor commented that they would submit this information by the fourth quarter of 2011. All patients being treated under the NIH protocol would be transitioned to the Sandoz product. The sponsor estimates that there are at least 10 more patients for whom treatment would be initiated in the near future. Depending on the timing of the submission of qualification information on the Sandoz manufacturing site and of FDA's review of the information, some or all of these new patients would be naive to treatment prior to starting use with Sandoz drug product.

FDA asked if Amylin would be able to obtain safety and efficacy data for the Sandoz material under the treatment IND. The firm responded that they would be collecting this information.

FDA thanked Amylin for their clarification and reiterated that a final response regarding submission of portions of the application for a rolling review should be possible by approximately mid-July.

Amylin thanked the Agency and offered to provide any additional information that might be needed in the future.

The meeting ended.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-101824	GI-1	AMYLIN PHARMACEUTICALS INC	Metreleptin

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/s/

PATRICIA J MADARA
07/09/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101824

MEETING MINUTES

Amylin Pharmaceuticals, Inc.
Attention: Orville Kolterman, M.D.
Sr. Vice President, Research and Development
9360 Towne Centre Drive
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for metreleptin.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	October 17, 2007
TIME:	10 AM – 11:30 AM
LOCATION:	White Oak Campus, Silver Spring, MD
APPLICATION:	IND 50,259
DRUG NAME:	metreleptin (recombinant-methionyl human leptin)
TYPE OF MEETING:	Type C; guidance

MEETING CHAIR: Eric Colman, M.D.

MEETING RECORDER:

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Division Director
Julie Golden, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader
John Gong, Ph.D.	Pharmacology/Toxicology Reviewer
Pat Madara, M.S.	Regulatory Project Manager

Division of Biometrics II

Janice Derr, Ph.D.	Statistical Reviewer @ DMEP

EXTERNAL CONSTITUENT ATTENDEES:

Amylin Pharmaceuticals, Inc

Alix Alderman	Associate Director, Regulatory Affairs
Simon Bruce, M.D.	Senior Director, Clinical Development
Michael Kim	Director, Regulatory Affairs
Sandra Matsumoto, Ph.D.	Manager, Regulatory Affairs
Christine Mendoza, Ph.D.	Principal Development Scientist, Product Development
Nico Pannacciulli, M.D., Ph.D.	Senior Clinical Scientist, Clinical Research
Lisa Porter, M.D.	Vice President, Clinical Development
Denis Roy, Ph.D.	Director, Nonclinical Drug Safety
Reshma Shringarpure, Ph.D.	Senior Medical Writer, Medical Writing
Christian Weyer, M.D.	Executive Director, Clinical Research
Phillip Gorden, M.D.	Clinical Consultant Investigator, Molecular and Cellular Physiology Section NIH/NIDDK, Clinical Endocrinology Branch

Background

Under IND 50,259, metreleptin (recombinant-methionyl human leptin) is being developed as a treatment for multiple indications. On August 22, 2001, IND 50,259 was granted orphan status for two indications: 1) treatment of metabolic disorders secondary to lipodystrophy and 2) treatment of leptin deficiency secondary to generalized lipodystrophy and partial familial lipodystrophy.

On May 16, 2001, an End-of-Phase 2 meeting was held between the former sponsor (Amgen) and DMEP. The current sponsor, Amylin Pharmaceuticals, assumed responsibility for this IND on March 3, 2006.

The purpose of this Type C guidance meeting was to confirm Amylin's interpretation of the EOP2 meeting minutes and to obtain DMEP guidance related to updated preclinical and clinical information for lipodystrophy.

Amylin submitted three specific questions for discussion. Draft pre-meeting responses were sent to the firm on October 12, 2007. Those responses are repeated below in normal font while additional comments made by Amylin at the meeting are in *italics*. Additional comments from FDA (made at the meeting) are in **bold** font.

Finally, Amylin provided additional explanatory background information at the meeting (slide presentation, handout). That document is attached to these minutes.

Questions and Answers

Question 1:

Does the Agency agree that the clinical safety and efficacy data on the 29 NIH enrolled subjects provided in Section 11 are sufficient to support an NDA filing for the orphan indication proposed above (Section 3)?

DMEP Response

At issue is whether your proposed indication is intended to include patients with HIV-associated lipodystrophy or lipoatrophy. Given that the number of patients with HIV-related lipodystrophy, metabolic derangements, and low leptin levels is presumably much larger than the number of patients with inherited or acquired lipodystrophy (other than HIV-related), we will need to discuss your plans regarding further study of this subgroup of patients.

We note that Dr. Garg estimates that in 2004 there were at least 100,000 patients with HIV-related lipodystrophy in the U.S. (Garb A. Acquired and inherited lipodystrophies. N Engl J Med 2004;350:1220). We request that you provide us with an updated estimate of the size of the population of patients with HIV-related lipodystrophy who would be appropriate candidates for treatment with leptin.

Additional Amylin Comment

The sponsor commented that they had no plans to include an indication for treatment of HIV related lipodystrophy in the NDA. They noted that while there is compelling evidence for metreleptin safety and efficacy in the non-HIV severe lipodystrophy (SLD) population, the HIV-related population is more diverse and effectiveness of treatment with metreleptin is not well established.

The patients with non-HIV related SLD treated with metreleptin represent all the various subtypes of lypodystrophy with the majority having generalized inherited or acquired severe lipodystrophy. These patients are representative of the epidemiology of the disease, although a few groups may be underrepresented.

Amylin's consultant, Dr. Phillip Gordon, believes an estimate of 1,000 patients in the U.S. is a "guess" but Amylin believes this is a fairly accurate number.

Amylin asked DMEP if the Agency would agree that the clinical safety and efficacy data on the 29 NIH enrolled subjects are sufficient to support an NDA filing for the orphan indications, given that they do not intend to seek an HIV-related lipodystrophy indication.

Additional DMEP Comment

The numbers of patients in your database are sufficient for an NDA that does not include an indication for treatment of HIV-related lipodystrophy.

Question #2

Does the Agency concur that the available nonclinical data (Section 15) are adequate to support an NDA filing for metreleptin in the above-mentioned orphan indication?

DMEP Response

As documented in the minutes from the 2001 EOP2 meeting, we requested PCNA staining of tissues from the 6 month mouse and dog toxicology studies with metreleptin. You indicate that PCNA analysis was completed for the 6 month dog and 1 month mouse studies. We do not consider one month an adequate dosing period for assessment of proliferative biomarkers in rodents. Please provide PCNA analysis of the tissue types listed in your background package for the 6 month mouse study to support filing of the NDA. We also wish to confirm that tissues from males and females have been evaluated.

Additional Amylin Comment

We do not have 6-month mouse PCNA data, however, we do have male and female dog data that would be submitted with the NDA. Given that we do not intend to include patients with HIV-associated lipodystrophy in the proposed indication, does the Agency agree that the available nonclinical data are adequate to support an NDA filing for the proposed orphan indications?

Additional DMEP Comment

No additional PCNA data will be required for the proposed orphan indications only.

Question #3

No additional discussion.

Additional Statistical Comment

The graphs shown in Figure 3 (page 43) and Figure 5 (page 84) of the briefing document are very helpful. You should present your data in the same manner when submitting the NDA.

8 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

Linked Applications	Sponsor Name	Drug Name
IND 50259	AMYLIN PHARMACEUTICALS INC	RECOMBINANT-METHIONYL HUMAN LEPTIN

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/s/

PATRICIA MADARA
11/19/2007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 50,259

Amgen Inc.
Attention: Dean Waters
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Waters:

Please refer to the meeting between representatives of your firm and FDA on May 16, 2001. The purpose of the meeting was to review results of the ongoing clinical trial (Study 991265) of (b) (4) A-100 in patients with severe metabolic disorders associated with lipodystrophy and to reach agreement between FDA and Amgen on the proposal for Phase 3 development and NDA filing of (b) (4) for treatment of lipodystrophy.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-480-8174.

Sincerely,

{See appended electronic signature page}

James T. Cross
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 16, 2001

TIME: 9:30am

LOCATION: Parklawn Conference Room K

APPLICATION: 50, 259/Recombinant-Methionyl Human Leptin, A-100

TYPE OF MEETING: End-of-Phase 2

MEETING CHAIR: David G. Orloff, M.D., Division Director

MEETING RECORDER: James Cross, M.S., Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division of Metabolic and Endocrine Drug Products (HFD-510)
1. David Orloff, M.D.	Division Director	
2. Kati Johnson, R.Ph.	Chief, Project Management Staff	
3. Eric Colman, M.D.	Medical Team Leader	
4. Jeri El-Hage, Ph.D.	Pharmacology/Toxicology Team Leader	
5. James Cross, M.S.	Regulatory Project Manager	
6. William Koch, R.Ph.	Regulatory Project Manager	
7. Patricia Beaston-Wimmer, M.D., Ph.D.	Medical Reviewer	
8. Bruce Schneider, M.D.	Medical Reviewer	
9. John Gong, Ph.D.	Pharmacology/Toxicology Reviewer	
Name of FDA Attendee	**Title**	**Office of Clinical Pharmacology and Biopharmaceutics (HFD-850)**
1. Hae-Young Ahn, Ph.D.	Team Leader	
2. Jim Wei, M.D., Ph.D.	Reviewer	

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Amgen Inc.
1. William Sheridan, M.D.	Vice President, Product Development	
2. Steve Swanson, Ph.D.	Director, Clinical Immunology	
3. Carl Lebel, Ph.D.	Associate Director, Product Development	
4. Alex DePaoli, M.D.	Associate Director, Clinical Research	
5. Donna Peterson	Associate Director, Regulatory Affairs	
6. Dean Waters	Manager, Regulatory Affairs	
		(b) (4)

BACKGROUND:

IND 50,259 for Recombinant-Methionyl Human Leptin, A-100 Injection (A-100) for the treatment of obesity was submitted March 29, 1996. Amgen has since pursued development of A-100 for the treatment of metabolic disorders associated with lipodystrophy. According to the firm, severe lipodystrophy is an extremely rare disease for which current therapies are inadequate. Leptin is a naturally occurring hormone found in adipose cells which has effects on appetite, and triglyceride and glucose utilization. The firm provided information on two types of leptin deficiency– primary and secondary. Primary leptin deficiency involves a genetic defect in which leptin is absent, resulting in a modest increase in appetite and triglyceride and glucose utilization. Secondary leptin deficiency involves a defect in the adipose tissue which produces leptin, leading to large increases in appetite, triglyceride and glucose utilization, and severe hepatomegaly. Amgen is conducting two ongoing Phase-2 studies for the lipodystrophy indication.

Amgen requested an End-of-Phase 2 meeting on March 20, 2001. A background package was submitted to IND 50,259 on April 16, 2001.

TODAY'S MEETING:

The firm provided a brief presentation on their ongoing Phase 2 studies:

1. *Study 991265*, an open label study enrolling 9 patients with low leptin levels and lipoatrophic diabetes treated with A-100 for 8 months. The firm stated that this NIH study was initiated at the same time the development program in obesity was discontinued. According to the firm, fasting glucose and triglyceride levels declined substantially (to the upper normal limit in some patients) following approximately 1-5

months of therapy. Four of the 9 patients enrolled were aged 15-17 years. The firm stated that the clinical response in these children was consistent with that seen in adults.

2. *Study 970161*, an open label, multiple ascending dose study enrolling 4 pediatric patients with congenital leptin deficiency. Data of up to three months were provided in the meeting package.

In response to a question from the Agency, the firm stated that the dose selected for each patient is based on age, gender, and body weight.

MEETING OBJECTIVES:

1. To review results of the ongoing clinical trial (Study 991265) of r-metHuLeptin, A-100 in patients with severe metabolic disorders associated with lipodystrophy.
2. To reach agreement between the Division and Amgen on the proposal for Phase 3 development and NDA filing of r-metHuLeptin for treatment of lipodystrophy.

DISCUSSION POINTS:

1. Does the FDA agree that ongoing Study 991265 is acceptable as an adequate pivotal trial for filing an NDA given the rare nature of this life-threatening disease?

   Agency Response:
   - In general, yes, assuming that the indication is narrowed to a very specific population such as treatment of lipodystrophic conditions associated with metabolic abnormalities. A pivotal study implies that additional supporting data are available, such as a study in which withdrawal of treatment in patients followed by deterioration is then reversed with re-initiation of therapy. The Agency emphasized that it does not want this drug to be used broadly off-label, such as in AIDS patients, when only nine patients with specific disorders associated with low endogenous leptin levels have been studied for any reasonable period of time. If leptin is eventually approved for the treatment of lipodystrophic conditions, this issue may be addressed through appropriate drug distribution mechanisms.

2. Is the proposed clinical data package for r-metHuLeptin acceptable and sufficient for the indication/claim being sought?

   Agency Response:
   - It appears acceptable for filing a NDA.
   - The Division requested PK data correlated with changes in injection site. The sponsor stated that the proposed package insert does not comment on the site of injection.

3. Is the overall r-metHuLeptin clinical safety package acceptable to support an NDA filing?

   According to the firm, approximately 1150 patients have received the drug. In addition to the studies already discussed, approximately 1140 patients have received the drug in obesity and diabetic studies.

   Agency Response:
   - It appears acceptable.

4. Based on the data proposed for the NDA, Amgen plans to seek an indication that includes all ages of the pediatric population. Is this proposal acceptable?

   Agency Response:

   - Although there are very limited data available in patients 16 years and younger, it would appear acceptable that the compound would be labeled for the entire pediatric patient population without specifically mentioning the age ranges in the "Indications" section of the labeling. A "Pediatrics Use" subsection of the labeling might describe the effects observed in pediatric patients without statements of strong support of safety/efficacy in this population.

5. Is the preclinical data package adequate to support an NDA filing?

   Agency Response:

   - The Division stated that the preclinical package was adequate to support a limited, well-defined indication for leptin deficient, severe lipodystrophic subjects in the labeling.
   - If Amgen plans to seek use in a broader population (e.g., HIV-related lipodystrophy patients), then PCNA staining of tissues from the six-month chronic dog and mouse studies would be required.

6. Is the proposed indication acceptable? The firm's proposed indication is as follows: (b) (4)

   (b) (4)

   Agency Response:

   - Given that we have not reviewed any data, it is premature at this time to determine the precise indication(s) for this compound.

7. Amgen believes that the medical benefits provided by leptin replacement therapy in patients with primary or secondary leptin deficiency represent significant improvements over existing therapies. Will FDA grant priority review status to the NDA?

   Agency Response:

   - FDA cannot state what the review status would be at this time. The decision as to whether an application warrants a priority review is made upon receipt of an application. The priority status of an application is not final until the filing date (60 days following receipt of the application).
   - If a priority review is requested, Amgen should ensure that the NDA is as complete as possible upon submission, since any amendment has the potential to extend the review clock.
   - In response to Amgen's question about sending safety updates during a priority review, it was said that Amgen can simply state there is nothing new to report if there are no ongoing studies.

MISCELLANEOUS COMMENTS:

1. In response to a question from the Division, the firm replied that there do not appear to be any pharmacokinetic differences by gender.

2. The Division asked why the dosing interval has changed from daily dosing in Phase 1 trials to BID dosing in Phase 2 trials. According to the sponsor, the BID dosing regimen more closely follows the circadian cycle of leptin levels found in normal subjects and added that the dose is not sufficiently large to require multiple daily administration. The firm also added that they want to investigate, in later studies, as to whether a QD regimen is a viable dosing interval.

3. The Division also asked whether the injection site for A-100 requires rotation. According to the firm, the package insert will not recommend rotation of injection sites. The firm said that they expect a more subtle titration regimen (based on response to previous dose). The Division responded that such expectations in the nature of the titration regimen need to be reflected in the drug label.

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/s/

James Cross
7/25/01 03:55:00 PM

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

LATE-CYCLE MEETING MINUTES

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Attn: Kinnari Patel, Pharm.D, R.Ph.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin for injection).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 20, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time:	November 20, 2013; 3:00 PM – 4:30 PM
Meeting Location:	White Oak Building 22, Conference Room Number: 1309 10903 New Hampshire Avenue Silver Spring, MD 20903
Application Number:	BLA 125390
Product Name:	Myalept (metreleptin for injection)
Sponsor/Applicant Name:	Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb Company)
Meeting Chair:	Eric Colman, M.D.
Meeting Recorder:	Patricia Madara

Office of New Drugs; Program for Rare Diseases

Larry J. Bauer	Regulatory Scientist

Office of New Drugs; Office of Drug Evaluation II

Mary H. Parks, M.D.	Deputy Director
Sara Stradley, Pharm.D.	Administrative Director for Regulatory Affairs

Office of New Drugs; Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy Egan, M.D., MPH	Deputy Director for Safety
James P. Smith, M.D., M.S.	Clinical Team Leader
Julie Golden, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Nonclinical Team Leader
Federica Basso, Ph.D.	Pharmacology/Toxicology Reviewer
Julie Van der Waag, MPH	Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Immo Zadezensky, Ph.D.	Clinical Pharmacology Team Leader
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer

Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment; Biotech Manufacturing Assessment Branch

Patricia Hughes, Ph.D.	Team Leader
Kalavati Suvarna, Ph.D.	Quality Microbiology Reviewer
Steven Fong, Ph.D.	Quality Microbiology Reviewer

Office of Pharmaceutical Science, Office of Biotechnology Products, Division of Therapeutic Proteins

Susan Kirshner, Ph.D.	Associate Laboratory Chief
Laura Salazar-Fontana, Ph.D.	Quality Reviewer
Ennan Guan, Ph.D.	Quality Reviewer
Cecilia Tami, Ph.D.	Quality Reviewer
Montserrat Puig, Ph.D.	Quality Reviewer

Office of Biostatistics; Division of Biometrics II

Mark Rothmann, Ph.D.	Team Leader
Bradley McEvoy, Ph.D.	Statistical Reviewer

Office of Surveillance and Epidemiology

Margarita Tossa	Safety Regulatory Project Manager

Office of Medication Error Prevention and Risk Management; Division of Risk Management

Cynthia LaCivita, Pharm.D.	Team Leader
Suzanne Robottom, Pharm.D.	Risk Management Analyst

Eastern Rearch Group Attendees

(b) (6)	Independent Assessor

Applicant Attendees (BristolMyers Squibb / Astrazeneca

Elisabeth Bjork, M.D.	Head of CV and Metabolism Global Medicine Development, Astrazeneca
Jean Chan, M.D.	Medical Director, BMS
Brenda Cirincione, M.S.	Director, Pharmacometrics, BMS
Fred Fiedorek, M.D.	Senior Vice President, Head of Development – Cardiovascular & Metabolics, BMS
Rob Johnson, Ph.D.	Senior Director, Pharmaceutical R&D, BMS
Sanchali Kasbekar, Pharm.D.	Rutgers Post-Doctoral Fellow, Global Reg Sciences, BMS
Joy Koda, Ph.D.	Senior Director, Medical Development, BMS
Nancy Kribbs, Ph.D.	Director, Global Regulatory Sciences, BMS
Joseph Lamendola, Ph.D.	Vice President, US Regulatory Sciences and Regulatory Policy, BMS
Karen Lutz, Ph.D.	Director, Medical Research, BMS

Peter Ohman, M.D.,Ph.D.	Executive Director, Medical Development, Astrazeneca
Kinnari Patel, Pharm.D.	Associate Director, US Regulatory Liaison, BMS
James Pratt, Ph.D.	Associate Director, Biostatistics, BMS
John Roth, Ph.D.	Executive Director, Global Regulatory Sciences – Metabolics, BMS
Denis Roy, Ph.D.	Non-clinical Drug Safety & Comparative Medicine, BMS Consultant
Larry Shen, Ph.D.	Vice President, Medical R&D QSMD, BMS
Annie Sturgess, Ph.D.	Executive Director, CMC Biologics, BMS
Mary Whealy, Ph.D.	Director, Global Regulatory Affairs, Astrazeneca
Mark White, M.D.	Vice President, Product Development, Astrazeneca
Helen Yu, M.D.,Ph.D.	Medical Director, Global Safety, BMS

1.0 Background

Proposed indication(s): 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.

PDUFA goal date: February 24, 2014

FDA issued a Background Package in preparation for this meeting on November 12, 2014.

2.0 Discussion

1. Discussion of Substantive Review Issues

   Each issue will be introduced by FDA and followed by a discussion.

   - Efficacy
   - Safety
   - Product Quality Microbiology
   - Chemistry

Discussion:

The Applicant thanked the Agency for the meeting and for the briefing document. They noted that they understood the challenges faced by the review team due to the study design and lack of a control arm.

FDA reiterated the difficulty reviewing the data due to the single arm design, lack of placebo and background of changing concomitant medications.

2. Information Requests

Clinical

- The status of fasting insulin, c-peptide, measures of insulin sensitivity (OGTT, insulin tolerance test), RMR / REE, hypothalamic-pituitary-gonadal / -thyroid / -adrenal axes, and 24hr urine protein and creatinine analyses and assessments, using the most recent data cut, as requested in the mid-cycle meeting minutes.
- Update on NIH Patient 90164: Category E neutralizing antibodies with 5 recent hospitalizations for bacteremia/sepsis
- Overall "sepsis" assessment
- Clarification requested on CRF errors/changes
- Renal adverse event / CPK query follow-up
- Psychiatric adverse events

Discussion:

The Applicant noted they were working to provide the information requested. Responses will be submitted as soon as possible.

Microbiology

- Provide the results of endotoxin recovery studies as described in our information request issued on November 8, 2013.

Discussion:

FDA noted that recent literature indicated endotoxin masking effects have been observed with certain protein formulations containing polysorbate. Therefore the Agency is requesting that companies determine if low endotoxin recovery effects are observed by conducting endotoxin spiking studies in undiluted drug product in the relevant containers. If necessary, a separate teleconference can be scheduled to discuss the best path forward.

Chemistry

- Provide an update on the status of the response to comment #6, sent in our information request issued on October 8, 2013, related to the validation of your immunogenicity assays.

Discussion:

The Applicant stated they thought this information had been submitted but would double-check the status.

FDA noted that there was considerable concern about the test results related to metreleptin stability in BWFI. It appeared that benzyl alcohol may adversely affect product stability and the Agency was unsure that BMS had an adequate understanding of the effect of benzyl alcohol on product stability or assay performance. FDA was having trouble understanding the conflicting data and test results and requested that the results be explained. Most of the

data provided on November 7, 2013, had been reviewed and the Agency was still having trouble understanding the test results.

BMS noted they had seen (b) (4) ***. The company has seen some data indicating*** (b) (4) ***but repeated the testing without getting the same results (compare data for lot 592053 in Table 30 of the original submission with Table 5-4 in the Sponsor's responses to our October 8, 2013 information request). They stated that benzyl alcohol contributes to the osmolality of the drug product. Since the purpose of the test is to determine whether the excipients had been formulated correctly osmolality is determined using water for injection. FDA and BMS agreed to have a separate T con to discuss whether additional information was needed at this time.***

3. Discussion of Upcoming Advisory Committee Meeting

Discussion:

BMS commented that they hoped the advisory committee would be provided background regarding the development of drugs to treat orphan diseases.

FDA noted that Drs. Brown and Gorden had been invited to the meeting. Dr. Gorden would be available to answer questions regarding the NIH protocols. Dr. Brown had been asked to give a presentation on lipodystrophy.

FDA stated they would discuss leptin's effects on the immune system and the potential implications of neutralizing antibodies to leptin on immune system homeostasis.

The issues that FDA would raise to the committee would include immunogenicity, lymphoma, efficacy (including the liver findings), and determination of the appropriate patient population for treatment.

BMS asked about FDA's concerns related to missing data. With respect to safety data, FDA did not have a lot of confidence in the completeness of the data collection due to the nature of the study design, in which patients traveled to the NIH from all over the country or world with often long durations between study visits. FDA noted that some adverse events were not captured or were reported some time after the event occurred. In some cases, patients did not return for follow up and outcomes were unclear. In addition, the interpretation of missing data was more difficult due to the lack of a placebo arm.

4. Postmarketing Requirements/Postmarketing Commitments

As conveyed to you in our Mid-Cycle Communication, postmarketing required studies and/or trials are still under discussion within the Agency. We will notify you of any postmarketing requirements by February 1, 2014.

Discussion:

FDA commented that postmarketing requirements and commitments would be sent to the company at a later date and they should not be discussed now. The Agency stated that concerns about low endotoxin recovery and the sensitivity of the neutralizing antibody assay might be addressed as postmarketing requirements / commitments.

5. Review Plans

- Review of responses to outstanding information requests
- Obtain feedback from Advisory Committee panel
- Completion of consults and tertiary reviews
- Completion of inspections
- Labeling discussions (as needed)

6. Wrap-up and Action Items

BMS will provide responses to outstanding information requests and these will be reviewed.

It should be noted that this application has not yet been fully reviewed by the signatory authority, division director, and cross-discipline team leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

ERIC C COLMAN
01/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

LATE CYCLE MEETING
BACKGROUND PACKAGE

Amylin Pharmaceuticals, LLC
(a subsidiary of Bristol-Myers Squibb Company)
Attn: Kinnari Patel, Pharm.D, R.Ph.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin for injection).

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 20, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	November 20, 2013; 3:00 PM – 4:30 PM
Meeting Location:	White Oak Building 22, Conference Room Number: 1309 10903 New Hampshire Avenue Silver Spring, MD 20903
Application Number:	BLA 125390
Product Name:	Myalept (metreleptin for injection)
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.
Sponsor/Applicant Name:	Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb Company)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

1 Clinical Data Supporting Efficacy and Safety. As we have previously conveyed at the mid-cycle meeting, the pivotal and supportive trials conducted to demonstrate safety and efficacy have provided many review challenges.

The study design and execution of the study protocols raises concern that the change in metabolic parameters that were observed may not reflect the true effect of metreleptin in the studied population. Confidence in these results is limited by:

- The single-arm design in a heterogeneous study population.
- Several patients increased use of diabetic and lipid-lowering medications during study follow-up. The accuracy of such usage is further limited by this information not being systematically collected during study follow-up. Furthermore, the guidance in Study 769 that concomitant medication was not to be increased appears to have been deliberately violated in order to maximize lipid and glycemic control with metreleptin (Protocol Amendment A, 2006).
- The degree of missing data in Studies 769 and 101.

We continue to have concerns that the safety profile of metreleptin has not been fully characterized. Determining the potential contribution of the drug to some of the adverse events (e.g., lymphoma) has been challenging. Additionally, we are trying to understand the clinical significance (safety and efficacy) of neutralizing antibodies in a patient population that is leptin-deficient, and how to appropriately monitor in the post-marketing setting. Confidence in the safety data is limited by:

- The single-arm design in a study population with many confounding co-morbidities
- Incomplete, delayed, or poorly documented adverse event reporting

2 Microbiology: Endotoxin Testing Methodology. The metreleptin drug product formulation contains excipients (e.g., polysorbate) that could result in low endotoxin recovery. You should provide results from studies conducted to assess if endotoxin recovery is affected by the polysorbate-containing Metreleptin drug product formulation. Undiluted drug product test samples should be spiked with endotoxin and satisfactory endotoxin recoveries should be demonstrated over time. The studies should be conducted in the same type of containers (e.g,

stainless steel formulation tank, glass vial) in which the product and samples are held prior to endotoxin testing. In the event that spiked endotoxin cannot be recovered from formulated drug product, a path forward must be found for endotoxin release testing of the drug product.

3 Chemistry: Based on our preliminary review of the information, we still have substantial concerns regarding the use of BWFI for reconstitution of metreleptin drug product. Please be prepared to discuss, with supportive data, the impact of Benzyl alcohol on metreleptin drug product quality attributes including but not limited to osmolality and (b) (4) (b) (4)

ADVISORY COMMITTEE MEETING

Date of AC meeting: December 11, 2013

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: November 20, 2013

Potential questions and discussion topics for AC Meeting are as follows:

We anticipate that AC members will be asked to discuss and vote on the overall risk-benefit of metreleptin for the proposed indication, as framed by the following considerations:

- The adequacy and strength of the efficacy data in the various lipodystrophy patient populations

- The adequacy and strength of the safety data, with particular emphasis on:
  - Lymphoma
  - Immunogenicity

We have discussed our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location: http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

REMS/RISK MANAGEMENT ACTIONS HAVE BEEN IDENTIFIED

FDA agrees that a REMS with elements to assure safe use is necessary to ensure that the benefits of metreleptin outweigh the risks of serious adverse sequelae caused by the development of neutralizing antibodies in non-lipodystrophy patients and lymphoma.

1 At this time we agree with the proposed elements including prescriber certification, pharmacy certification, and documentation of safe use conditions through a prescription authorization form.

2 We agree with your proposal to consider the Medication Guide part of labeling, not part of the REMS.

3 We expect on-going analysis of data provided in your BLA along with discussion at the December 11, 2013 EMDAC to inform further the risk mitigation strategy.

4 We expect to provide you more detailed comments and revisions on the REMS after the December 11, 2013 EMDAC.

LCM AGENDA

1. Introductory Comments

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

   Each issue will be introduced by FDA and followed by a discussion.

   - Efficacy
   - Safety
   - Product Quality Microbiology
   - Chemistry

3. Additional Applicant Data (Applicant)

4. Information Requests

   Clinical

   - The status of fasting insulin, c-peptide, measures of insulin sensitivity (OGTT, insulin tolerance test), RMR / REE, hypothalamic-pituitary-gonadal / -thyroid / -adrenal axes, and 24hr urine protein and creatinine analyses and assessments, using the most recent data cut, as requested in the mid-cycle meeting minutes.
   - Update on NIH Patient 90164: Category E neutralizing antibodies with 5 recent hospitalizations for bacteremia/sepsis
   - Overall "sepsis" assessment
   - Clarification requested on CRF errors/changes
   - Renal adverse event / CPK query follow-up
   - Psychiatric adverse events

   Microbiology

   - Provide the results of endotoxin recovery studies as described in our information request issued on November 8, 2013.

Chemistry

- Provide an update on the status of the response to comment #6, sent in our information request issued on October 8, 2013, related to the validation of your immunogenicity assay.

5. Discussion of Upcoming Advisory Committee Meeting

6. REMS or Other Risk Management Actions

7. Postmarketing Requirements/Postmarketing Commitments

   As conveyed to you in our Mid-Cycle Communication, postmarketing required studies and/or trials are still under discussion within the Agency. We will notify you of any postmarketing requirements by February 1, 2014.

8. Major labeling issues

Content of the following sections:

- Indication
- Warnings and Precautions
- Clinical Studies

9. Review Plans

- Review of responses to outstanding information requests
- Obtain feedback from Advisory Committee panel
- Completion of consults and tertiary reviews
- Completion of inspections
- Labeling discussions (as needed)

10. Wrap-up and Action Items

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

/s/

ERIC C COLMAN
11/12/2013