

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200677Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 200677

SUPPL # N/A

HFD # 510

Trade Name Signifor

Generic Name pasireotide injection

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known December 14, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES X NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES X NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES X NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO X

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO X

If yes, explain:

N/A

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study CSOM230B2305: A randomized, double-blind study to assess the safety and efficacy of different dose levels of pasireotide (SOM230) s.c. over a six-month treatment period in patients with de novo, persistent or recurrent Cushing's disease

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO X

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO X

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study CSOM230B2305: A randomized, double-blind study to assess the safety and efficacy of different dose levels of pasireotide (SOM230) s.c. over a six-month treatment period in patients with de novo, persistent or recurrent Cushing's disease

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 068635 YES X ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:
N/A

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO X

If yes, explain:

N/A

=====
Name of person completing form: Jennifer Johnson
Title: Regulatory Health Project Manager
Date: December 14, 2012

Name of Office/Division Director signing form: Mary H. Parks, M.D.
Title: Director, Division of Metabolism and Endocrinology Products

APPEARS THIS WAY ON ORIGINAL



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

/s/

JENNIFER L JOHNSON
12/18/2012

MARY H PARKS
12/18/2012

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

NDA/BLA#: 200677 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: Metabolism and Endocrinology Products (DMEP) PDUFA Goal Date: December 17, 2012 Stamp Date: 2/17/2012

Proprietary Name: Signifor

Established/Generic Name: pasireotide

Dosage Form: subcutaneous injection

Applicant/Sponsor: Novartis Pharmaceuticals Corporation

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) None
(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: treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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}

Jennifer Johnson
Regulatory Project Manager

(Revised: 6/2008)

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

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

/s/

JENNIFER L JOHNSON
12/18/2012

Debarment Certification

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Sandip Roy, PhD
Director, Drug Regulatory Affairs

February 17, 2012

Date

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Friday, November 30, 2012 5:44 PM
To: Roy, Sandip (sandip.roy@novartis.com)
Subject: NDA 200677 (Signifor): Carton/container labeling comments

Dear Sandip,

We have the following comments and recommendations from DMEPA regarding your carton and container labels submitted to NDA 200677 on February 17, 2012. Please note that we may have further comments later on but wanted to send what we have as of now:

All Carton Labels:

1. Relocate the strength statement to immediately follow the established name statement.

For example:

Signifor
(pasireotide)

(b) (4)

0.9 mg/1 mL

2. Bold the dosage form statement as it is currently more prominent than that of the established name.

3. Present the strength statement in a font color that differs from that of the proprietary name. Consider aligning your strength presentations and trade dress of each strength to match the colors on the necks of their corresponding ampoules.

0.6 mg/1 mL Strength Carton Label:

1. We recommend revising the color for the trade dress of this carton, as it currently overlaps the font color used for the proprietary name statement across the product line and confusion may occur when there is overlap between a specific strength's trade dress and the proprietary name presentation.

Ampoule Labels (All Strengths):

1. Use multiple colors to present the information on your ampoule labels. Presentation of all information in one color makes the important information (such as strength) difficult to discern as currently presented.

2. Decrease the size of the manufacturer statement as it is currently as prominent as all other information on the label.

3. Relocate the dosage form statement to immediately follow that of the established name.

For example:

Signifor
(pasireotide)

(b) (4)

0.9 mg/1 mL

4. Increase the size of the strength statement as it is currently not prominently displayed.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@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/

JENNIFER L JOHNSON
11/30/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Tuesday, November 20, 2012 2:39 PM
To: Roy, Sandip (sandip.roy@novartis.com)
Subject: NDA 200677 (Signifor): Post-marketing Requirements

Dear Sandip,

Per our teleconference yesterday, here are the three post-marketing requirements for Signifor:

1. **Clinical:** A clinical trial to assess hyperglycemia management in patients with Cushing's disease treated with pasireotide.

Submit dates for Final Protocol Submission, Trial Completion, and Final Report Submission. A protocol is not considered final until FDA and sponsor have reached agreement on it. Allow sufficient time for protocol review, comment, and agreement by FDA (3-6 months).

2. **Epidemiology:** A long-term prospective observational cohort study (registry) of patients with Cushing's disease treated with pasireotide. The registry will continue for (b) (4) years from the date of last patient enrollment and will address the following safety issues: serious (treatment in Emergency Department, hospitalization, or death) cases of hyperglycemia, liver-related adverse events, deaths (including causes of death), (b) (4)

(b) (4) and events potentially related to QT prolongation), atypical infections, and adrenal insufficiency.

Submit dates for Final Protocol Submission, Annual Assessment and Summary Report Submission, Study Completion, and Final Report Submission. A protocol is not considered final until FDA and sponsor have reached agreement on it. Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months).

3. **Pharmacovigilance:** Enhanced pharmacovigilance program for reports of serious (b) (4) (b) (4) hospitalization, or death) hyperglycemia, acute liver injury, and adrenal insufficiency in patients with Cushing's disease treated with pasireotide for a period of (b) (4) years from the date of approval to collect data that will be analyzed to better define these risks. (b) (4)

(b) (4)

Submit dates for Final Protocol Submission, Annual Assessment and Summary Report Submission, Study Completion, and Final Report Submission. A protocol is not considered final until FDA and sponsor have reached agreement on it. Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months).

We also have a few clarifying questions for you concerning your planned registry:

1. Will information on transaminases be available from the registry? If so, how will it be collected/reported/standardized? Will a certain frequency of transaminase monitoring be "encouraged" for the registry?
2. Could you please provide us with a copy of the collection form you are proposing to use in the registry?

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
11/20/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Monday, October 29, 2012 6:14 PM
To: Roy, Sandip (sandip.roy@novartis.com)
Subject: NDA 200677 (Signifor): First draft of FDA edits to package insert
Attachments: Signifor PI FDA edits Oct 29 2012.doc

Dear Sandip,

We have made edits to your most recently submitted Signifor package insert. I have attached our first draft to this email.

Please note that only nonclinical edits have been made, and more from other disciplines will be forthcoming. We ask that you respond to this version by next Monday, November 5th.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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JENNIFER L JOHNSON
10/29/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, October 18, 2012 2:55 PM
To: Roy, Sandip (sandip.roy@novartis.com)
Subject: NDA 200677 (Signifor): Clinical Information Request

Dear Sandip,

We have a clinical information request for your team:

Please comment on the overall frequency of worsening/development of hyperglycemia/diabetes in your trial C2305 of pasireotide LAR (vs. octreotide LAR) for the treatment of acromegaly. What parameters were specifically measured compared to those measured in Study B2305 (Signifor/pasireotide s.c.)?

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
10/18/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, October 10, 2012 3:04 PM
To: Roy, Sandip (sandip.roy@novartis.com)
Subject: NDA 200677 (Signifor): Clinical Information Request

Dear Sandip,

We have a clinical information request for you:

Approximately 16% of the 900 mcg group had Grade 1 abnormalities for hemoglobin. Related to this finding, please respond to the following:

- 1. Indicate the location in the NDA or provide mean summary data for hemoglobin (both groups and overall).**
- 2. Provide an explanation for the high percentage of subjects with hemoglobin abnormalities.**

We would like to receive a response by Monday, October 15th. Let me know if you have any questions.

Many thanks to you and your team in advance.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

10/10/2012

IR received from clinical reviewer Naomi Lowy on 10/10/12

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, October 03, 2012 3:27 PM
To: Roy, Sandip (sandip.roy@novartis.com)
Subject: NDA 200677 (Signifor): Clinical Information Requests

Dear Sandip,

We have two clinical information requests for your team.

1. For Study CSOM230B2305, please provide all versions (original plus any amendments) of your monitoring plan at the five clinical sites for which we requested monitoring visit reports.
2. For all compassionate use studies conducted in the SOM230 program, how many patients have been enrolled? (Please include current active enrolled patients plus those who have discontinued, including any deaths.)

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

10/11/2012

Clinical and OSI information requests received 10/3/12

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, September 20, 2012 11:41 AM
To: Roy, Sandip (sandip.roy@novartis.com)
Subject: NDA 200677 (Signifor): Clinical Information Requests

Dear Sandip,

We have two clinical information requests for your team regarding NDA 200677, Signifor (pasireotide s.c.):

1. Please populate this table regarding pasireotide doses in Study B2305:

Mean total daily doses for both dose groups at various timepoints

	600 µg bid			900 µg bid		
	n	Mean total daily dose (SD)	Min, Max	n	Mean total daily dose (SD)	Min, Max
Month 1						
Month 2						
Month 3						
Month 4						
Month 5						
Month 6						
Month 12						

2. The Glucose Metabolism Report discusses your attempt to look at the reversibility of the glucose changes by measuring FPG and HbA1c 4 weeks after the last dose (p. 105). This links to an Appendix that give the individual data. If not already provided, could you please send descriptive statistics (mean, SD, range) for these parameters in the 2 groups at this post 4-week visit?

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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JENNIFER L JOHNSON
09/20/2012

Executive CAC

Date of Meeting: August 21, 2012

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP, Pharm/Tox Supervisor
Miyun Tsai-Turton, Ph.D., M.S., DMEP, Presenting Reviewer

Author of Draft: Miyun Tsai-Turton

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 200-677

Drug Name: SOM230 (pasireotide)

Sponsor: Novartis

Background

SOM230 is a somatostatin analogue, with a high binding affinity profile to somatostatin receptors 1, 2, 3, and 5, to treat Cushing's disease. The applicant submitted two carcinogenicity studies in their NDA. The carcinogenicity of SOM230 was evaluated in a 2-year rat study and a 6-month transgenic rasH2 mouse study via daily subcutaneous injection. SOM230 was not genotoxic in the Ames test, chromosomal aberration test in human peripheral lymphocytes and in the in vivo mouse bone marrow micronucleus test.

Rat Carcinogenicity Study

Wistar rats (50/sex/group) were dosed once daily by subcutaneous (SC) injection for 104 weeks with SOM230 at 0.01, 0.05, and 0.3 mg/kg/day or vehicle (acetate buffered solution, pH4.5). Dose selections received Exec CAC concurrence. Survival over the course of the study was acceptable between 72-90% in males and 68-84% in females. Increased panniculus muscle degeneration at the injection site was observed in the mid and high dose groups. Retinal atrophy was seen in all groups in a non-dose dependent manner. No neoplasms were statistically significantly increased in dosed groups.

Tg.rasH2 Mouse Carcinogenicity Study

Transgenic rasH2 mice (25/sex/group) were dosed once daily by SC injection for 26 weeks with SOM230 at 0.5, 1.0, and 2.5 mg/kg/day or control (vehicle - acetate buffered solution, pH4.5 or positive – MNU). Exec CAC did not concur with dose selection. Various neoplastic findings were found with low incidences across all groups. Non-neoplastic findings included zymogen granule accumulation in the pancreas and injection

site inflammation, hemorrhage, and fibrosis.

Executive CAC Recommendations and Conclusions

Rat

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in rats.

Tg.rasH2 mouse

- The Committee concluded that the study had suboptimal dose selection and that lower dose groups were not evaluated as expected for a transgenic mouse study. Prior Exec CAC concurrence on dose selection was not achieved.
- The Committee agreed that an additional carcinogenicity study in mice is not necessary.
- The Committee concurred that there were no drug-related neoplasms in mice.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\n
/Division File, DMEP
/Karen Davis-Bruno, Ph.D., Pharm/Tox Supervisor, DMEP
/Miyun Tsai-Turton, Ph.D., M.S., Reviewer, DMEP
/Jennifer Johnson, Project Manager, DMEP
/Adele Seifried, OND IO

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/s/

ADELE S SEIFRIED
08/22/2012

ABIGAIL C JACOBS
08/22/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, August 09, 2012 3:12 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Clinical Information Request

Dear Sandip,

As a follow-up to our teleconference held on Monday, July 30th, we have the following clinical information request.

Please complete the following hepatic safety table utilizing data from your pivotal Study C2305, entitled, "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly", and submit to NDA 200677, Signifor (pasireotide) s.c. Injection.

Study X	N	ULN<A _x T≤ 3xULN n (%)	A _x T >3xULN n (%)	A _x T >5xULN n (%)	A _x T >10xULN N n (%)	A _x T >20xULN n (%)	Tbili >ULN to <2xULN n (%)	Tbili ≥2xULN n (%)	ULNs>3x A _x T, ≥2x Tbili, <2x AP n (%)
Pasireotide LAR									
Octreotide LAR									

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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JENNIFER L JOHNSON
08/09/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Monday, July 30, 2012 3:45 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Clinical Information Requests

Dear Sandip,

As a follow-up to today's teleconference, we have requests for further information:

1. The issue of low variability of blood pressure (BP) readings at Chinese site #771 discovered upon inspection was discussed at the teleconference today. We also note the following other sites with zero BP variability at certain visits (from our own analyses, not discovered upon inspection): Italy #708, Turkey #841, Mexico #731, Greece #382. Please comment on the issue of low variability, including potential explanations for this clinically unusual scenario and what impact you believe this has on BP data overall.

2. Please submit monitoring reports for all clinical trial sites for Study B2305.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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JENNIFER L JOHNSON

07/30/2012

Information requests from Naomi Lowy (Clinical Reviewer) and Jean Mulinde (OSI Medical Reviewer)

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, July 26, 2012 5:14 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Statistical Information Request

Dear Sandip,

I have the following statistical information request for your team:

Please provide a drug summary .xpt dataset with drug intensity of up to month 3 and up to month 6. Drug intensity for month 3 is the total drug taken up to month 3/total duration up to month 3, and drug intensity for month 6 is the total drug taken up to month 6/total duration up to month 6.

The format should be similar to the ADARSUM.xpt in the som230b2305 analysis dataset folder.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

07/26/2012

Stats info request from Lee Pian on 7/26/12

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, July 26, 2012 3:40 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Clinical Pharmacology Information Request

Dear Sandip,

We have the following clinical pharmacology information request for your team:

According to the population PK analysis, estimated CL/F was ~6.7 L/h and ~3.8 L/h for healthy volunteer (HV) and Cushing's disease patients, respectively. However, the population PK model was developed for HV and Cushing disease patient separately. Please submit a population PK model to fit the pooled PK data from both healthy volunteers and Cushing's disease patients and evaluate the effect of covariates, including disease status (i.e., HV and Cushing's disease patients).

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

07/26/2012

Clinical Pharmacology information request from Jingyu (Jerry) Yu on 7/26/12

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Monday, July 16, 2012 4:18 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Clinical Information Requests

Dear Sandip,

We have new clinical information requests for NDA 200677, Signifor (pasireotide s.c.) Injection:

1. In Table 12-9, there are high percentages of subjects with both PTT and PT-INR elevations. What is your proposed explanation for these unexpected elevations? Please explain why the denominators (64, 53) for Grade 1 below are different than for the other Grades.

PTT	Grade 1	64	26	40.6	53	13	24.5	117	39	33.3
	Grade 2	79	1	1.3	73	2	2.7	152	3	2.0
	Grade 3	79	5	6.3	73	0	0	152	5	3.3
	Grade 4	79	0	0	73	0	0	152	0	0

Also, in regards to these PTT and PT abnormalities, please explain the following:

- It does not appear that the coagulation abnormalities were captured in the "Coagulation related AEs" category in the AEs of special interest. Please explain why the category was not set up to capture these obvious abnormalities.
- Describe subjects with clinically relevant (including bleeding) coagulation abnormalities.
- Did any of the subjects with abnormal PTT and/or PT-INR also have concurrent hepatic laboratory abnormalities?

2. For the Patient Narrative for Subject B2305-0205/00002, the text discusses her hypotension and hospitalization as occurring on Day 369 but the resolution of her hypotension occurring on Day 360. Please clarify or correct. Also, clarify whether this subject was suspected to have adrenal insufficiency—it appears that she was treated with saline and steroids. Was cortisol measured at the time of her symptoms?

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

07/16/2012

Information requests from clinical reviewer Naomi Lowy on 7/16/12

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Friday, July 13, 2012 12:02 PM
To: 'Roy, Sandip'
Subject: RE: NDA 200677 (Signifor): Clinical Information Requests
Sensitivity: Confidential
Follow Up Flag: Follow up
Due By: Monday, July 16, 2012 1:00 AM
Flag Status: Yellow

Dear Sandip,

Thank you for sending this so quickly.

We also have an unrelated question. Can you please clarify the basis for selection of 15% cortisol normalization rate as a threshold for efficacy for the primary efficacy analysis? It may be in the NDA so let us know where the justification is in the application if we missed it.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

From: Roy, Sandip [<mailto:sandip.roy@novartis.com>]
Sent: Thursday, July 12, 2012 10:18 PM
To: Johnson, Jennifer
Subject: RE: NDA 200677 (Signifor): Clinical Information Requests
Sensitivity: Confidential

Dear Jennifer,

As discussed this afternoon, we have started working on a response document to address the following comments/questions. This is just a quick e-mail to address comment #5 and clarify that we did indeed conduct bile salt excretory pump studies [BSEP] as recommended by our consultants. We have referred to these in the hepatic report [Also attached is the **Study Report DMPK R110042**] –

In page 35:

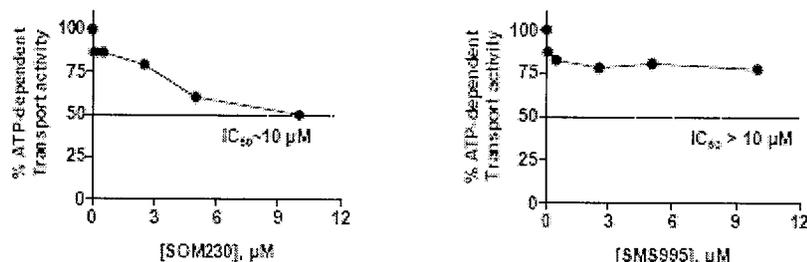
The potential of pasireotide [DMPK R1100482] or octreotide [DMPK R1100804] to inhibit MRP2 and BSEP was assessed using inside-out membrane vesicles isolated from insect cells over-expressing recombinant human efflux transporters. This potential was determined by testing the effect of increasing concentrations of pasireotide or octreotide (from 0.1 to 10 μM) on the accumulation of respective probe substrates, [^3H]estradiol-17-glucuronide and [^3H]taurocholic acid for MRP2 and BSEP, respectively.

In page 69-70:

4.6.3 MRP2

At the test concentrations of pasireotide up to 10 μM [DMPK R1100482], pasireotide showed weak but concentration-dependent inhibition (IC_{50} : ~ 10 μM) on MRP2. However, octreotide did not show concentration-dependent inhibition on MRP2 [DMPK R1100804] (Figure 4-1).

Figure 4-1 Assessment of pasireotide and octreotide as MRP2 inhibitors

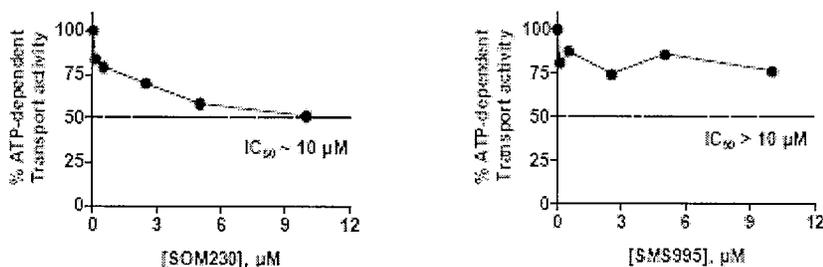


Since the predicted pasireotide $C_{\text{max},35}$ in human liver would be < 0.23 μM (Section 4.5.2), it is unlikely for pasireotide to inhibit MRP2 in vivo.

4.6.4 BSEP

At the test concentrations of pasireotide up to 10 μM [DMPK R1100482], pasireotide showed weak but concentration-dependent inhibition (IC_{50} : ~ 10 μM) on BSEP. However, octreotide did not show concentration-dependent inhibition on BSEP [DMPK R1100804] (Figure 4-2).

Figure 4-2 Assessment of pasireotide and octreotide as BSEP inhibitors



Since the predicted pasireotide $C_{\text{max},35}$ in human liver would be < 0.23 μM (Section 4.6.2), it is unlikely for pasireotide to inhibit BSEP in vivo.

Sincerely,

Sandip

Sandip Roy, PhD
 Director, Oncology Drug Regulatory Affairs
 Novartis Pharmaceuticals Corporation
 One Health Plaza, USFP 104, 3K/28
 East Hanover, NJ 07936-1080
 USA

Phone +1 862 7780015
Fax +1 9737818265
sandip.roy@novartis.com
www.novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Tuesday, July 10, 2012 5:09 PM
To: Roy, Sandip
Subject: NDA 200677 (Signifor): Clinical Information Requests
Sensitivity: Confidential

Dear Sandip,

In preparation for our Signifor mid-cycle review teleconference scheduled for Monday, July 30, 2012, from 10:00-11:30 am, we request that you please prepare responses to the following comments/questions related to the liver test abnormalities reported in the Hepatic Report dated January 26, 2012 (submitted to NDA 200677):

1. Provide an explanation/hypothesis of the many cases of very rapid, almost immediate rise in serum bilirubin concentration that preceded and often surpassed the rise in serum aminotransferase levels.
2. If there is no impressive rise in serum alkaline phosphatase activity to indicate biliary epithelial cell injury, and there is no time for gallstone formation, does pasireotide exert some form of inhibition on bile secretion or clearance by the liver in these healthy subjects and patients?
3. Provide an explanation for the following observations: The elevated serum aminotransferase activities that caused so much alarm generally fell fairly promptly after stopping pasireotide injections, but elevated serum bilirubin levels more slowly so.
4. These signs and symptoms related to elevated liver tests may be alarming to physicians treating patients with Cushing's disease, and should be understood and explained before they have to make difficult decisions. How do you propose to adequately inform physicians of this?
5. At a meeting held on August 17, 2011, your consultants recommended that bile salt excretory pump studies be done, which do not seem to be included in the Hepatic Report of January 2012. Were these studies done or do you plan on doing them? Would any other studies be more appropriate to explain the observed effects on the liver?

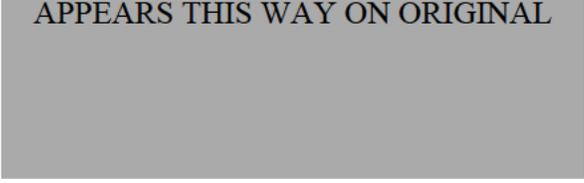
Overall, it is important that you provide a valid explanation to account for the liver test abnormalities observed. We encourage you to consult with your experts on liver function and disease, and we would like to know the outcome of such consultations.

Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL



Johnson, Jennifer

From: Johnson, Jennifer
Sent: Tuesday, July 10, 2012 5:09 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Clinical Information Requests

Dear Sandip,

In preparation for our Signifor mid-cycle review teleconference scheduled for Monday, July 30, 2012, from 10:00-11:30 am, we request that you please prepare responses to the following comments/questions related to the liver test abnormalities reported in the Hepatic Report dated January 26, 2012 (submitted to NDA 200677):

- 1. Provide an explanation/hypothesis of the many cases of very rapid, almost immediate rise in serum bilirubin concentration that preceded and often surpassed the rise in serum aminotransferase levels.**
- 2. If there is no impressive rise in serum alkaline phosphatase activity to indicate biliary epithelial cell injury, and there is no time for gallstone formation, does pasireotide exert some form of inhibition on bile secretion or clearance by the liver in these healthy subjects and patients?**
- 3. Provide an explanation for the following observations: The elevated serum aminotransferase activities that caused so much alarm generally fell fairly promptly after stopping pasireotide injections, but elevated serum bilirubin levels more slowly so.**
- 4. These signs and symptoms related to elevated liver tests may be alarming to physicians treating patients with Cushing's disease, and should be understood and explained before they have to make difficult decisions. How do you propose to adequately inform physicians of this?**
- 5. At a meeting held on August 17, 2011, your consultants recommended that bile salt excretory pump studies be done, which do not seem to be included in the Hepatic Report of January 2012. Were these studies done or do you plan on doing them? Would any other studies be more appropriate to explain the observed effects on the liver?**

Overall, it is important that you provide a valid explanation to account for the liver test abnormalities observed. We encourage you to consult with your experts on liver function and disease, and we would like to know the outcome of such consultations.

Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

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Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
07/10/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Monday, July 09, 2012 5:43 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Information Requests (CMC and DMEPA)

Dear Sandip,

Following our mid-cycle review team meeting for NDA 200677, Signifor (pasireotide s.c.) Injection, we have the following information requests:

Chemistry, Manufacturing and Controls (CMC)

1. We note that you have included executed batch records in section 3.2.R of your application. Confirm that the production process for these representative batches is identical to your proposed process for commercial drug product batches or amend your process description in 3.2.P.3 to include the operating ranges (and set-points) defined in the executed batch record.
2. Include the structure of pasireotide in section 11 of the package insert.
3. Provide all available stability data (and updates) for registration/commitment batches 885168_S0001 through S003 (0.3 mg/mL ampoule), 885169_S0001 (0.6 mg/mL ampoule), and 885170_S0001 through S0003 (0.9 mg/mL ampoule).
4. Section 3.2.P.8.1 (summary) states that testing for subvisible particulate matter, bacterial endotoxins, and visible foreign particles is included in section 3.2.8.3 for the clinical lots with 5 years of stability data. Please specify which file contains this data.

Division of Medication Error Prevention and Analysis (DMEPA)

1. What is the planned placement of the ampoule label on the ampoule (as the samples provided were not labeled and the submitted proposed labels are not shown in perspective to the size of the ampoule)? Will the label completely cover the lower half of the ampoule, or will there be some open space left for visual inspection of the contents prior to administration?

2.

(b) (4)

3. Please provide package labeling for the needles included in the kit, and any other features of the needles that will differentiate them from one another (physical differences, color of hub, etc.). What are the lengths and gauges of each of these needles?
4. What is the rationale behind placing the instruction of certain patients being told to use both needles included in the kit, and others only being instructed to use one in the Patient Instructions for Use (as there is no specific reference to the rationale in the Package Insert Labeling)? Is one of the needles included in the kit a filter needle (the "Long needle")? Is use of the longer needle (whether a filter needle or not) necessary to properly extract all volume from the ampoule? How were the doses prepared in the clinical trials?

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration

301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
07/09/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, June 20, 2012 1:54 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Follow-Up Information Request

Dear Sandip,

In response to your June 11, 2012, submission containing responses to our comments and requested datasets for Study PopPK-QT in the letter which issued on March 23, 2012, we are requesting the following information:

Please provide the NONMEM codes for the population PK model, effect compartment model for DDQTcI and codes used for simulation. The following are the general expectations for submitting pharmacometric data and models:

*Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps should be provided.*

*We request that you submit this information by **June 25th, 2012.***

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

06/20/2012

Information request from QT-IRT

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, June 20, 2012 1:45 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Clinical Information Request

Dear Sandip,

We have a clinical follow-up question for you:

Regarding Table 4-6 in the Hepatic Report, please resend this table with "Study Days" along with the visit dates as well as the amount above the upper limit of normal (2xULN, for example) along with the actual values.

Please respond by this Friday, June 22nd.
Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

06/20/2012

Info request from clinical reviewer Naomi Lowy

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, May 24, 2012 12:25 PM
To: 'Roy, Sandip'
Subject: NDA 200677: Signifor (pasireotide s.c.) Clinical Information Requests

Dear Sandip,

As we continue to review NDA 200677, Signifor (pasireotide s.c.), we have the following clinical questions for you:

1. In Study B2305, of the subjects who became hypocortisolemic (13 subjects), how many were considered responders at the primary efficacy timepoint? In your response, please include the subjects IDs of the 13 subjects.
2. Regarding Tables 14.3-1.2 and 14.3-1.5 in the Study Report for B2305, resubmit the table, grouping all insulin products together. Note: we acknowledge the tables in the Glucose Metabolism Report, which summarize anti-diabetic usage *by treatment at baseline*.
3. It is apparent that metformin was commonly initiated as anti-diabetic therapy in Study B2305. However, Study B2124 suggested that metformin is not useful in the treatment of pasireotide-induced hyperglycemia. Have you done any analyses comparing the glycemic profiles of study subjects who were treated with metformin compared to those anti-diabetic medications that appear to reduce glucose in pasireotide-induced hyperglycemia (e.g., insulin, glinides, DPP-IV inhibitors)?
4. Regarding Table 12-6 from Study Report B2305, please submit a similar table using only the first 6 months of data (primary efficacy timepoint).
5. Regarding Tables 5-40 and 5-42 in the Glucose Metabolism Report, submit the same tables with mean changes from baseline values, rather than absolute values.

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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JENNIFER L JOHNSON

05/24/2012

Info requests from clinical reviewer Naomi Lowy on 5/24/12



NDA 200677

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Sandip Roy, PhD
Director, Drug Regulatory Affairs

Dear Dr. Roy,

Please refer to your New Drug Application (NDA) dated and received on June 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pasireotide Injection, 0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL. Please also refer to your resubmission to this NDA, dated and received February 17, 2012.

We also refer to your February 17, 2012, correspondence, received February 17, 2012, requesting review of your proposed proprietary name, Signifor. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Signifor, will be re-reviewed 90 days prior to the approval of the NDA. 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 February 17, 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 Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0997. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Jennifer Johnson at (301) 796-2194.

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
05/16/2012



NDA 200677

FILING COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Sandip Roy, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Roy:

Please refer to your New Drug Application (NDA) dated and received February 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Signifor (pasireotide) Injection, 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL.

We also refer to your amendments dated March 13, April 3 and 12, 2012.

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 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **December 17, 2012**.

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, midcycle, 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 commitment requests by **October 29, 2012**.

During our filing review of your application, we identified the following potential review issues, and request that you submit the following information:

1. datasets and model codes for study reports 'pkpd-hepatic-modeling' and 'poppk-cd-12m'.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Redundancy of information in the Highlights of Prescribing Information section. Please remove the duplicate statements at the beginning of this section and in the Adverse Reactions subsection of Highlights.
2. Patient Counseling Information. Change [REDACTED] (b) (4) to “See FDA-approved patient labeling (Patient Information and Instructions for Use)”.

We also have the following additional labeling comments:

General Comments:

- Your proposed Patient Package Insert (PPI) and Instructions for Use (IFU) has a Flesch Reading Grade Level of 9.3 and a Flesch Reading Ease Score of 53.3. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.
- Simplify the language in the PPI and IFU to improve the readability scores as described above. In general, use active voice and non-technical language as much as possible in the PPI and IFU.
- To make medical information more accessible for patients with vision loss, patient labeling materials should be in fonts such as Verdana, Arial, or APFont at a font size of 11 point or greater. We recommend using Verdana 11 point font.
- Please reference CFR 208.20 for guidance on standard headings used in patient labeling.

Patient Package Insert (PPI):

- Disease specific information can be included after the ingredients section of the PPI, but it is not encouraged. The purpose of patient information is to enhance appropriate use and to provide important information to patients about the medication. Preferably, disease specific information should be addressed with the patient separately from the product specific information.
- Warnings and Precautions should be listed under the section heading titled, “What are the possible side effects of SIGNIFOR?” with a subheading titled, “SIGNIFOR can cause serious side effects, including:”

Instructions For Use (IFU):

- The standard header and introductory paragraph in the IFU should be the same as the drug products PPI. Place a header at the top of the document similar to the one at the top of the PPI but title it, “Instructions for Use” instead of, [REDACTED] (b) (4)
- Following the introductory paragraph, include a bulleted list of the all the supplies needed.
- Include a labeled figure showing the SIGNIFOR glass ampoule with the location of the expiration date clearly shown.
- Instructions that are not sequential should be bulleted.

- Instructions that are sequential should be noted as “Step 1, Step 2” etc. and a labeled figure should be placed immediately adjacent to the related step (e.g. “See Figure A, See Figure B”). All figures should be labeled as “Figure A, Figure B” etc.
- Within the figures, there should be detailed labeling for each part of the device that the patient is expected to become familiar with (e.g. a syringe should have the plunger, numbering, and markings on the barrel of the syringe clearly labeled). The numberings and markings should be clearly visible and easy for the patient to read.
- If instructions should be repeated more than once, do not repeat steps. Refer the patient back to listed steps (e.g. "Repeat steps 3 to 5").
- Include at the end of the IFU:
 - Storage instructions exactly as written in the PPI.
 - "This Instructions for Use has been approved by the U.S. Food and Drug Administration."
 - Manufacturer's name and address
 - Issued: Month/Year

We request that you resubmit labeling that addresses these issues by May 18, 2012. The resubmitted labeling will be used for further labeling discussions.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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) and patient PI (as applicable). 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 (PI) and patient PI (as applicable), 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.

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), 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.

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 drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

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/

JENNIFER L JOHNSON

05/01/2012

Signing on behalf of Mary Parks, M.D.

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Thursday, March 29, 2012 1:20 PM
To: 'Roy, Sandip'
Subject: NDA 200677 (Signifor): Clinical Information Requests

Dear Sandip,

We are reviewing NDA 200677, Signifor (pasireotide), and have the following requests for information.

Follow-up Question to Deficiency Responses:

- 1) Regarding Subject 0704/00011:
 - a) Is Subject 0704/00011 considered a responder?
 - b) The case report form for this subject appears to be missing. Please provide the report or specify the location.
 - c) The subject had 2 screening collections (Study Days -29, -28), followed by 4 collections at Study Days -4 though -1. Given that this subject had neither the pre-specified minimum number of collections for screening nor a baseline muFC value greater than 2x ULN, explain why was this subject was randomized.

General Questions:

- 2) In Table 14.2-2.8 in the Clinical Study Report for B2305, at Month 6 the n changes from 52 to 25 under "Change from baseline: actual" to "Change from baseline: percent". Please clarify why the n changes for the percentage calculation.
- 3) Regarding Tables 11-12 and 11-13 in the Clinical Study Report for 2305, resubmit the tables using only 2 categories: controlled and uncontrolled (to include PC and UC).
- 4) No males in the 900 μ g group were responders according to the primary efficacy endpoint. Elaborate on this notable finding.

We kindly request a response by Thursday, April 12th.

Let me know if you have any questions - many thanks in advance for your help.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
03/29/2012

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Monday, March 26, 2012 2:14 PM
To: 'Roy, Sandip'
Subject: NDA 200677: Signifor (pasireotide) Information Request

Dear Sandip,

We have consulted the Study Endpoints and Labeling Development (SEALD) team regarding the use of the Quality of Life questionnaire for Cushing's disease used in your pivotal study SOM230B2305, and the data generated from it [REDACTED] (b) (4)

To assist in their review, could you please provide the following:

1. A copy of this literature reference:

Webb SM, Badia X, Barahona MJ, et al (2008) Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur J Endocrinol;158: 623-630.

2. A copy of the QoL instrument (CushingQoL Questionnaire) used in the pivotal trial, or if submitted in the NDA application, point us to its location.

Let me know if you have any questions.

Many thanks for your help!

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
03/28/2012



NDA 200677

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Sandip Roy, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Roy:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Signifor (pasireotide) Injection, 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL

Date of Application: February 17, 2012

Date of Receipt: February 17, 2012

Our Reference Number: NDA 200677

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **April 17, 2012**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 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 NDA 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. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
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/

JENNIFER L JOHNSON
03/01/2012

9/2/11



NDA 200677

**ACKNOWLEDGE REQUEST
TO WITHDRAW PENDING NDA**

Novartis Pharmaceuticals Corporation
Attention: Leslie Bennett, RAC
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Bennett:

We have received your August 19, 2011, correspondence on August 19, 2011, notifying us that you are withdrawing your new drug application (NDA) for Signifor (pasireotide) Injection, 0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL.

In accordance with 21 CFR 314.65, this application is withdrawn as of August 19, 2011. If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission.

In addition, the resubmitted application should address the following deficiencies identified during our preliminary review of the withdrawn application:

Chemistry, Manufacturing and Controls

1. FDA does not routinely designate official names of drugs. Apply for a U.S. Adopted Name for your drug substance (reference is made to the U.S. Pharmacopeia Dictionary for details) and advise us of the progress of your application.
2. Confirm that there was no major manufacturing change associated with the drug substance manufacturing transfer from [redacted] (b)(4)
3. In section 3.2.P.2, regarding the qualification of the proposed [redacted] (b)(4) you state that no leachable was found greater than the detection limit of [redacted] mcg/mL (later changed to [redacted] (b)(4) mcg/mL with an optimized test method). Provide information in support of the detection limit being an appropriate safety threshold.
4. Provide the location in the NDA of the information on the functionality testing of the assembled pre-filled syringe, which should cover attributes such as plunger release force and travel force.

5. The primary stability batches submitted in the NDA are Y0670704, Y0690704, Y0710804, Y0730704, Y0750704, and Y0770804, all packaged in the [redacted] syringes. In section 3.2.P.8.1 you indicate that these batches were manufactured at [redacted] and in section 3.2.P.5.4 the same batches were manufactured at [redacted]. Clarify the manufacturing site of the primary stability batches and provide information (e.g., process, equipment) to compare the manufacturing site of the stability batches to the commercial manufacturing site.

6. In section 3.2.P.8.2 you indicate that three production scale batches of the 0.3 mg/mL and 0.9 mg/mL strengths were manufactured in [redacted] each batch packaged in the proposed commercial pre-filled syringes from [redacted]. Confirm that these production scale batches were manufactured at the commercial site Novartis Stein. You also state that these batches were placed on stability studies. Explain why stability data from these batches are not included in the NDA.

7. Considering the increasing trend in degradation and decreasing trend in assay results observed in the primary stability batches when stored at 25 °C/60% RH and 30 °C/70% or 75% RH, we advise you to label the product for long-term storage under refrigerated conditions based on the better stability profile at 5 °C.

8. Regarding the synthesis of the Pasireotide diaspertate drug substance:
 - a. [redacted]
 - b. Your process description uses the term “In a typical run” preceding several of the unit operations of the [redacted]. Replace this description with a narrative that describes the proposed manufacturing process at proposed commercial scale that includes the typical [redacted].
 - c. [redacted]
 - d. Does concentration of [redacted] impact the [redacted] and acceptable range for the concentration of [redacted]. If so, what is the target [redacted].
 - e. [redacted]

9. Regarding the validation of the [redacted] accuracy on the [redacted] showed considerable variability. How will the [redacted] be used in the control strategy, and justify the use of this variable method.

10. Regarding extractable and leachable studies for the drug product container closure system, have [redacted] been observed? Have soluble [redacted] been monitored by ICP-MS or ICP-OES via a silicon signal in extractable/leachable studies?

Clinical/Statistical

Please note that the following questions refer to the clinical study report for Study 2305, unless otherwise specified.

11. In Table 11-3, 5 subjects in the 600 mcg group and 4 subjects in the 900 mcg group are missing baseline UFC data. Are the excluded data from those subjects those with major protocol deviations?
12. Populate the following table, which should summarize the number of enrolled subjects, organized by their baseline UFC.

Baseline mUFC category	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
> ULN to ≤ 2xULN	n/N (%)		
> 2xULN to ≤ 5xULN			
> 5xULN to ≤ 10xULN			
> 10xULN			
Missing			

13. Were any subjects enrolled with a baseline mUFC value of > ULN to ≤ 1.5xULN?
14. Regarding Table 10-1:
- Four subjects are listed as discontinued due to protocol deviations. Please detail these 4 protocol deviations, including when they occurred.
 - Regarding “unsatisfactory therapeutic intervention”, were these discontinuations due to protocol-specific criteria?
15. Assemble a table similar to Table 11-9, but include only 2 columns, one for responders (using the primary efficacy definition) and non-responders.
16. Are all reported UFC values absolute or derived from the formula provided on p. 5275 of the clinical study report for Study 2305? If so, describe support for the use of the formula, versus the actual 24 hour urine cortisol value.
17. If values were formula-derived, was this pre-specified in the protocol?
18. Table 14.3-2.42 summarized extreme lab values for 24 hour urine creatinine. Were any UFC values excluded because of abnormal 24 hour creatinine values that indicated inadequate collection? Of the abnormally low 24 hour urine creatinine values at any of the timepoints up to and including Month 6, how many of those values had a concomitant UFC ≤ ULN?
19. Were any of the low values for more than one collection per timepoint per subject? In other words, did any one subject have more than one of these extreme low values any timepoint?

20. Summarize, by dose group and timepoints, the number of low volume urine collections. Were any collections discarded because of low volume?
21. The NDA documents display Study B2305 lab-related values in SI units. You provided two lab-related Study B2305 datasets, one in SI units and a corresponding dataset in US units. Please include a column variable for lab unit in the dataset Aeffvis (SI unit e.g., LB SIUNIT) and Aeffvisu (US unit e.g., LB USUNIT) to display their respective UFC units.
22. Indicate which variable in dataset Aeffsum to use in order to get the number of responders at Month 7 as listed in the Final Report Table 11-4 (12 in the 600 mcg group and 21 primary endpoint responders in the 900 mcg group).
23. For the analysis of response (primary efficacy endpoint) at Month 6 by baseline mUFC using the logistic regression model, send the SAS proc logistic program for Figure 14.2-2.10.
24. At the Pre-NDA meeting, a delta graph was requested to present the change of HbA1c from baseline to the end of study by patient. Please indicate the location of the graph.

Labeling

25. Provide color mock-ups of your draft carton and container labels.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

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
09/02/2011



NDA 200677

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Leslie Bennett, RAC
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Bennett:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Signifor (pasireotide) Injection, 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL

Date of Application: June 21, 2011

Date of Receipt: June 21, 2011

Our Reference Number: NDA 200677

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **August 20, 2011**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 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 NDA 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. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

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

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

/s/

JENNIFER L JOHNSON
06/27/2011

Pre-NDA meeting minutes
issued on January 27, 2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 068635

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Leslie Bennett
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Bennett:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SOM230B (pasireotide) Injection.

We also refer to the meeting between representatives of your firm and the FDA on August 30, 2010. The purpose of the meeting was to discuss your planned orphan NDA submission for the treatment of Cushing's Disease.

A copy of the official minutes of the meeting 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) 796-2194.

Sincerely,

{See appended electronic signature page}

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

Enclosure: FDA Version of Pre-NDA Meeting Minutes for SOM230B (pasireotide) Injection

Reference ID: 2897458

Reference ID: 3236009



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Monday, August 30, 2010, 10:00-11:00 am
Meeting Location: CDER, White Oak Campus

Application Number: 068635
Product Name: SOM230B (pasireotide) Injection
Indication: Treatment of Cushing's Disease
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Mary H. Parks, M.D.
Meeting Recorder: Jennifer Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Mary Parks, M.D.	Director
Dragos Roman, M.D.	Clinical Team Leader
Naomi Lowy, M.D.	Clinical Reviewer
Amy Egan, M.D., M.P.H.	Deputy Director for Safety
Karen Davis Bruno, Ph.D.	Supervisory Pharmacologist
Miyun Tsai-Turton, Ph.D.	Pharmacology/Toxicology Reviewer
Enid Galliers	Chief, Project Management Staff
Jennifer Johnson	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Sally Choe, Ph.D.	Clinical Pharmacology Team Leader
Lokesh Jain, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics II

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

Office of New Drug Quality Assessment III, Division of Premarketing

Suong Tran, Ph.D.	CMC Lead
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Office of Orphan Products Development

Reference ID: 2897458

Reference ID: 3236009

Meeting Minutes
Type B, Pre-NDA
August 30, 2010

Division of Metabolism and Endocrinology Products

Jeff Fritsch, R.Ph.
Kui Xu

Regulatory Reviewer Officer
Regulatory Review Officer

SPONSOR ATTENDEES

Representing Novartis Pharmaceuticals Corporation

Lynne McGrath, MPH, Ph.D,	VP, NA Head Drug Regulatory Affairs
Pio Zapella, Ph.D.	Global Program Regulatory Director SOM
Leslie Bennett, RAC	Senior Associate Director, Drug Regulatory Affairs
Johannes Eisinger, M.D.	Lead Brand Safety Leader
Paul Vancutsem, DVM, Ph.D.	Director PCS - PTR
Kapildeb Sen, Ph.D.	Associate Director, Oncology Biometrics and Data Management
Antonella Maniero, Ph.D.	Global Head Biostatistics Clinical Development I
Germo Gericke, M.D.	VP Global Program Head Oncology
Mike Hu, Ph.D.	Sr. Fellow Clinical Pharmacologist
Gabriela Gruia, M.D.	SVP & Global Head DRA Oncology Development
Pablo Cagnoni, M.D.	SVP Global Head Oncology Clinical Development
Mario Maldonado-Lutomirsky, M.D.	Senior Global Clinical Leader
Herbert Opitz, PhD,	Global Program Team Director
Kris Grzegorzewski, M.D.	Sr. Medical Director, US CDMA Oncology
Michelle Hack, RAC	Associate Director, Drug Regulatory Affairs
Donna Kapples, M.S.	Sr. Associate Director Global Regulatory CMC

(b) (4)

Reference ID: 2897458

Reference ID: 3236009

1.0 BACKGROUND

SOM230B (pasireotide) s.c. Injection, a somatostatin analog and new molecular entity (NME) is being developed for the treatment of Cushing's disease. Pasireotide received orphan designation for the treatment of Cushing's disease on July 27, 2009. The sponsor intends to market this product as a twice daily s.c. injection in three dosage strengths: 0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL. (b) (4)

(b) (4) Studies with SOM230B have also been conducted in patients with acromegaly and metastatic carcinoid tumors. (b) (4)

Pasireotide exerts its pharmacologic activity via binding to somatostatin receptors (sst), of which there are five known (sst 1, 2, 3, 4 and 5) and are expressed in different tissues under normal physiological conditions. Somatostatin receptors are strongly expressed in many solid tumors, including the pituitary adenomas that cause Cushing's disease. Currently approved somatostatin analogs (octreotide and lanreotide) have a high affinity to the receptor subtype 2 (sst 2), with moderate or no affinity to the remaining subtypes. Pasireotide, however, has a broader binding profile with high affinity to four of the five known receptor subtypes (sst 1, 2, 3, and 5), with an especially high binding affinity to receptor subtype 5 (sst5).

Currently, there are no FDA-approved therapies for the treatment of Cushing's disease; pituitary surgery is the currently available medical therapy. To support the NDA for Cushing's disease, the sponsor will be submitting data from a single pivotal Phase 3 Study SOM230B2305, entitled, "A randomized, double-blind study to assess the safety and efficacy of different dose levels of Pasireotide (SOM230) s.c. over a 6 month treatment period in patients with *de novo*, persistent or recurrent Cushing's disease". This study included a 6-month treatment period, followed by a 6-month open-label extension phase. The sponsor also plans to submit efficacy data from Study B2208, entitled, "A multicenter, open-label phase 2 study to assess the safety and efficacy of 600 µg b.i.d. SOM230, administered subcutaneously, in patients with Cushing's disease", and its study extension phase, B2208E.

The sponsor submitted IND 068635 to the Division of Metabolism and Endocrinology Products (DMEP) on November 17, 2003. The IND was placed on full clinical hold on December 18, 2003, and removed from clinical hold on March 10, 2004. A Special Protocol Assessment (SPA) for Stability was submitted on June 25, 2004, and a No Agreement Letter was issued on August 12, 2004.

An End-of-Phase 2 meeting was held between the sponsor and DMEP on May 15, 2006, and meeting minutes issued on June 5, 2006.

The sponsor also submitted other SPA requests (Carcinogenicity on September 11, 2006; Clinical on October 12, 2006). A SPA-No Agreement advice letter was issued on November 22, 2006.

The sponsor submitted on March 20, 2008, a request for review by the QT Interdisciplinary Review Team of its protocol CSOM230B2113, entitled "A randomized, double-blind, placebo and active controlled, crossover study to investigate the effects of pasireotide (SOM230) s.c. at MTD on cardiac intervals in healthy volunteers". A letter issued on June 3, 2008.

The sponsor submitted to (b) (4) requests for review of its proposed proprietary name Signifor on (b) (4) a conditionally acceptable letter issued. However, the sponsor should submit a request for review of the proprietary name again once the NDA is submitted.

A request for Fast Track Designation for pasireotide was received on June 3, 2010, and a denial letter was issued on August 24, 2010.

The sponsor submitted for review by the QT Interdisciplinary Review Team a second QT study protocol B2125, entitled, "A single center, phase I, randomized, placebo and active controlled, blinded crossover study to investigate the effects of subcutaneous pasireotide (SOM230) on cardiac intervals in healthy volunteers".

The sponsor submitted a Pre-NDA meeting briefing document on July 28, 2010, and preliminary comments were sent via e-mail to the Sponsor on August 26, 2010.

2. DISCUSSION

QUESTIONS FOR THE AGENCY

Questions from the sponsor's briefing document are repeated below (regular text), followed by the FDA Preliminary Response (bolded text), followed by meeting discussion and FDA Final Responses (bolded/italicized text).

Question 1: Overall Content of the NDA

Does the Agency agree that the content described in the proposed NDA Table of Contents together with the information provided in this briefing document is acceptable to support a complete NDA?

FDA Preliminary Response:

CMC:

We remind you to provide the following in the NDA:

(1) A confirmation that the manufacturing and testing facilities listed on the Form FDA 356h are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product and that they are ready for inspection;

(2) A table listing the identification information on all toxicology, clinical, and stability batches, information such as drug product batch number, associated drug substance batch number, drug substance manufacturing process (e.g., commercial, developmental), drug product manufacturing process (e.g., commercial, developmental), toxicology and/or clinical study number, and IND phase for the clinical batches; and

(3) Information on the suitability of the drug-contact components of the container closure systems used to package the drug substance and drug product. This should include information on the protective properties of the system, safety (including extractables and leachables), and compatibility (primary stability batches should be packaged in the proposed commercial systems).

Microbiology:

An overall CTD Table of Contents was submitted and appears to be appropriate. For ease of review of the NDA, we request that you submit the following microbiology-related information in the CTD sections shown below:

- Include all information related to drug product (b) (4) cycle validation in CTD Section 3.2.P.3.5.
- Include all information related to drug product container/closure integrity testing in CTD Section 3.2.P.2.5.
- Provide all information related to drug product bacterial endotoxin test procedures and assay qualifications in submission section 3.2.P.5.3.5.

Clinical Pharmacology:

At this stage, proposed clinical pharmacology contents for this application seem acceptable, except that effect of renal impairment on pasireotide PK has not been evaluated.

With the recent amendments in renal guidance, PK study in patients with impaired renal function are not only required for drugs which are substantially eliminated renally, but also for drugs which are primarily metabolized or secreted in bile. Also, such PK studies are recommended for most drugs intended for chronic use.

Therefore, you should address the effect of renal function impairment on pasireotide PK in your NDA submission. Some of the possible options are: (1) conduct a dedicated study in renally impaired subjects, or (2) analyze the effect of renal impairment in population PK and PK-PD analysis using Phase 3 data.

Clinical:

From a clinical perspective, the Table of Contents appears acceptable. However, please confirm that the Summary of Clinical Efficacy and Summary of Clinical Safety will be submitted under Module 2.7 (Clinical Summary).

Discussion during FDA meeting: *The sponsor sought clarification regarding the two options presented for addressing the effect of renal function impairment on pasireotide PK in the NDA submission (Clinical Pharmacology section of response to Question 1), and stated that it intends to provide option 2 in the submission. It was noted that there are 20 patients with renal impairment in the dataset; FDA requested clarification as to which category (i.e., mild, moderate, severe) these patients should be classified. The sponsor stated that it expected most cases would be mild to moderate and did not expect many severe cases. FDA stated that this would be a review issue.*

Question 2: Summary of the Clinical Efficacy

- a) Does the Agency agree with Novartis' proposal to present the efficacy data from studies B2208, B2208E1, and B2305 separately (rather than pooled) in the Summary of Clinical Efficacy (SCE)?

FDA Preliminary Response:

A separate presentation of efficacy data by study for the SCE is acceptable.

Discussion during FDA meeting: *None; sponsor accepts FDA Preliminary Response.*

- b) Does the Agency agree with the proposal to satisfy the ISE requirements?

FDA Preliminary Response:

Yes.

Discussion during FDA meeting: *None; sponsor accepts FDA Preliminary Response.*

Question 3: Scope Summary of Clinical Safety

- a) Does the Agency agree with the proposed approach for evaluating safety in the Summary of Clinical Safety?

FDA Preliminary Response:

Your proposal is acceptable. Regarding the integrated safety reports (glucose metabolism and cardiovascular events), it is unclear which adverse event terms will be used and what methodology is planned to generate and present these reports. Please provide more detail about these analyses. Furthermore, given the stark differences between the 2 trials (study duration, dosing) the pooling of terms may not provide

useful data on which to draw conclusions about the safety of pasireotide. Also, discuss whether the terms were defined *a priori*.

Discussion during FDA meeting: Refer to sponsor's slides at the end of this document. The sponsor stated that 34 MedDRA Preferred Terms from SMQ ("Hyperglycemia/new onset diabetes mellitus") were used, and that all terms were defined *a priori* in the analysis plan of pivotal study B2305 prior to the month 6 analysis database lock. All patient studies are presented individually and HV studies were pooled if appropriate. For the cardiovascular studies, all results have been pooled. FDA sought further clarification regarding the one patient in the database with a severe adverse event of "convulsion". The sponsor stated that this SAE was unexpected, and that the 54-year-old patient, who had a history of aneurysm, had been on study medication for 21 days. The term "convulsion" was added after the database lock. This explanation was sufficient for FDA.

b) Does the Agency agree with the proposal to satisfy the ISS requirements?

FDA Preliminary Response:

Yes. If feasible, present the data by gender, age, and racial subgroups.

Discussion during FDA meeting: None; sponsor accepts FDA Preliminary Response.

Question 4: Risk Management

Given that the safety risks identified by Novartis are generally common to the SSA class of drugs, Novartis proposes to submit a RMP instead of a REMS, does the Agency agree?

FDA Preliminary Response:

At this time, FDA does not have a defined format for risk management (other than a REMS). Therefore your proposal to submit in the EU format is acceptable. A complete review of the full risk management plan after the NDA is submitted will be necessary to determine whether it is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

Discussion during FDA meeting: None; sponsor accepts FDA Preliminary Response.

Question 5: Additional TQT Study

Does the Agency agree with the proposal that in order to support safety labeling and risk management discussions, Novartis will submit additional safety information that will become available during the review of the NDA application?

FDA Preliminary Response:

The data from your proposed second QT study should be submitted at the time of the NDA submission and not with the safety update.

Discussion during FDA meeting: Refer to the sponsor's slides at the end of this document. FDA reiterated that all data should be complete at the time of NDA submission, consistent with CDER policy. The IRT-QT team will need to be consulted, as well as other Divisions within the Agency. An Advisory Committee meeting may need to be scheduled. Receiving necessary data at the time of the safety update could delay review of the application. If the second QT study is submitted with the safety update, the Agency would not be obligated to review it; however, if the study results were deemed to be needed for support of application approval, and the data is submitted at the time of the safety update, a complete response (CR) action is a possibility. The sponsor replied that a complete package will be submitted, and that it is possible that the second QT study results replicate those of the first QT study. If not, labeling could be updated accordingly.

Question 6: Safety Update

Novartis intends to submit the NDA in December 2010 based on results of study B2305 with supporting information provided by the phase 2 study B2208 and its extension. Does the Agency agree with content of the safety update?

FDA Preliminary Response:

Yes. Please refer also to our response to question 5.

Discussion during FDA meeting: See also discussion for question 5, and refer to the sponsor's slides at the end of this document. Note: the timeline for NDA submission has been altered from the originally planned December 2010 submission.

Question 7: CRT requirements

The CRTs for studies B2201, B2201E1, B2103 and B2202 will not be provided, does the agency agree?

FDA Preliminary Response:

Yes.

Discussion during FDA meeting: None; sponsor accepts FDA Preliminary Response.

Question 8: Electronic datasets

Novartis plans to submit case report tabulations for review of safety and effectiveness of Cushing's disease in the following studies and integrated reports:

- All raw and derived datasets for pivotal study B2305 and studies B2208 and B2208E1 in Cushing's disease
- Selected raw and derived datasets for clinical pharmacology studies in healthy volunteers and hepatically-impaired patients: B2101, B2102, B2106, B2107, B2108, B2112, B2113, B2114, C2101
- All derived datasets for the integrated reports concerning glucose metabolism and cardiovascular safety
- PK and PKPD analysis datasets
- Population PK analysis datasets

Does the Agency agree with the proposal to submit the above-mentioned datasets?

FDA Preliminary Response:

We request that the raw and derived datasets be submitted as SAS transport files. We request the use of structure and formats for datasets that follow the principles for data submission and analysis, as outlined by the Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM); (see www.cdisc.org). The file structure and the accompanying documentation in define.pdf files should enable us to readily confirm the results from key endpoints, and to conduct additional supportive analyses.

Present laboratory results in US rather than SI units. Provide normal ranges for all tests.

Discussion during FDA meeting: Refer to sponsor's slides at the end of this document. The sponsor clarified that the NDA submission could include a separate database with lab values and normal ranges in US units for the pivotal Phase 3 study B2305. Additionally, raw and derived datasets will be submitted in SAS XPORT transport file format. The annotated case report form will be provided in pdf format. The data definition table will be submitted as define.pdf which provides the source derivation for each variable in the datasets. The hypertext link will also be provided from the define.pdf to the SAS transport files and the annotated case report form. The sponsor plans to follow the CDISC principle generally, although not exactly. FDA said that this was acceptable.

FDA Final Response: The proposed plans for electronic datasets are acceptable.

Question 9: Dataset programs

Does the Agency agree with the SAS dataset program proposal?

FDA Preliminary Response:

Please clarify what is meant in part 2.2.8.1 of the briefing document by "nonexecutable" analysis programs in SAS for the analysis of the primary and key secondary efficacy endpoints. It may be useful to provide an example.

Discussion during FDA meeting: Refer to sponsor's slides at the end of this document. The sponsor stated that the SAS programs will be provided in text format which is platform independent and will not be immediately executable. Instructions for executing programs will be provided. FDA stated that this proposal was acceptable.

FDA Final Response: The proposed plans for SAS dataset programs are acceptable.

Question 10: Statistical analysis plan

Does the Agency agree that the statistical analyses for the pivotal phase 3 study described in the analysis plan (especially with regard to the primary and secondary endpoints for efficacy) submitted to the IND (SN 104 dated November 16, 2009) and amended [Appendix 10] are adequate to support the filing of the application?

FDA Preliminary Response:

Statistics:

The Statistical Analysis Plan (SAP) with respect to the primary and secondary endpoints for efficacy submitted to the IND on November 16, 2009, and amended in Appendix 10 does address the following recommendations as described in the letter from the Division dated November 28, 2006, in response to the request for a Special Protocol Assessment:

- a) For the month 6 primary efficacy analysis, we recommended that patients who meet the stopping criteria at month 3 are classified as "non-responders". Patients who meet the "non-responder" criteria at month 3 then have their treatment assignment unblinded, and switch over to open-label treatment. They therefore continue to contribute supportive efficacy and safety data. All other patients continue their same randomized, blinded pasireotide dose through month 6. This approach addresses the concern that we expressed at that time that any partial unblinding prior to the month 6 primary efficacy period could substantially limit interpretation of the safety and efficacy of each dose due to potential confounding between dose and responder status.
- b) The definition of the Intent-to-Treat population (ITT) includes all randomized patients who received at least one dose of pasireotide.
- c) The SAP includes acceptable pre-specified plan for dealing with missing UFC measurements.
- d) For the primary analysis, patients who are "responders" before Month 6 but not at Month 6 are considered as "non-responders" for the primary analysis.

e) For the primary efficacy analysis, two 95% confidence intervals of the percentage of responders, one for each dosage group, are calculated without adjustment for multiple comparisons.

f) The SAP includes the additional supportive analyses as recommended in the letter dated November 28, 2006.

Clinical Pharmacology:

Your plans for PK analyses and PK-PD assessment appear reasonable. However, the adequacy of the conclusions made from your analyses will be a review issue. Please submit all the datasets and corresponding codes for these analyses. We encourage you to refer to the following pharmacometric data and models submission guidelines:

All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.,: myfile_ctl.txt, myfile_out.txt). Provide a model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion during FDA meeting: *None; sponsor accepts FDA Preliminary Response.*

Question 11: Case Report Forms/Patient narratives

Does the Agency agree that the Novartis proposal will fulfill the NDA review requirements with respect to CRFs and patient narratives?

FDA Preliminary Response:

We agree with your proposal. Please confirm whether these terms were assembled *a priori*.

Discussion during FDA meeting: *None; sponsor accepts FDA Preliminary Response.*

Question 12: Priority Review

Novartis intends to request priority review based on the justification that there is no approved medical treatment for the Cushing's disease population making it an unmet medical need. Does the Agency agree that justification provides a basis for priority review?

FDA Preliminary Response:

The decision for Priority review is made at the time of NDA filing.

Discussion during FDA meeting: *None; sponsor accepts FDA Preliminary Response.*

Additional Clinical Comments:

- 1) Regarding Study 2208, please offer more detail about the 5 responder subjects versus the non-responders. Specifically, what was the status of their Cushing's (*de novo*, persistent, or recurrent)? Of the subjects with persistent or recurrent disease, which prior therapies were used?
- 2) Regarding Study 2305, the NDA should present an in-depth breakdown of the diabetes/glucose intolerance status of the Phase 3 subjects. This, at a minimum, should include:
 - an analysis of the percentage of subjects with diabetes/glucose intolerance at baseline and throughout the study
 - data regarding antidiabetic therapy at baseline (including dosage) and throughout the study
 - the addition of antidiabetic therapy and/or up or down-titration of such therapy
 - discontinuation of antidiabetic drugs during the study
- 3) You should present HbA1c data in the form of a delta graph in order to appreciate changes in individual's glycemic profiles. An example of this graph is attached.
- 4) Given the small number of subjects enrolled and the lack of a control group, it would be beneficial for you to submit individual patient profiles. At a minimum, each profile should include:
 - Subject information: patient ID, sex, age, race, ethnicity, responder/non-responder status, date of first exposure to treatment, date of last exposure to treatment, reason for discontinuation, duration of treatment)
 - Timeline indicating study visits
 - Brief history of the subject's Cushing's disease
 - Diagnostic criteria met for study inclusion
 - Medical history
 - Vital signs at each study visit
 - Blood pressure-lowering medications (including starting and ending dates)
 - Fasting blood glucose and HbA1c values (by date)
 - Glucose lowering medications (start and stop dates)
 - Cortisol and ACTH data
 - Study drug exposure list of adverse events
 - List of concomitant medications

Discussion during FDA meeting regarding Additional Clinical Comment #2: Refer to sponsor's slides at the end of this document. The sponsor stated that it can supply all requested information except dosing information, which was not collected. Patient profiles with concomitant medications (with start and end dates) can be provided. The sponsor stated that it is interested in filing for priority review and requested FDA's advice regarding efficacy. FDA noted that the response rate was about 20% for cortisol normalization and asked if this seemed relevant to the sponsor. The sponsor's expert consultant replied that there is no approved medical treatment for Cushing's Disease, and a 20% cortisol normalization response rate would be regarded as a useful therapeutic tool by practitioners. FDA asked for further information about the data and individual patients. Were the patients studied de novo, or did they have prior therapy? If so, what were the other therapies? The sponsor stated that there were two analysis points, at 6 months and 12 months, in addition to intermittent urinary free cortisol (UFC), as well as other parameters. FDA asked if a trend could be seen. The sponsor replied that pasireotide works quickly in the first month, with a decrease in UFC. Within two months, non-responders can be predicted for the 6-month and 12-month time points. (The sponsor followed the prior FDA recommendation to follow patients to 12 months.) FDA asked about the subjects who did not initially respond. For those who were up-titrated, how many patients responded? The sponsor replied that only 3 patients were up-titrated and ended up responding with a further decrease in UFC.

FDA noted that the 600 mcg dose indicated minimal response, while there was response to the 900 mcg dose. The sponsor said that the duration of the Phase 2 (dose-finding) study was only 15 days, yielding mild-to-moderate cortisol level changes. Patients were randomized to 600 mcg and 900 mcg doses, and at baseline there was an imbalance between these two groups, with the 600 mcg group having a higher baseline mean UFC level.

FDA asked the sponsor to clarify what is its proposed dose considering the lower responder rate for the 600 mcg dose. The sponsor reminded FDA that the 900 mcg dose met the primary endpoint, so will begin with this dose and continue to look at the response over the first two months of treatment. If there is no clinical benefit (i.e., reduction in UFC), then discontinuation from drug treatment will be recommended. FDA replied that this proposal appears reasonable and that it will be a review issue.

FDA inquired as to whether there would be a wash-out period for patients receiving other prior treatment. The sponsor replied that the per-protocol analysis included elimination of such patients who had such prior therapy. FDA asked what percentage of patients studied was naïve. The sponsor noted that the drug typically was not a first-line therapy (i.e., approximately 85% of patients had prior surgery), and that analyses for both naïve and treated patients would be conducted.

The sponsor mentioned that there were all-comers in the trial who were not surgical candidates; patients did not have to have elevated cortisol levels in order to be included in the study. Some were responders who wanted additional treatment. The sponsor stated that concomitant medications were not routinely recorded at each study visit.

FDA noted that the sponsor should elaborate on this in the submission (b) (4) and provide data on cortisol levels before patients were taken off therapy.

The sponsor noted that all laboratory work (UFC levels) was conducted by a centralized lab. Patients were studied in 19 countries at 68 clinical sites. There were about 5 patients on average enrolled per month, as it was difficult to recruit subjects (a significant number of patients did not have 1.5-2X ULN urinary free cortisol levels). The population could be described as being shifted to the right; with this particular patient population, it is unethical to have a placebo arm in the clinical trial. For mild Cushing's patients, treatment could be more effective but the study design utilized in this clinical trial cannot ascertain this.

FDA asked if de novo patients were less severely affected than patients receiving previous therapy and then washout. The sponsor replied that as there were only 15% of patients who fell into this category, it would be hard to say. However, the efficacy was not that different between de novo and recurrently treated Cushing's patients. The sponsor committed to providing these data.

Discussion following FDA meeting regarding Additional Clinical Comment #4:

On December 21, 2010, Leslie Bennett of Novartis sent via secure electronic mail to Jennifer Johnson of this Division, a sample template to address Additional Clinical Comment #4 regarding individual patient profiles. This sample template is acceptable to our clinical and statistical reviewers. You should also include a profile plot of the primary endpoint over time for each patient.

Additional Comments from Division of Scientific Investigations (DSI):

Sections I and II concern submission of data to the NDA that will be used for inspections of the clinical site and sponsor. Section III and the document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" are information requests concerning the DSI pilot "risk based site model" computer program. This program uses a computer model to choose clinical sites for inspection.

- I. Request for general study related information as well as specific Clinical Investigator (CI) information to be used in site selection:
 - A. Please include the following information in a tabular format for the clinical trial:
 1. Site number
 2. Primary investigator
 3. Location: City State, Country, including contact information (phone, fax, email)
 - B. Please include the following information in a tabular format by site for the clinical trial:
 1. Number of subjects screened at each site by site

2. Number of subjects treated at each site by site
3. Number of subjects treated who prematurely discontinued at each site by site

C. Please include the following information in a tabular format for the clinical trial:

1. Name, address and contact information of all Contract Research Organizations (CROs) used in the conduct of the clinical trials
2. 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
3. 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.)

D. Sample blank case report form

II. Request for Individual Patient Data Listings to be used for inspections:

For Protocol CSOM230B2305 entitled “A randomized, double-blind study to assess the safety and efficacy of different dose levels of pasireotide (SOM230) s.c. over a 6 month treatment period in patients with *de novo*, persistent or recurrent Cushing’s disease”, please submit site-specific individual subject data (“line”) listings from the datasets:

1. Line listings for each site listing the subject number screened and reason for subjects who did not meet eligibility requirements
2. Line listings by site and subject, of treatment assignment and treatment administered.
3. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
4. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
5. Line listings by site and subject, of AEs, SAEs, deaths and dates
6. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
7. Line listings by site and subject, of the primary endpoint efficacy parameter, mean urinary free cortisol (UFC), and the individual values used to calculate the mean
8. Line listings by site and by subject, of concomitant medications including those medications used to treat glucose intolerance.

III. Request for Site Level Data for the risk based model

DSI 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 the attached document, “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 datasets, as outlined, for the study submitted in your application.

Discussion during FDA meeting: None.

Additional Discussion During FDA meeting

Denial of Fast-Track Designation Request:

The sponsor inquired further regarding the reason for the denial of fast track designation (the sponsor submitted a request for fast-track designation on July 2, 2010, and a denial letter was issued on August 14, 2010). What did FDA mean by stating in the letter that the sponsor did not address a serious aspect of the disease?

FDA replied that it followed the requirement listed in the FDA Guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf>) which stated that the sponsor had to meet a serious medical need, and noted that the primary endpoint (urinary free cortisol levels) is well-established as a valid diagnostic measure. However, what other surrogate biomarkers would be measured to bolster this endpoint (i.e., decreased hospitalization rates)? The sponsor noted that it has been shown that a decrease in UFC levels has led to an increased quality of life. The FDA replied that it is cautious about accepting quality of life endpoints, especially in clinical trials that are not placebo-controlled. It probably would not be an acceptable endpoint for addressing the serious aspect of the disease, as required by the Guidance pertaining to fast track designation requests.

(b) (4)

(b) (4)

The sponsor asked if FDA would consider objective measures (i.e., blood pressure, weight, total cholesterol/triglycerides, photographic evidence (before and after) for blinded patients, and decline in BMI (surrogate of cardiovascular outcomes endpoint). The FDA replied that these measures can be submitted again if they weren't included in the original request.

FDA noted that other drugs that used these biomarkers have not received fast-track designation in the past, and recognized that Cushing's Disease is a rare condition with an unmet medical need. However, the Agency is not sure that these biomarkers would qualify pasireotide for fast-track designation, though. Such biomarkers need to be clinically relevant to qualify.

Pediatrics:

FDA recommended that the sponsor submit a Proposed Pediatric Study Request (PPSR) for studying pasireotide in the pediatric population, but the indication studied does not have to be Cushing's Disease.

(b) (4)

There was discussion of whether Cushing's disease in pediatric patients

should be studies since pediatric patients do develop Cushing's Disease (and would be used off-label). The sponsor's expert consultant confirmed that Cushing's Disease is present in the pediatric population and that pediatric patients are treated in the same way as adult patients (i.e., treated first with surgery). Concern exists in treating pediatric patients with radiation (which is a second-line therapy for adult patients), as neurocognitive damage can result. The sponsor stated that it is not prepared to discuss pediatric use further at this time.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

- Slides presented by Novartis Pharmaceuticals Corp. at Pre-NDA meeting
- Industry Site Level Data Request document from Division of Scientific Investigations
- Sample delta graph supplied by FDA (pertaining to Additional Clinical Comment #4)

Pasireotide Pre-NDA meeting Cushing's Disease

August 30, 2010
10 a.m. – 11 a.m.



Pre-NDA Meeting Agenda

- Introductions
- Novartis accepts the preliminary responses to questions 2, 4, 7, 10-11 and with all additional comments with the exception of Additional Clinical Comment 2
- The following questions will be discussed:
 - Clinical (Geromo Gericke)
 - Questions 1, 3, 5, 6
 - Additional clinical comment #2
 - Statistical (Antonella Maniero)
 - Question 8 and 9

Question 1: Overall Contents of NDA

Renal Impairment

- FDA's Preliminary Response – Clinical Pharmacology:
 - *Renal function are not only required for drugs which are substantially eliminated renally, but also for drugs which are primarily metabolized or secreted in bile. Also, such PK studies are recommended for most drugs intended for chronic use.*
 - *Therefore, you should address the effect of renal function impairment on pasireotide PK in your NDA submission. Some of the possible options are: (1) conduct a dedicated study in renally impaired subjects, or (2) analyze the effect of renal impairment in population PK and PK-PD analysis using Phase 3 data.*
- Novartis intends to provide option 2 in the submission

Question 3: Scope Summary of Clinical Safety

□ FDA's Preliminary Response

Your proposal is acceptable. Regarding the integrated safety reports (glucose metabolism and cardiovascular events), it is unclear which adverse event terms will be used and what methodology is planned to generate and present these reports. Please provide more detail about these analyses. Furthermore, given the stark differences between the 2 trials (study duration, dosing) the pooling of terms may not provide useful data on which to draw conclusions about the safety of pasireotide. Also, discuss whether the terms were defined a priori.

Question 3: Glucose Metabolism

- 34 MedDRA Preferred Terms from SMQ “Hyperglycemia/new onset diabetes mellitus” were used
- All terms were defined *a priori* in the analysis plan of pivotal study B2305 (prior to Month 6 analysis database lock)
- All patient studies are presented individually and HV studies were pooled if appropriate

Question 3 cont'd

Glucose Metabolism Report: Analyses

- Summary of preclinical glycemia-related results
- HV Studies
 - Descriptive summaries of Glucose, Insulin and Glucagon levels
 - Dedicated mechanistic study (hyperglycemic clamp; euglycemic clamp and OGTT)
- Patient Studies
 - Descriptive summaries of measures of glycemia
 - Predictive factors for clinically significant hyperglycemia
 - Analysis of hyperglycemia-related AEs

Question 3 cont'd

Cardiovascular Report - Overview

- Preclinical Summary of the cardiovascular effects including cardiac repolarization
- HV Studies (pooled analysis)
- Patient Studies
 - Detailed analysis of B2305 including narratives
 - Pooled analysis across entire clinical program
- Safety database review for QT-related SAEs using the full SMQ “Torsades de pointes/QT prolongation” plus additional preferred term “convulsion”
- Terms defined a priori in the analysis plan of pivotal study B2305 (prior to Month 6 database lock)¹

¹ the term (“convulsion”) was added after the database lock:
7 | Pre-NDA Meeting | Novartis | August 30, 2010 | Business Use Only

Question 5 and Question 6

- FDA's Preliminary Response to Question 5
The data from your proposed second QT study should be submitted at the time of the NDA submission and not with the safety update.

- FDA's Preliminary Response to Question 6
Yes. Please refer also to our response to question 5.

Question 5: Additional TQT Study

Question 6: Safety Update Contents

- Outlined in the briefing package the NDA will include:
 - An E14 compliant B2113 TQT study
 - Primary endpoint of QTcF does not rule out QT prolongation
 - A cardiovascular report across the entire program
 - Proposed Label and RMP will reflect the results of B2113
 - *Is this submission acceptable for filing in December?*
- Additional data from TQT Study 2125 is anticipated in March 2011
 - Further characterizes the TQT effect using QTcI
 - *What is the potential impact if this study is submitted during the review?*

Question 8: Electronic datasets

FDA Preliminary Response:

We request that the raw and derived datasets be submitted as SAS transport files. We request the use of structure and formats for datasets that follow the principles for data submission and analysis, as outlined by the Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM); (see www.cdisc.org). The file structure and the accompanying documentation in [define.pdf](#) files should enable us to readily confirm the results from key endpoints, and to conduct additional supportive analyses.

Present laboratory results in US rather than SI units. Provide normal ranges for all tests.

Question 8: Electronic Datasets – SI/US Units

- The NDA could include a separate database with lab values and normal ranges in US units for the pivotal study B2305

Question 8 cont'd: Electronic datasets

- Raw and derived datasets will be submitted in SAS XPORT transport file format.
- Annotated case report form will be provided in pdf format.
- Data definition table will be submitted as define.pdf which provides the source derivation for each variable in the datasets. The hypertext link will also be provided from the define.pdf to the SAS transport files and the annotated case report form.

Question 9: “Nonexecutable” analysis programs

┆ FDA Preliminary Response:

Please clarify what is meant in part 2.2.8.1 of the briefing document by “nonexecutable” analysis programs in SAS for the analysis of the primary and key secondary efficacy endpoints. It may be useful to provide an example.

Question 9: Dataset and Analysis programs

- Programs were written in SAS version 9.2 under UNIX environment.
- The SAS programs will be provided in text format which is platform independent and not immediately executable
- Instructions for executing programs will be provided
 - The programs can be executed after setting up the global programming environment (libnames and file references for locating datasets and outputs) and the study-specific environment (macros provided)

Additional Clinical Comment #2

□ FDA Preliminary Response:

2) Regarding Study 2305, the NDA should present an in-depth breakdown of the diabetes/glucose intolerance status of the Phase 3 subjects. This, at a minimum, should include:

- *an analysis of the percentage of subjects with diabetes/glucose intolerance at baseline and throughout the study*
- *data regarding antidiabetic therapy at baseline (including dosage) and throughout the study*
- *the addition of antidiabetic therapy and/or up or down-titration of such therapy*
- *discontinuation of antidiabetic drugs during the study*

□ Novartis can supply all requested information except dosing information which was not collected. An extensive analysis of glucose metabolism is provided in the Phase 3 CSR, GMR, SCS and RMP.

Pasireotide NDA

- Cushing's disease is an unmet medical need
- This is the largest Phase 3 study ever conducted in this disease
- We consider the proposed NDA package to be complete
- Will include the requested additional analysis as outlined in the preliminary responses

Summary Level Clinical Site Data for
Data Integrity Review and Inspection
Planning in NDA and BLA
Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. 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 and are not intended to support evaluation of efficacy. 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 Variance (TRTEFFV) – the variance 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 Variance (SITEEFFV) – the variance 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.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

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). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Summary Level Clinical Site Data Elements

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/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
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount (\$USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
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: General Structure of Data Submission Template

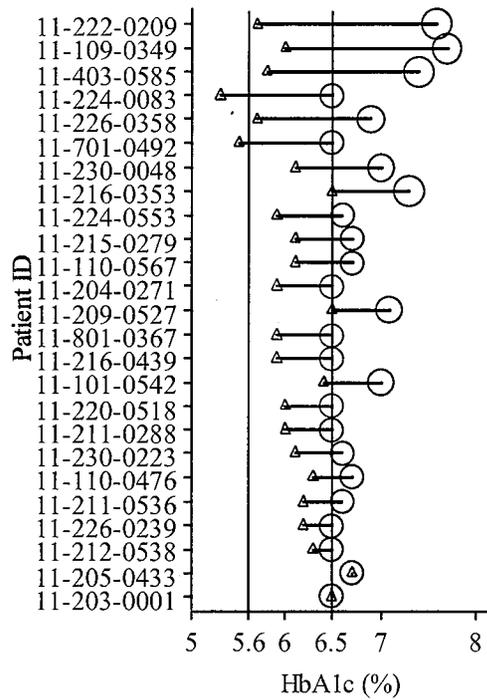
IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	0	1	0.00	Lincoln	Abraham	555-987-6543

FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Pre-NDA Meeting
 IND 068635
 Sample delta graph to accompany Additional Clinical Comment #3

CTR-1011



Sorting is by delta amount
 (smallest sort value at bottom)
 TRT1P at start:
 ■ TH9507 2 MG
 ■ PLACEBO
 Δ Start
 ○ End (sized to value of HbA1c)

Reference ID: 2897458

Reference ID: 3236009

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

/s/

JENNIFER L JOHNSON
01/27/2011

Reference ID: 2897458

Reference ID: 3236009

June 5, 2006



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 68,635

EOPA mtg.

Novartis Pharmaceuticals, Corporation
Attention: Lisa L.P. Tran, MSc.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Tran:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SOM230B (pasireotide) s.c. Injection.

We also refer to the meeting between representatives of your firm and the FDA on May 15, 2006. The purpose of the meeting was to discuss your Phase 3 clinical development program and the requirements for registration of this drug product for the treatment of Cushing's disease.

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 301-796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology
Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 15, 2006
TIME: 10:30 AM – 11:40 AM
LOCATION: White Oak, B. 21, R. 1539
APPLICATION: IND 68,635
DRUG NAME: SOM230 s.c. (Pasireotide Subcutaneous Injection)
TYPE OF MEETING: End of Phase 2
MEETING CHAIR: Theresa Kehoe, M.D.
MEETING RECORDER: Enid Galliers

FDA ATTENDEES:

Robert J. Meyer, MD, Director, Office of Drug Evaluation II (ODE II), Office of New Drugs (OND), CDER

Curtis Rosebraugh, MD, Deputy Director, ODE II

Mary Parks, MD, Acting Director, Division of Metabolism and Endocrinology Products (DMEP), ODE II

Theresa Kehoe, MD, Acting Medical Team Leader, DMEP

Joanna K. Zawadzki, MD, Medical Officer, DMEP

Karen Davis-Bruno, PhD, Supervisory Pharmacologist, DMEP

Dylan Yao, PhD, Pharmacology Reviewer, DMEP

Enid Galliers, CPMS, DMEP

Jim Wei, PhD, Biopharmaceutics Reviewer, Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics (OCPB), Office of Translational Sciences (OTS)

Todd Sahlroot, PhD, Biometrics Team Leader, Division of Biometrics II (DB II), OB, OTS

Janice Derr, PhD, Biometrics Reviewer, DB II

EXTERNAL CONSTITUENT ATTENDEES:

Novartis

Lisa Tran, MSc, Associate Director, Drug Regulatory Affairs (DRA)

Pio Zapella, PhD, Manager, Global DRA

Gabriela Gruia, MD, Executive Director, Group Leader, Clinical Research

Joan Glusman, MD, Medical Director, Clinical Project Leader, Clinical Research

Yanfeng Wang, PhD, Team Leader, Clinical Pharmacology

Bo Gao, PhD, Associate Director, Biostatistics & Statistical Reporting

Mokash (Moke) Sharma, Project Leader

Chin Koerner, FDA Liaison Office

External Consultant

[Redacted block with (b) (4) label]

BACKGROUND:

SOM230 subcutaneous injection is a somatostatin analog that is being developed for Cushing's disease (under review in DMEP) [Redacted block with (b) (4) label]

[Redacted block with (b) (4) label] An End of Phase 2 (EOP2) meeting was held between DODP and Novartis for the carcinoid indication on April 27, 2005.

This meeting was requested in a letter dated March 14, 2006, and the meeting package (background information), dated April 14, 2006, was received April 17, 2006.

MEETING OBJECTIVES:

- To obtain concurrence that the preclinical safety program for the DODP indication is adequate to support registration of the Cushing's disease indication.
- To obtain concurrence that the proposed hepatic impairment study and the QT study designs are acceptable to support the clinical pharmacology program for Cushing's disease.
- To obtain concurrence that the proposed study design for the single, Phase 3 clinical trial is adequate to support registration of the Cushing's disease indication.

DISCUSSION POINTS AND DECISIONS (AGREEMENTS) REACHED:

Questions from the sponsor's briefing document are in bolded text, and FDA preliminary responses (communicated by secure email on May 10, 2006) are shown in italicized text.

Additional discussion at the May 15 meeting and Novartis' additional questions/proposals are represented in bold, italicized text.

Nonclinical

Question 1

Reference is made to an EOP2 meeting between Novartis and the (b) (4)

(b) (4) Questions, company position and FDA response to the questions posed in the briefing book can be found in Appendix 5. Novartis gained agreement with the DODP that the proposed preclinical safety program adequately supports the registration of (b) (4) SOM230 for the treatment of symptoms in patients with (b) (4) tumors, as well as agreement to file results from the 2-year rat carcinogenicity study as a post-approval commitment. Does the Division of Metabolism and Endocrinology Products (DMEP) find these agreements made with the DODP to be acceptable, i.e. does the Agency agree that the proposed preclinical safety program adequately supports the registration of SOM230 s.c. [subcutaneous (s.c.)] for the treatment of Cushing's disease patients, and that the 2-year rat carcinogenicity study can be filed as a post-approval commitment?

FDA RESPONSE: *The proposed preclinical safety program appears adequate to support SOM230 s.c. for the Cushing's indication.* (b) (4)

- ***Novartis:*** *The transgenic mouse carcinogenicity study will be filed with the NDA.* (b) (4)

- ***FDA Response:*** *No, this plan is not acceptable.* (b) (4)

Clinical

Questions 2 and 3 seek advice on the proposed clinical program supporting the initial filing of SOM230 s.c. in the proposed indication [i.e., for the treatment of Cushing's disease in patients

for whom medical therapy is adequate] and Questions 4 to 7 focus on the Clinical Pharmacology program.

Question 2

In study CSOM230B2305 Novartis intends to enroll 85 patients in an open-label, single arm study in which patients will receive SOM230 s.c. 600 µg b.i.d. for 6 months. A $\geq 50\%$ reduction from baseline in urinary free cortisol after 3 months treatment will be the primary endpoint for the study. For detailed information on design, see Section 3.4.3 and Appendix 8.

a) Novartis considers that the proposed 'inclusion and exclusion' criteria are adequate to define the target population for label in which the efficacy and safety of SOM230 s.c. in the treatment of Cushing's disease (for which medical therapy is appropriate) is being assessed. Do you agree?

FDA RESPONSE:

We believe the inclusion and exclusion criteria are adequate to define the target population. However, the population for which the drug may eventually be indicated may not be the same as the inclusion and exclusion criteria. Since Cushing's disease can be surgically cured, surgical treatment should not be denied or excessively delayed for patients who are surgical candidates.

- ***Novartis:*** *In the proposed registration study, the de novo patients who have not had surgery will be restricted to those for whom surgery will be deemed not recommended, inadequate, inappropriate, not feasible, or extensively delayed due to medical condition or concomitant, contraindicated medication(s). In addition, de novo patients who may have had surgery but have not had drug therapy will be restricted to those who have failed surgery or have recurrent disease.*
- ***FDA response:*** *This more specific description of inclusion and exclusion criteria is acceptable.*

(b) (4)

FDA RESPONSE:

(b) (4)

- ***Novartis:*** *Based on FDA comments and suggestions Novartis is proposing the following definition of response for the primary endpoint:*

(b) (4)

Does the Agency agree?

- **FDA response:** *This definition of response for the primary endpoint is an improvement in that it excludes patients with persistent very high levels of cortisol from the responder group.* (b) (4)

c) Novartis considers that the proposed duration of study CSOM230B2305 is adequate to assess the safety and efficacy of SOM230 s.c. in the studied population. Do you agree?

FDA RESPONSE:

No. Cushing's disease is a chronic disease, and we believe that the primary endpoint should be measured at six months of therapy with SOM230, (b) (4) Patients should be followed for an additional 6 months to evaluate the maintenance of the response.

- **Novartis:** *We agree with the Agency's proposal to measure the primary endpoint at 6 months with an additional 6 month follow-up. The NDA will contain 100% of the 6-month treatment data, (b) (4) Does the Agency agree that the remainder of the data can be filed at the time of the 120-day safety update?*
- **FDA response:** (b) (4) *(b) (4) especially since SOM230 is a new molecular entity, and durability needs to be documented for the proposed chronic use of this drug. We can further discuss the content of the NDA submission at the pre-NDA meeting.*
- *The possibility of a priority (6-month) review of the NDA was mentioned.*

[As a reference, we quote the definitions of the priority NDA designation (MAPP 6020.3 Priority Review Policy dated 4/22/96):

[P – Priority review]

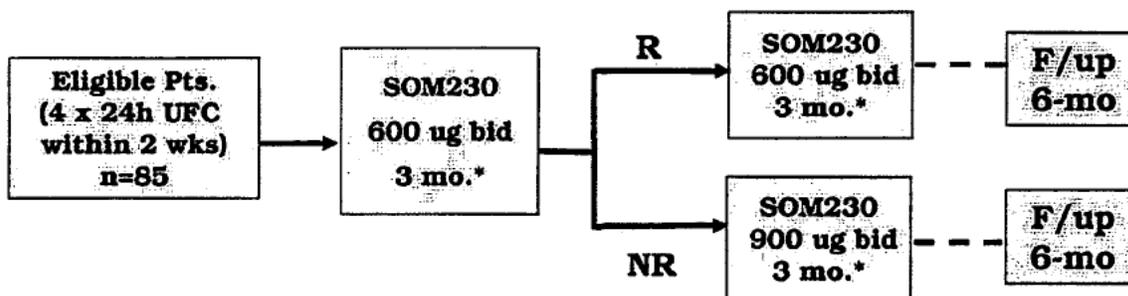
The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.]

- **d) Novartis considers that the selected doses of SOM230 s.c. are appropriate. Do you agree?**

FDA RESPONSE:

The sponsor has not conducted a dose ranging study and has not shown whether 600 ug BID is an optimal dose. We do not believe there is sufficient data available to support the appropriateness of the selected doses. We recommend further dose-ranging data be collected.

- **Novartis:** Novartis will collect additional dose ranging data in the proposed registration study and proposes the following study design in response to FDA's comments:



•Dose decrease for tolerability allowed at any time

R = responder; NR = non-responder

Endpoints:

- 1° - [REDACTED] (b) (4)
- 2° - **time to response**
 - **normalization of UFC at month 6**
 - **serum cortisol, plasma ACTH**
 - **improvement in clinical signs + symptoms**
 - **GOL**



Based on study 2208, 600 ug BID is an appropriate starting dose

- most patients remained at 600 ug BID throughout the study
- dose reduction to 450 ug BID was rare (n=1) and short term (!1 month)
- dose increase to 900 ug BID was available; of the 6/14 patients who dose escalated, 3 normalized UFC.

Dose titration reflects expected clinical usage

- **Novartis:** Regarding the comparison of two doses of SOM230, Novartis commented that the FDA-recommended approach might enable observation of a numerical difference between 2 dose levels, which would provide indirect evidence of treatment effect. Novartis' proposed design could enable additional efficacy to be observed at a higher dose level. The firm believes that this alternative approach could also provide evidence of treatment effect and its approach only exposes those patients who require additional efficacy to a higher dose.

- *Novartis had studied dose ranging (SOM230 200 µg bid, SOM230 400 µg bid, and SOM230 600 µg bid) in patients with acromegaly. The sponsor reported that the SOM230 600 µg bid dose was optimal as it had twice the efficacy of the SOM230 400 µg bid dose. In the Cushing's disease Phase 2 15-day core study, the SOM230 600 µg bid dose was tested.*

FDA response:

- *FDA recommended inclusion of a lower dose (e.g., SOM230 300 µg bid) to assess tolerability, justify the higher dose, and document that the dose proposed for marketing is the lowest effective dose.*
- *The interpretability of the responder (R) and non-responder (NR) groups was discussed in the context of (1) a cutpoint versus gradient of response and (2) absence of randomization of the two groups. It was noted that it was difficult to apply traditional trial design methodology to patients with Cushing's disease, but FDA emphasized that the data would need to be convincing (i.e., that the data could not be a result of chance alone) to meet approval of the proposed indication.*

Post-Meeting Note: *FDA noted a concern that the study design proposed by Novartis may produce results that are difficult to interpret. The proposed design confounds the dosage with responder status at 3 months. Responder status may define two different patient populations. With the proposed study design, it would not be possible to separate the effect of dose from the effect of responder status at 3 months.*

e) Novartis considers that an open-label, single arm design is appropriate to assess the safety and efficacy of SOM230 s.c. in Cushing's disease. Do you agree?

FDA RESPONSE:

Though it is appropriate not to have a placebo treatment group in a serious, progressive, chronic disease that can be surgically treated, the absence of a comparator arm may limit interpretation of the final efficacy and safety data., The following additions to the study design may improve the interpretability of the data:

- *A four-week baseline period, with at least weekly measurement of UFC, to account for the normal variability of cortisol measurements seen in the population.*
- *Comparison of two treatment arms at two doses of SOM230 for 3 months, followed by increase to the higher dose for the next three months.*
- *Stopping rules should be included in the protocol so that patients who are not responding receive adequate treatment.*
- ***Novartis:*** *For baseline urinary free cortisol (UFC) measurement, Novartis proposed four (4) 24 hr urine collections for UFC, creatinine, and volume within a 2 week period (to overcome ethical concerns about delaying or withholding treatment to patients with Cushing's disease and improve clinical feasibility). In addition, the sponsor's consultant noted that the periodic hormonogenesis (or cyclic) variant of Cushing's disease can vary from 12 hour to 3 month cycles and that the urinary free cortisol measurements are predominantly borderline or just slightly above normal in these patients. Thus, a four-week rather than a two-week baseline would not necessarily identify patients with cyclic*

Cushing's disease, and the inclusion criterion of $UFC \geq 2x$ ULN would exclude patients with cyclic Cushing's disease.

- **FDA response: The four 24-hour baseline UFC measurements over a 2-week period are acceptable. The sponsor may use a mean of these four values, the lowest value as the baseline, or some other summary measure (see Additional FDA Comments.). In addition, since the study is uncontrolled, obtaining a multiplicity of different, objective measurements at baseline and end of treatment could prove useful in assessing the efficacy and safety of treatment with SOM230 in patients with Cushing's disease.**

See also comments under Question 2d.

Post-Meeting Note: The protocol should clarify how each pre-treatment UFC collection will be used in: (1) evaluating a patient's eligibility and (2) estimating the patient's baseline UFC. Because the study does not have a randomized placebo control group and will enroll patients on the basis of UFC values that are higher than normal levels, it is important to minimize the regression to the mean effect. Approaches that can minimize the contribution of the regression to the mean effect to the overall estimate of the clinical effect of SOM230 are: (1) Separating the UFC collections for eligibility from the UFC collections used to estimate baseline; (2) Using more than one UFC collection for each event, e.g., eligibility, baseline, 3 months, 6 months and 12 months; (3) Collecting information on several related clinical variables.

f) Novartis believes that enrollment of 85 patients is adequate to analyze the proposed primary efficacy endpoints. Do you agree?

FDA RESPONSE:

The enrollment will depend on the intra-patient variability of UFC and the degree of response. Since Cushing's disease is rare, it may be difficult to conduct a study with a much larger enrollment.

Question 3

Given that Cushing's disease is a very rare, serious debilitating and life-threatening condition for which there is currently no satisfactory medical therapy available, Novartis believes that the evidence provided by a single registration trial (CSOM230B2305), supported by the POC trial CSOM230B2208, is sufficient and adequate to demonstrate the efficacy and safety of SOM230 and support the filing of SOM230 solution for subcutaneous injection in the proposed indication. Do you agree?

FDA RESPONSE:

A single study may be adequate if there is sufficient data to support the proposed dosing as well as substantial convincing evidence that the decreases in UFC did not occur spontaneously. The interpretation of the safety data will be limited in an uncontrolled study.

Clinical Pharmacology

Question 4

Because SOM230 is expected to be predominantly eliminated via the hepatic route, Novartis intends to conduct a hepatic-impairment study. However, recruitment of subjects, particularly those who are severely hepatically-impaired, may be difficult and rate-limiting

for the submission of SOM230. Considering the high medical need for an effective therapy for Cushing's disease, Novartis believes that interim data on the hepatic impairment study would be sufficient to support the filing of SOM230. Does the agency agree?

FDA RESPONSE:

We agree that the interim data for hepatic impairment study may be submitted at filing time. A continuous effort should be made to complete the study with severely impaired hepatic patients.

Question 5

Preclinical data show no evidence that SOM230 carries a pro-arrhythmic potential. However, Novartis acknowledges that the data can not fully exclude the possibility of QTc prolongation in humans. In order to address this issue, we propose to conduct a 2-stage "thorough" QTc study (CSOM230B2113) in healthy volunteers. The 1st stage will guide the selection of a SOM230 dose to be used in the 2nd stage of the study. The 2nd stage will attempt to "rule-out" a positive QT effect. The study design in the 2nd stage will employ a single s.c. dose in 67 healthy volunteers, using a randomized, blinded, 3-period, 3-treatment (SOM230, placebo, moxifloxacin) design. For more detailed information on the study design please refer to Appendix 9. Novartis believes that:

a) A (b) (4) dose study at a dose of (b) (4) s.c. or above is appropriate to provide adequate exposure. Do you agree?

FDA RESPONSE:

a) *No. we disagree with (b) (4) s.c. single dose for the QT study. Since the drug's elimination half life is long (more than 13 hours) and 600 µg once a day regimen led 40 % accumulation, the 600 µg BID regimen will have more accumulation. We recommend (b) (4) doses for QT study using a highest tolerable dose with BID regimen to reach steady state exposure for QT assessment. The duration of the twice a day dosing may range from 3 to 7 days, depending on the final dose for subcutaneous administration.*

b) Novartis believes that the proposed sample size of 67 is adequate. Do you agree?

FDA RESPONSE:

b) *The sponsor should conduct a power calculation using variability.*

c) In the absence of a positive QTc signal in study CSOM230B2113, Novartis plans to collect ECGs in subsequent studies in accordance with the current investigational practices for the intended indications. Do you agree ?

FDA RESPONSE:

c) *Yes, we agree.*

Question 6

Reference is made to an EOP2 meeting between Novartis and the DODP held on April 27, 2005 and briefing book submitted on March 15, 2005 (b) (4) Questions, company position and FDA response to the questions posed in the briefing book can be found in Appendix 5. Novartis gained agreement with the DODP that further DDI [drug-drug interaction] studies with CYP450 substrates and inhibitors would not be necessary. Does the DMEDP also accept this agreement?

FDA RESPONSE:

We agree that CYP mediated DDI is remote for the compound and agree with prior agreement with DODP. In addition, P-glycoprotein (P-gp) involvement should be studied.

Question 7

Novartis believes that the proposed Clinical Pharmacology Development Plan is adequate to support the filing of SOM230. Do you agree?

FDA RESPONSE:

Yes, we agree.

Additional FDA Comments:

1. *What is the intra-patient variability in UFC measurements that are obtained on two subsequent days (as in the Core study at baseline and at follow-up)?*
- ***This topic was not discussed at the meeting. One of the Novartis representatives noted that the analysis is pending.***

Post-meeting note: *We would like to have more information about the within-patient variability of UFC levels. This information may be available from study B2208. This information may help:*

- *Develop the best way to characterize a patient's baseline UFC levels. For example, a geometric mean may be the best way to characterize a patient's baseline UFC, if UFC levels tend to have a lognormal distribution.*
- *Develop the best way to characterize a patient as a "responder." For example, it may be possible to identify a criterion for "responder" in a way that is not likely to occur by chance, based on the within-subject variability of UFC.*

We suggest that this information could be included in the protocol for study B2305.

2. *In the central laboratory, which methodology for measuring UFC is used?*
 - ***The sponsor has not yet decided which assay methodology will be used. An antibody-based methodology was used for the free cortisol measurements in the Phase 2 core study. Apparently, this assay is not specific for cortisol and the values may include metabolites. For this reason, the upper limit of normal for that assay is high (276 nmol/day).***
 - ***The sponsor would prefer to use HPLC methodology and will submit the selected methodology in the protocol submission.***
 - ***Also, was the reference range based on the laboratory's own measurements in healthy, unstressed adult volunteers or is it a literature reference range?***
 - ***The sponsor concurred that an assay with the laboratory's own reference range is preferable.***

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/s/

Enid Galliers

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