

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200677Orig1s000

OTHER REVIEW(S)

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

Label, Labeling and Packaging Review

Date: December 14, 2012

Team Leader: Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Division Director: Carol A. Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Signifor (Pasireotide) Injection, 0.3 mg/mL,
0.6 mg/mL and 0.9 mg/mL

Application Type/Number: NDA 200677

Applicant/sponsor: Novartis

OSE RCM #: 2012-473

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

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Signifor NDA 200677 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

NDA 200677 was submitted to the Agency (after a prior withdrawal) for review on February 17, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 17, 2012 proprietary name submission.

- Active Ingredient: Pasireotide
- Indication of Use: Somatostatin analogue indicated for the treatment of patients with Cushing's disease who require medical therapeutic intervention.
- Route of Administration: Subcutaneous Injection
- Dosage Form: solution for injection
- Strength: 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL
- Dose and Frequency: The recommended initial dose is 0.9 mg subcutaneously twice daily. An initial dose of 0.6 mg twice a day may be considered for patients with pre-diabetes or diabetes mellitus. The recommended initial dose for patients with moderate hepatic impairment (Child Pugh Class B) is 0.3 mg twice daily. A maximum dose of 0.6 mg twice daily is recommended for patients with moderate hepatic impairment.
- How Supplied: Boxes of 60 ampules
- Container Closure: Glass Ampule with Paper Label
- Storage: Store at 77° F, protect from light

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

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

- Container Labels submitted February 17, 2012 (Appendix A)
- Carton Labeling submitted February 17, 2012 (Appendix B)
- Insert Labeling submitted December 6, 2012

3 RECOMMENDATIONS

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

A. Ampule Container Labels (All Strengths)

1. Revise the expression of strength so that the strength is expressed per mL without the use of the number one. For example:

XX mg per mL or XX mg/mL

2. Relocate the dosage form statement to appear immediately following the active ingredient. The finished dosage form is a component of the established name. Additionally, revise the dosage form to read “for injection” rather than (b) (4) Moreover, ensure the word injection appears in the same font and style and with the same prominence as “pasireotide”. For example:

Signifor
(Pasireotide) Injection
0.9 mg/mL

3. Decrease the size of the manufacturer statement as it appears as prominent as the proprietary and established names and product strength. The proprietary and established names and strength should be the most prominent information on the labels.

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

4. Increase the size and prominence of the statement of strength.
5. Increase the prominence of the middle four numbers of your National Drug Code (NDC) number, as this is an added method of differentiation between your product strengths.
6. The yellow font color used on your 0.9 mg/mL label is difficult to read. Revise the label to use a different font color to improve readability.

B. Carton Labeling (all strengths)

1. Relocate the dosage form statement to appear immediately following the active ingredient. The finished dosage form is a component of the established name. Additionally, revise the dosage form to read “for injection” rather than (b) (4). Moreover, ensure the word injection appears in the same font and style and with the same prominence as “pasireotide”. For Example:

Signifor
(Pasireotide) Injection
0.9 mg/mL

2. Revise the expression of strength so that the strength is expressed per mL without the use of the number one. For example:

XX mg per mL or XX mg/mL

3. Although the strength is surrounded by a color block, the statement of strength is presented in the same color (red) across all carton labeling. This diminishes the product strength differentiation within the product line. Revise your labeling to present the three strengths in a different color as seen on your container labels. Additionally, revise the font color of the proprietary name to match the presentation on the container labels as well (e.g., black for (0.03 mg/mL)

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

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

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

/s/

JAMIE C WILKINS PARKER
12/14/2012

CAROL A HOLQUIST
12/14/2012

Cushing's disease is a rare disease in which the pituitary gland releases excess adrenocorticotrophic hormone (ACTH), triggering the production and release of excess amounts of cortisol by the adrenal glands. Cushing's disease is caused by a tumor or hyperplasia of the pituitary gland. Signifor (pasireotide diaspertate) is indicated for the treatment of patients with Cushing's disease for whom surgery is not an option or for whom surgery is not curative. Signifor (pasireotide diaspertate) was granted an orphan drug designation for the treatment of Cushing's disease. Known and potential safety concerns include: serious (requiring treatment in Emergency Department, hospitalization, or death) cases of hyperglycemia, liver-related adverse events (b) (4), events potentially related to QT prolongation, deaths (including causes of death), atypical infections, and adrenal insufficiency. Given the small population affected by this disorder, the small number of patients studied, and the short duration of clinical trials, a postmarketing registry is required to generate additional person-years of exposure to assess risks related to the long-term use of the drug.

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

The paucity of long-term safety data on Signifor (pasireotide diaspertate) remains a concern. Because of the rarity of Cushing's disease, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Signifor (pasireotide diaspertate) is limited. The clinical development program revealed known and potential serious risks associated with Signifor (pasireotide diaspertate) use including hyperglycemia, liver-related adverse events, QT prolongation, atypical infections, and adrenal insufficiency.

The goal of the registry is to generate additional person-years of exposure to assess these serious risks related to Signifor (pasireotide diaspertate) use. The registry will include a sample of patients prescribed Signifor (pasireotide diaspertate) and followed for 3 years from the date of last patient enrollment.

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

- **Which regulation?**

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

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

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

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

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

A long-term prospective observational cohort study (registry) of patients with Cushing’s disease treated with Signifor (pasireotide diaspertate). The registry will continue for 3 years from the date of last patient enrollment and will address the following safety issues: serious (requiring treatment in Emergency Department, hospitalization, or death) cases of hyperglycemia, liver-related adverse events (b) (4), events potentially related to QT prolongation, deaths (including causes of death), atypical infections, and adrenal insufficiency.

The registry will include an adequate sample of patients prescribed Signifor (pasireotide diaspertate) and followed for at least 3 years to describe the following:

- Patient age, sex, and race
- Country of treatment
- Medical history
- Concomitant medications, including start and stop dates
- Signifor (pasireotide diaspertate) dose, duration of use, start date, discontinuation date, reasons for discontinuation, person-years of exposure
- Liver enzyme monitoring frequency

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # 200677
Product Name: Signifor (pasireotide diaspertate)

PMR/PMC Description: An assessment and analysis of spontaneous reports of hyperglycemia, acute liver injury, and adrenal insufficiency in patients with Cushing's disease treated with Signifor (pasireotide diaspertate). Specialized follow-up should be obtained on these cases to collect additional information on the events

PMR/PMC Schedule Milestones:

Final Protocol Submission:	06/30/2013
Interim Report Submissions:	12/31/2013
	12/31/2014
	12/31/2015
	12/31/2016
Study/Trial Completion:	12/31/2017
Final Report Submission:	06/30/2018
Other:	_____

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

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

Cushing's disease is a rare disease in which the pituitary gland releases excess adrenocorticotrophic hormone (ACTH), triggering the production and release of excess amounts of cortisol by the adrenal glands. Cushing's disease is caused by a tumor or hyperplasia of the pituitary gland. Signifor (pasireotide diaspertate) is indicated for the treatment of patients with Cushing's disease for whom surgery is not an option or for whom surgery is not curative. Signifor (pasireotide diaspertate) was granted an orphan drug designation for the treatment of Cushing's disease. Known and potential safety concerns include: acute liver injury, hyperglycemia, and adrenal insufficiency. Given the small population affected by this disorder, the small number of patients studied, and the short duration of clinical trials, enhanced pharmacovigilance is required to generate additional data to better assess risks related to the long-term use of the drug.

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

The paucity of long-term safety data on Signifor (pasireotide diaspertate) remains a concern. Because of the rarity of Cushing's Disease, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Signifor (pasireotide diaspertate) is limited. The clinical development program revealed known and potential serious risks associated with Signifor (pasireotide diaspertate) including acute liver injury, hyperglycemia, and adrenal insufficiency. Several patients in the pivotal trial had elevations in hepatic transaminases with pronounced early rise in bilirubin levels. Four patients receiving Signifor (pasireotide diaspertate) outside of the pivotal trial developed biochemical Hy's law (ALT or AST > 3x ULN and bilirubin > 2x ULN). As well, while treatment with Signifor (pasireotide diaspertate) reduced cortisol levels, it also impaired insulin secretion resulting in dysglycemia and marked increases in HbA1c from baseline. Lastly, although hypocortisolism can be seen as a sign of efficacy for Signifor (pasireotide diaspertate), adrenal insufficiency was observed in 13 patients in the pivotal trial.

The goal of the enhanced pharmacovigilance program is to gather additional data to better assess risks related to the long-term use of the drug. The program will continue for a period of 5 years from the date of approval.

The enhanced pharmacovigilance program will include the following:

a) Active query of reporters to obtain additional clinical information related to reports of acute liver injury, hyperglycemia, and adrenal insufficiency. The sponsor should actively query reporters for the following information:

(i) For reports of hepatic abnormalities: liver-related laboratory test results, imaging and pathology results, duration of Signifor (pasireotide diaspertate) exposure, and other risk factors for hepatic abnormalities in relation to diagnosis.

(ii) For reports of hyperglycemia with a serious outcome (resulting in death, hospitalization, life-threatening, or disability): Diabetes-related laboratory test results, duration of Signifor (pasireotide diaspertate) exposure, and other risk factors for severe hyperglycemia or diabetes in relation to diagnosis.

(iii) For reports of adrenal insufficiency: Laboratory data, including cortisol and ACTH levels, vital signs, clinical symptoms, treatment, duration of Signifor (pasireotide diaspertate) exposure, concomitant medications, medical history, and other risk factors for adrenal insufficiency in relation to diagnosis.

b) Expedited reporting to FDA of all initial and follow-up reports of acute liver injury [MedDRA search terms: Hepatic and hepatobiliary disorders (HLGT), Hepatobiliary investigations (HLGT), Liver transplant (PT)], hyperglycemia [MedDRA search term: Glucose metabolism disorders (HLGT)], and adrenal insufficiency [MedDRA search term: Adrenal cortical hypofunctions (HLT)] with a serious outcome (resulting in death, hospitalization, life-threatening, or disability).

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report and recommendation at the conclusion of the monitoring period. Based upon the final report and recommendation, FDA will make a determination whether to continue the enhanced pharmacovigilance program for an additional specified time period.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Enhanced pharmacovigilance program for reports of serious (resulting in death, hospitalization, life-threatening, or disability) hyperglycemia, acute liver injury, and adrenal insufficiency in patients with Cushing's disease treated with Signifor (pasireotide acetate) for a period of 5 years from the date of approval. The enhanced pharmacovigilance program includes the following: a) active query of reporters to obtain additional clinical information related to reports of serious hyperglycemia, acute liver injury, and adrenal insufficiency; b) expedited reporting to FDA of all initial and follow-up reports of serious hyperglycemia, acute liver injury, and adrenal insufficiency. Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Enhanced pharmacovigilance program
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # 200677
Product Name: Signifor (pasireotide diaspertate)

PMR/PMC Description: A multi-center, randomized, clinical trial investigating the management of Signifor (pasireotide diaspertate)-induced hyperglycemia in patients with Cushing's disease. (b) (4)

PMR/PMC Schedule Milestones: Final Protocol Submission: 09/30/2013
Study/Trial Completion: 02/28/2017
Final Report Submission: 06/30/2017
Other: _____

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

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

There are limited options for the medical treatment of Cushing's disease. Korlym is approved "for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery." However, there are no other approved medical treatments for patients with Cushing's disease.

Signifor (pasireotide diaspertate)-induced hyperglycemia was a major safety issue in the pivotal trial of Signifor (pasireotide diaspertate) for the treatment of Cushing's disease. Mechanistic studies conducted by the sponsor suggest that this finding is due to decreases in insulin secretion and incretin hormones; however, the Sponsor has not demonstrated how this anticipated adverse effect can be effectively managed in the clinical setting.

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

In the pivotal trial for Signifor (pasireotide diaspertate) for the treatment of Cushing's disease, there was an unexpectedly high frequency of the development of hyperglycemia and diabetes. Given that insulin resistance is a major component and cause of morbidity in Cushing's disease and given that cortisol levels are reduced by Signifor (pasireotide diaspertate), this finding is troubling. Furthermore, since the degree of hyperglycemia was not anticipated (somatostatin analogues do cause some hyperglycemia), the protocol did not require aggressive monitoring or treatment of the hyperglycemia. Although theoretically the hyperglycemia can be treated, the Sponsor has not demonstrated this. Furthermore, it has not been established whether certain anti-diabetic agents are more effective than others in treating Signifor (pasireotide diaspertate)-induced hyperglycemia.

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

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
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- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

A multi-center, randomized, clinical trial evaluating the safety and efficacy of intensive glucose control in patients with Cushing's disease treated with Signifor (pasireotide diaspertate). (b) (4)

Eligible subjects should be randomized to either an insulin-only arm or an arm that includes an algorithm for treating Signifor (pasireotide diaspertate)-induced hyperglycemia. The algorithm can include the use of incretin mimetics.

The primary endpoint of the trial should be the mean change in HbA1c from baseline at Week 16. In order to adequately treat the anticipated hyperglycemia, an aggressive monitoring and treatment approach should be implemented with early and frequent glucose monitoring for patients, regardless of baseline glycemc status.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

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

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-

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

/s/

AMY G EGAN
12/14/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion**

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

Memorandum

Date: December 7, 2012

To: Jennifer Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

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

Samuel Skariah, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP), OPDP

Subject: NDA 200677
OPDP labeling comments for Signifor[®] (pasireotide diaspartate)
injection, for subcutaneous use

In response to DMEP's April 30, 2012, consult request, OPDP has reviewed the draft Prescribing Information (PI), Medication Guide and Instructions for Use for Signifor[®] (pasireotide diaspartate) injection, for subcutaneous use (Signifor).

OPDP's comments on the proposed draft PI are based on the version located in the eRoom entitled "Signifor-5-Dec Novartis edits to FDA version Nov 30 2012.doc" last modified on December 7, 2012. OPDP's comments on the proposed draft Medication Guide and Instructions for Use are based on the versions sent via email from Lashawna Hutchins (DMPP) on December 7, 2012. These comments are provided directly on the marked version of the label below.

If you have any questions regarding the proposed draft PI, please contact Samuel Skariah at 301-796-2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions regarding the proposed draft Medication Guide or Instructions for Use, please contact Kendra Jones at 301-796-3917 or Kendra.Jones@fda.hhs.gov.

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

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/s/

KENDRA Y JONES
12/07/2012

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

PATIENT LABELING REVIEW

Date: **December 07, 2012**

To: Mary Parks, MD
Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

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

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

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

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

Drug Name
(established name): SIGNIFOR (pasireotide diaspertate)

Dosage Form and
Route: Solution for Subcutaneous Injection

Application
Type/Number: NDA 200-677

Applicant: **Novartis Pharmaceuticals Corporation**

1 INTRODUCTION

On February 17, 2012 Novartis Pharmaceuticals Corporation, submitted for the Agency's review a New Drug Application (NDA 200-677) for SIGNIFOR (pasireotide diaspertate) indicated for the treatment of patients with Cushing's disease for whom surgery was not an option or for whom surgery has failed. This application was originally submitted on June 21, 2011 and was withdrawn by the Applicant on August 19, 2011.

On March 07, 2012, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SIGNIFOR (pasireotide diaspertate). On October 12, 2012, the Applicant submitted revised labeling, converting the Patient Package Insert (PPI) to a Medication Guide (MG).

This review is written in response to the DMEP request for DMPP to review the MG and IFU for SIGNIFOR (pasireotide diaspertate).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate review of the Prescribing Information (PI), MG and IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft SIGNIFOR (pasireotide diaspertate) MG and IFU received on October 12, 2012.
- Draft SIGNIFOR (pasireotide diaspertate) Prescribing Information (PI) received on October 12, 2012, revised by the Review Division throughout the current review cycle, and received by DMPP on November 30, 2012.

3 REVIEW METHODS

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

In our review of the MG and IFU we have:

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

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

/s/

SHAWNA L HUTCHINS
12/07/2012

MELISSA I HULETT
12/07/2012

LASHAWN M GRIFFITHS
12/07/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 15, 2012

TO: Jennifer Johnson, Regulatory Project Manager
Naomi Lowy, M.D., Medical Officer
Roman Dragos, M.D., Clinical Team Leader
Division of Metabolism and Endocrinology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 200677

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: SIGNIFOR[®] (pasireotide) injection

NME: Yes

REVIEW PRIORITY: Standard Review

INDICATION: For the treatment of patients with Cushing's disease who require medical therapeutic intervention.

CONSULTATION REQUEST DATE:	February 29, 2012
CLINICAL INSPECTION SUMMARY DATE:	October 17, 2012
DIVISION ACTION GOAL DATE:	December 17, 2012
PDUFA DATE:	December 17, 2012

I. BACKGROUND:

SIGNIFOR® (pasireotide, SOM230) injection is a cyclohexapeptide, injectable somatostatin analog; it is a peptide hormone commonly known as somatotropin release-inhibiting factor. Like natural peptide hormones 244 somatostatin-14 and somatostatin-28 (also known as Somatotropin Release Inhibiting Factor [SRIF]) and other 245 somatostatin analogues, pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst). Pasireotide exerts its pharmacological activity by binding to four of the five known somatostatin receptors (SSTR) (i.e. sst1, sst2, sst3, and sst5). These receptors are expressed in different tissues, and the pattern of expression may be altered under pathological conditions. Somatostatin analogs activate these receptors with different potencies, which results in reduced cellular activity and inhibition of hormone secretion (e.g. ACTH, growth hormone). The Applicant states that they have developed pasireotide as a medical treatment for Cushing's disease; the goal of pasireotide therapy is thus inhibiting the release of ACTH and consequently decreasing adrenal corticosteroid production in both de novo patients and in patients with persistent or recurrent disease.

According to the Applicant, the most common adverse events ($\geq 20\%$) occurring in subjects enrolled in the pasireotide development program were hyperglycemia, diarrhea, nausea, abdominal pain, and cholelithiasis. Additional serious events that are included as warnings and precautions in the proposed label include: hypercortisolism (cortisol withdrawal), ^{(b) (4)} cardiac rhythm abnormalities (bradycardia, arrhythmia, or conduction abnormality), elevated liver enzymes, and gallbladder abnormalities (ultrasounds of gallbladder are recommended prior to starting therapy and at six month intervals while on therapy). While no adverse events attributable to prolonged QT interval (syncope, sudden death, torsade de pointes, etc.) were observed in clinical studies, because pasireotide has been demonstrated to increase the QT interval in QT studies, caution is recommended when co-administering it with anti-arrhythmic medicines and other drugs that may prolong the QT interval. Caution is also recommended when administering pasireotide with cyclosporine (co-administration may result in decreased cyclosporine levels) and bromocriptine (co-administration may result in increased bromocriptine levels).

In support of the efficacy and safety of SIGNIFOR® (pasireotide, SOM230) for the treatment of adults with Cushing's disease, the Applicant has submitted data from one pivotal Phase 3 study (CSOM230B2305). A brief description of this study follows.

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”

Study CSOM230B2305 was a Phase 3 multi-center, double-blind, randomized study conducted to evaluate the safety and efficacy of different dose levels of SOM230 over a 12-month treatment period in subjects with Cushing’s disease who had persistent or recurrent disease or de novo subjects for whom surgery was not indicated or had refused surgery. Once determined to be eligible [a key eligibility criterion required a baseline urinary free cortisol (UFC) >1.5 x ULN] subjects were randomized to receive a dose of either 0.6 mg s.c. b.i.d. or 0.9 mg s.c. b.i.d. of SOM230. After three months of treatment, subjects with a mean 24-hour UFC \leq 2.0 x ULN and below or equal to their baseline values continued blinded treatment at the randomized dose until Month 6. Subjects who did not meet these criteria were unblinded and the dose was increased by 0.3 s.c. mg b.i.d. After the initial six months in the study, subjects entered an additional 6-month open-label treatment period. Dosage could be increased by 0.3 mg s.c. b.i.d. if response was not achieved at Month 6 or the response was not maintained during the open-label treatment period. The maximum dose administered to subjects was 1.2 mg s.c. b.i.d. The dose could be reduced by 0.3 mg b.i.d. decrements at any time during the study for intolerability.

The study was conducted at 53 clinical investigator sites in 18 countries: Argentina (3), Belgium (2), Brazil (4), Canada (3), China (3), Germany (3), Denmark (2), Spain (2), Finland (1), France (7), Greece (1), Israel (2), Italy (7), Mexico (2), Poland (1), Portugal (1), Turkey (2), and USA (7). A total of 165 subjects were randomized into the trial and 162 subjects were treated with study drug. The first subject was enrolled in the study December 22, 2006 and data reported through March 17, 2010 were included in the study report submitted in the NDA. (Date of database lock: May 18, 2010. Date of final study report: August 5, 2010). According to the NDA submission, Novartis Pharmaceuticals Corporation contracted study related items listed below to contract research organizations (CRO), responsibility for items not listed, including monitoring of study sites, remained with Novartis.

Contract Research Organization	Contracted Role/Responsibility
(b) (4)	

The primary efficacy endpoint was the proportion of responders in each of the pasireotide dose

groups at Month 6. A responder was defined as a subject with a Month 6 mean UFC \leq ULN and no up-titration of dose (relative to the randomized dose) prior to the Month 6 mean UFC. [If Month 6 mean UFC was missing then it was imputed by the last available mean UFC (of at least 3 specimens) between (and including) Month 3 and Month 6.] Safety measurements included assessment of adverse events, the number of laboratory values that fell outside of pre-determined ranges, physical examinations, vital signs, ECGs, and gallbladder ultrasound results.

The clinical investigator sites were selected for inspection based on enrollment characteristics, impact of site data on efficacy outcomes, pattern of protocol violations reported for the sites, and their lack of prior inspection history. In addition, a sponsor inspection was conducted to evaluate the sponsor's overall conduct of the study.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Zimeng Jin, MD Peking Union Medical College Hospital, No.1 Shuai Fu Yuan Wang Fu Jing.Dongcheng District Beijing, 100730 China	Protocol: CSOM230B2305 Site: #771 Subjects Enrolled: 15	April 11-18, 2012	VAI
Luc Van Gaal, MD U.Z. Antwerpen, Wilrijkstraat 10 Edegem, 2650 Belgium	Protocol: CSOM230B2305 Site: #204 Subjects Enrolled: 5	May 7-11, 2012	VAI
Annamaria Colao, MD Policlinico II Università degli Studi di Napoli, via Pansini, 5 Napoli, NA 80131 Italy	Protocol: CSOM230B2305 Site: #704 Subjects Enrolled: 14	June 4-6, 2012	NAI
Novartis Pharma AG Form 1 4002 Basel Switzerland	Protocol: CSOM230B2305	June 4-8, 2012	Pending (Preliminary Classification VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

Pending = Preliminary classification based on information on EIR review and additional documents submitted by

Applicant. Final correspondence has not yet issued.

1. Zimeng Jin, MD

Peking Union Medical College Hospital, No.1 Shuai Fu Yuan Wang Fu
Jing.Dongcheng District
Beijing, 100730
China
Site #771

a) What was inspected:

For Study CSOM230B2305, at this site, 22 subjects were screened, 15 subjects were enrolled, and 5 subjects completed the study. Six randomized subjects' records were reviewed in depth during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to inclusion/exclusion criteria compliance, primary efficacy endpoint data, concomitant medication usage, quality of life questionnaires administered to subjects, identification of adverse events, and reporting of AEs in accordance with the protocol. One hundred percent of the informed consent documents were reviewed during the inspection to ascertain compliance with subject consenting, as well as format of informed consent documents (accuracy, verbiage, and presence of required elements). The FDA field investigator also evaluated the site's GCP and study specific training, subject randomization procedures, test article accountability, delegation of responsibility logs, monitoring and sponsor correspondence with the site, Ethics Committee (EC) approvals and correspondence, and blood pressure data for 10 randomized subjects. There were no limitations to the inspection.

b) General observations/commentary:

In China, patients routinely retain possession of their own medical records, which are usually in a bound notebook. During their visits to the physician's office, they present this notebook and the physician makes appropriate entries, and then returns the notebook to the patient. As such there were no routine medical records available for review for the subjects enrolled in this study at this site. However, study binders containing study related source documents were present for each subject at the site.

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 200677 were compared. Procedures for collection of primary efficacy data, and the reporting of that data in the NDA, appeared to be adequate. Although throughout the inspection Novartis staff present at the site stated repeatedly that the study was not required to be conducted under IND or in compliance with FDA regulations, Dr. Jin did sign a Form FDA 1572; therefore, the CI is responsible for conduct of the study in accordance with FDA regulations as stated on the Form FDA 1572. A Form FDA 483 was issued to the CI for:

- i. The informed consent document lacked an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights [21 CFR 50.25(a)(7)]. Specifically, the informed consent document failed to identify who was to be contacted if the subject had questions regarding their rights as study subjects. During the inspection site staff explained that subjects were given a separate patient contact sheet that included contact information for the doctor and a back-up person, as well as the sponsor.

OSI Reviewer Comment: While this observation does represent a regulatory violation as it does not appear that the informed consent had all of the required elements as described in 21 CFR 50.25, it does appear that subjects were provided this information separately. Based on inspectional findings it does not appear that subjects were harmed by this omission.

- ii. The informed consent document did not contain a description of the procedures to be followed [21 CFR 50.25(a)(1)]. Specifically, the informed consent document failed to describe how much of the test article the subject was to draw up from drug ampoules for injection.

OSI Reviewer Comment: This observation may represent a regulatory violation. Of primary concern to the FDA field investigator during the inspection was that the actual ampoules provided to the site were labeled as containing 1 mL (300, 600, or 900 µg pasireotide per 1 mL), but the actual volumes in the ampoules were 1.1 mL. This raised the concern that if subjects were not adequately instructed to withdraw only 1 mL that they may have withdrawn the entire ampoule amount and essentially received an extra 10% of the prescribed dose. While this potential exists, it seems likely that in the process of preparing doses for injection that some residual would remain in the ampoule and/or syringe used for dosing. OSI defers however, to the review division as to whether this issue is of significant concern (if so, this issue may be present for data from all study sites).

- iii. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for:
 - a. There was no documentation that the blood samples collected for pharmacokinetics were processed within 20 minutes as required by the protocol (Section 7.9.1.1).
 - b. There was no documentation that the blood pressures were taken at the same time of day at each visit or that measurements were taken at one to two minute intervals as required by the protocol (Section 7.4.2.6).

The ORA field investigator noted in the EIR that there appeared to be an unusual pattern of blood pressure values recorded for many of the 10 subjects' records that she reviewed in detail (See Attachment 1 for Table of blood pressure data points). Specifically, the protocol required that at each visit the subjects' blood pressure was to be taken three times while seated, at one to two minute intervals, and that it was then to be taken once with the subject standing. Review of the recorded blood pressure values for these subjects suggests that intended or unintended errors may have been made in these assessments as the pattern of reported values for individual subjects' within a given visit and across multiple visits appears clinically unlikely.

OSI Reviewer Comment: This observation was discussed with the clinical and statistical reviewers for this application, who concur that the lack of variability in reported blood pressures for subjects appears clinically unlikely. As BP analysis results are considered an important secondary endpoint in the determination of risk versus benefit for this product, the statistical reviewer for this application further evaluated data variability for blood pressure readings across all CI sites enrolling subjects in this study, Site #771 (Dr. Jin) was a clear outlier for low variability, as were four other CI sites (Sites #708, #841, #731, and #382). Of note, however, only Site #771 enrolled more than 1-2 subjects.

The issue related to lack of data variability was also discussed with the Applicant in a telecon on July 30, 2012. For further evaluation related to this finding, please see discussion under the Sponsor inspection of Novartis, below.

Dr. Jin responded to the Form FDA 483, Inspectional Observations, in a letter, attached to an e-mail to FDA District Office, dated May 3, 2012. In the letter Dr. Jin acknowledged the observations and promised corrective actions would be put in place at the site to prevent the occurrence of similar issues in ongoing and future studies.

c) Assessment of data integrity:

Based on review of blood pressure assessments for 10 of the 15 subjects enrolled at this site, the values of which appear to be clinically unlikely, OSI recommends that blood pressure assessments from this site not be considered reliable and suggests that blood pressure values from this site be excluded from secondary efficacy analyses. Notwithstanding the other observations noted above, the balance of data provided by Dr. Jin's site for Study CSOM230B2305, including data for the primary efficacy and safety assessments, that were submitted to the Agency in support of NDA 200677 appear to be adequately reliable and acceptable for use in support of the pending application.

2. Luc Van Gaal, MD

U.Z. Antwerpen, Wilrijkstraat 10
Edegem, 2650

Belgium
Site #204

a) What was inspected:

For Study CSOM230B2305, at this site, 9 subjects were screened, 5 subjects were enrolled, and 4 subjects completed the study. All subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, randomization, inclusion/exclusion criteria compliance, urinary free cortisol levels, DEXA, ultrasound and bone density scans, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated test article accountability, financial disclosure reporting, monitoring and sponsor correspondence with the site, and EC approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:

The Principal Investigator, Dr. Roger ABS, and the study nurse that started this study left the study after 12 months. Dr. Van Gaal took over the study in June of 2009. Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 200677 were compared. Study CSOM230B2305 was not conducted under IND at this site; therefore, Dr. Van Gaal did not sign a Form FDA 1572 for this study. A Form FDA 483, Inspectional Observations, was issued to the CI for:

- i. Failure to obtain an investigator statement, form FDA-1572, before permitting an investigator to participate in an investigation [21 CFR 312.53(c)(1)].

OSI Reviewer Comment: This observation is not considered a regulatory violation. Under 21 CFR 312.120, the sponsor can submit information to FDA from a foreign clinical study that was not conducted under an IND to support marketing approval. While Dr. Van Gaal was not required to sign a Form FDA 1572, the sponsor of the study remains responsible for assuring that the study was conducted in accordance with Good Clinical Practice.

- ii. Failure to include in the informed consent document a statement that the Food and Drug Administration might inspect the records [21 CFR 50.25(a)(5)].

OSI Reviewer Comment: This observation is not considered a regulatory violation. As stated in the Investigator's June 4, 2012 response to Form FDA 483 Inspectional Observations, while the consent does not specifically state that FDA may inspect subject records, it does include a more generic statement that regulatory authorities may have access to the subjects' records.

- iii. The informed consent document lacked an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and in the event of a research-related injury to the subject [21 CFR 50.25(a)(7)].

OSI Reviewer Comment: While technically a valid observation as this information was not printed on the template IEC approved consent form, based on the Investigator's response to this Form FDA 483 observation and review of exhibits submitted with the Establishment Inspection Report (EIR) the information was actually hand written onto each subject's informed consent form so the appropriate contact information was provided to study subjects.

- iv. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for:
 - a. Delayed reporting of a SAE (cholecystectomy) for one subject (Subject #020400007).
 - b. Subject #020400003 did not tolerate a 300 µg s.c. b.i.d. dose and rather than withdraw the subject from the study, as was required by the protocol, the CI treated the subject with a lower dose (150 µg s.c. b.i.d.). This subject was also permitted to use only a portion of standard dose ampoules, but the protocol did not provide any patient instructions for how fractional doses were to be drawn up, nor did site records document that the patient was instructed on how to do this.
 - c. Investigational drug receipt and disposition records were inadequate.
 - d. Protocol required IVRS notification for a failed patient randomization was delayed for one subject.
 - e. The most current version of the IEC informed consent document was not signed by two subjects at their next study visit, although they were signed at subsequent visits.
 - f. Although the protocol does not describe re-screening procedures, two subjects were rescreened for study entry after originally failing screening. Subject #020400002 was assigned #020400003 on October 23, 2007, passed screening and was randomized on November 16, 2007. Subject #020400005 was assigned #020400008 on December 4, 2008 but failed the screening step again and was not entered into the study.
 - g. Subject #020400007 was seen for multiple study visits outside of protocol specified visit windows (1-10 days outside of protocol described visit windows).
 - h. Source documents for some laboratory results were missing from subjects' files.
 - i. Subject #020400007 was randomized into the study before a bone density test was performed.

OSI Reviewer Comment: While the observations above are considered valid, they are unlikely to significantly impact primary efficacy or safety analyses. Of note, the protocol did not provide re-screening procedures, it also did not prohibit subject re-screening. In the Investigator's response to Form FDA 483 observations that was received on June 4, 2012, the CI acknowledged these observations and promised corrective actions, as appropriate.

- v. Failure to assure that an IRB was responsible for the initial and continuing review and approval of a clinical study [21 CFR 312.66]. Specifically, the first subject was randomized at this site on August 17, 2008, but the yearly review form summarizing the first year of the study was not submitted to the IEC until February 24, 2009.

OSI Reviewer Comment: This observation is considered valid. The Investigator acknowledged this GCP deviation in his response to the Form FDA 483 that was received by the FDA on June 4, 2012.

c) Assessment of data integrity:

Notwithstanding the observations noted above, the data provided by Dr. Van Gaal's site for Study CSOM230B2305 that were submitted to the Agency in support of NDA 200677 appear to be adequately reliable and acceptable for use in support of the pending application.

3. Annamaria Colao, MD

Policlinico II Università degli Studi di Napoli, via Pansini, 5
Napoli, NA 80131
Italy
Site #704

a) What was inspected:

For Study CSOM230B2305, at this site, 16 subjects were screened (five subjects were screened multiple times resulting in a total of 25 subject screenings), 14 subjects were enrolled, and 5 subjects completed the study. Thirteen subjects' records (six randomized subjects and seven screen failures) were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, medication dosing, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated drug accountability records, concomitant medication usage, staff qualifications, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements

reported by the Applicant to the Agency in NDA 200677 were compared and verified. Study CSOM230B2305 was not conducted under IND at this site; therefore, Dr. Colao did not sign a Form FDA 1572. The investigator's execution of the protocols, however, was found to be adequate and a Form FDA 483 was not issued to the CI.

c) Assessment of data integrity:

The data provided by Dr. Colao's site for Study CSOM230B2305 that were submitted to the Agency in support of NDA 200677 appear to be reliable and acceptable for use in support of the pending application.

4. Novartis Pharma AG

Form 1

4002 Basel

Switzerland

Sponsor Inspection

a) What was inspected:

The Sponsor, Novartis Pharma AG, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Study CSOM230B2305 was conducted globally, and during this sponsor/monitor inspection clinical site records for the CI sites listed in the table above were focused on. The record review included review of documents associated with the IRB/IEC approvals, site and investigator qualifications, monitoring activities, randomization procedures, data handling procedures, drug accountability records, serious adverse event reporting, and registration and updating of the study on Clinicaltrials.gov.

b) General observations/commentary:

Study CSOM230B2305 was considered during the inspection to have been generally well executed by the Sponsor. The Sponsor's oversight of IRB/IEC approvals at CI sites was reviewed in detail and the lapse in approval that occurred at Dr. Van Gaal's site appears to have been an isolated occurrence.

The ORA field investigator did not have information related to lack of expected BP variability at Dr. Jin's site during the inspection of the Sponsor; therefore, this issue was not specifically followed-up on during the inspection. As previously noted this issue was discussed directly with the Applicant during a telecon between the FDA and the Applicant on July 30, 2012. At that time the Applicant agreed to perform their own analyses to evaluate the lack of BP variability identified at Dr. Jin's site as well as other sites identified during the review division's evaluation. In addition the Applicant agreed to provide monitoring reports for Dr. Jin's site, as well as other sites where similar issues were identified. The Applicant provided these reports, and a summary of their related findings, in an amendment to the NDA dated September 7, 2012. Based on review of this submission it appears that at some sites the apparent lack of expected BP variability may have been caused by

site practice of rounding readings to the nearest multiple of 5 mmHg; at some sites study monitors identified this as an issue and appear to have appropriately retrained site staff to document exact measurements rather than rounded values. Findings at Dr. Jin's site were not, however, explained by rounding of values, nor was there any evidence in monitoring reports that the site monitors had ever identified the unusual patterns of BP measurements reported for multiple subjects at the site. As monitors failed to identify this issue, no corrective action was initiated at Dr. Jin's site; therefore, OSI considers the following regulatory violation of Sponsor responsibilities to have occurred:

Failure to ensure proper monitoring of a study and ensure that the study was conducted in accordance with the investigational plan [21 CFR 312.50].

Specifically, for the Sponsor's failure to identify the improbable pattern of blood pressure reporting at Site #771 (Dr. Jin), and failure to implement corrective actions to prevent the ongoing occurrence of this finding at the site.

c) Assessment of data integrity:

OSI recommends that the Review Division exclude blood pressure data from Site #771 (Dr. Jin) in secondary efficacy analyses evaluating the effect of the study drug on blood pressure as blood pressure data from this site are considered to be unreliable. The Review Division may also wish to perform sensitivity analyses (for the secondary endpoint related to effect on blood pressure) in which data from other sites with similarly low variability in blood pressure readings has been identified. The balance of data reported for Study CSOM230B2305, by the Applicant, are considered adequately reliable for use in support of the pending Application.

Note: The EIR and associated exhibits, as well as the Applicant's September 7, 2012 amendment to the NDA have been reviewed; however, final correspondence for this inspection has not yet issued to the Applicant/Sponsor. It is not anticipated that conclusions will change prior to issuance of final correspondence to the Applicant/Sponsor.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of inspectional findings for the sponsor inspection of Novartis Pharma AG, as well as inspectional findings for clinical investigators Dr. Jin, Dr. Van Gaal, and Dr. Colao, with the exception of blood pressure data from Dr. Jin's site, the data submitted by the Applicant for Study CSOM230B2305 appear reliable in support of NDA 2000677.

The final classification for the inspection of Dr. Colao (Site #704) is No Action Indicated (NAI).

The final classifications for the inspections of Dr. Jin (Site #771) and Dr. Van Gaal (Site #204) are Voluntary Action Indicated (VAI). While regulatory violations occurred at these sites, with the exception of observations related to blood pressure assessments at Dr. Jin's site, they

are considered minor in nature and unlikely to significantly impact primary safety or efficacy analyses, nor were they likely to have jeopardized subject safety.

The preliminary classification for the inspection of Novartis Pharma AG is Voluntary Action Indicated (VAI) based on their failure to identify blood pressure related observations at Dr. Jin's site, which resulted in persistence of the issue throughout the study at this site.

Note: The EIR and associated exhibits for the inspection of Novartis Pharma AG, as well as the Applicant's September 7, 2012 amendment to the NDA have been reviewed; however, final correspondence for this inspection has not yet issued to the Applicant/Sponsor. It is not anticipated that conclusions will change prior to issuance of final correspondence to the Applicant/Sponsor.

{See appended electronic signature page}

Jean Mulinde, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
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CONCURRENCE:

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Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Attachment 1

Table: Blood Pressure Values

Sub. #	Visit	date	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Standing Diastolic	Standing Systolic	have 2 identical values	have 3 identical values	have 4 identical values
1	2	05/13/08	110	75	108	73	107	74	100	70			
1	3	05/27/08	120	80	130	90	130	90	120	80	1		
1	4	06/11/08	102	80	106	80	106	80	96	68	1		
1	5	06/26/08	120	88	120	88	120	82	130	100	1		
1	6	07/11/08	106	80	108	82	100	80	82	80			
1	7	07/25/08	108	80	108	80	110	90	108	88	1		
1	8	08/11/08	110	84	112	84	110	82	122	110			
1	17	08/25/08	126	100	120	100	120	96	120	90			
1		09/09/08	120	80	120	80	118	84	118	90	1		
2	1	04/12/08	120	90	120	88	120	88	110	80			
2	2	05/06/08	130	88	130	85	128	86	110	80			
2	3	05/20/08	120	88	118	85	120	86	118	90			
2	4	06/05/08	124	100	124	100	122	98	122	98	1		
2	5	06/20/08	102	88	104	88	104	88	105	80	1		
2	6	07/07/08	120	100	120	100	118	98	120	100		1	
2	7	07/21/08	120	80	120	80	120	80	118	82		1	
2	8	08/05/08	110	80	110	80	104	80	118	70	1		
2	9	09/04/08	120	90	120	90	122	88	110	90	1		
2	10	10/05/08	120	88	118	88	120	88	122	88	1		
2	11	11/04/08	110	70	110	70	112	72	100	68	1		
2	12	12/04/08	115	70	112	70	114	70	110	70			
2	13	01/04/09	120	80	120	80	120	80	110	70		1	
2	14	02/01/09	110	78	110	80	110	80	110	80		1	
2	15	03/03/09	110	70	110	70	110	74	110	70			1
2	17	04/23/09	100	70	100	70	100	70	96	68			1
6	1	07/31/08	140	100	136	100	140	108	135	105			
6	2	08/15/08	140	110	138	110	140	106	135	105			
6	3	08/29/08	120	88	120	88	116	90	102	68	1		
6	4	09/11/08	118	90	118	90	120	98	110	80	1		
6	5	09/27/08	122	90	122	90	120	88	110	82	1		
6	6	10/13/08	120	90	116	88	118	88	116	90			
6	7	10/27/08	138	102	134	100	138	102	110	85	1		
6	8	11/11/08	120	90	120	90	118	88	110	70	1		
6		12/17/08	120	100	130	100	130	98	120	80			
9	1	08/31/08	140	106	140	108	136	104	130	100			
9	2	09/12/08	140	110	140	108	140	108	140	100	1		
9	3	09/27/08	120	100	120	98	120	96	90	70			

Table: Blood Pressure Values

Sub. #	Visit	date	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Standing Diastolic	Standing Systolic	have 2 identical values	have 3 identical values	have 4 identical values
9	4	10/10/08	110	90	110	90	108	88	106	78	1		
9	5	10/27/08	110	98	112	94	112	98	112	90			
9	6	11/11/08	102	80	102	80	100	78	98	78	1		
9	7	11/25/08	110	90	110	90	105	85	100	84	1		
9	8	12/10/08	120	80	120	80	116	80	110	76	1		
9	9	01/09/09	118	80	118	80	116	80	110	76	1		
9	10	02/09/09	110	80	110	80	110	80	100	78			1
9	11	03/10/09	110	80	110	80	110	80	100	78			1
9	12	04/10/08	120	80	120	80	118	80	110	78	1		
9	13	05/08/09	110	80	110	80	110	80	106	78		1	
9	14	06/09/09	110	78	110	78	108	78	108	78	1		
9	17	06/30/09	108	78	108	78	104	78	100	76	1		
9	of safel	07/16/09	100	78	100	78	100	78	100	74		1	
10	1	11/14/08	128	80	128	80	125	80	126	80	1		
10	2	11/25/08	130	90	130	90	130	88	132	86	1		
10	3	12/10/08	156	100	156	100	152	98	140	90	1		
10	4	12/24/08	140	100	140	100	138	98	122	88	1		
10	5	01/08/09	130	90	130	88	130	88	128	88	1		
10	6	01/22/09	138	100	138	96	136	96	130	90	1		
10	7	02/06/09	130	90	130	90	130	90	128	80		1	
10	8	02/23/09	130	90	130	90	130	90	120	80		1	
10	9	03/06/09	130	88	130	88	128	88	120	80	1		
10	10	04/23/09	120	80	120	80	120	80	110	80		1	
10	11	05/22/08	124	80	124	80	120	80	112	70	1		
10	12	06/22/09	120	80	120	80	120	80	112	72		1	
10	13	07/22/09	120	80	120	80	118	80	116	78	1		
10	14	08/21/09	120	80	120	80	120	78	110	78	1		
10	15	09/21/09	150	90	150	90	150	85	150	100			
10	16	10/20/09	125	80	125	85	125	85	130	90	1		
10	17	11/19/09	148	90	148	90	148	90	142	90	1		
12	1	11/28/08	148	100	148	100	142	98	130	98	1		
12	2	12/12/08	150	100	150	100	148	98	138	98	1		
12	3	12/26/08	124	100	124	100	120	100	106	96	1		
12	4	01/09/09	130	80	130	80	130	80	118	80		1	
12	5	01/22/09	140	100	138	100	136	100	110	90	1		
12	6	02/09/09	130	90	130	90	130	90	120	88	1		
12	7	02/23/09	120	90	120	90	118	90	112	80	1		

Table: Blood Pressure Values

Sub. #	Visit	date	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Standing Diastolic	Standing Systolic	have 2 identical values	have 3 identical values	have 4 identical values
12	8	03/11/08	122	92	122	92	120	90	112	88	1		
12	9	04/10/08	118	90	118	90	118	88	110	80	1		
12	10	05/11/09	122	98	122	98	122	98	120	96	1		
12	11	06/09/09	126	96	126	96	126	96	118	94		1	
12	12	07/10/09	136	90	136	90	134	90	120	88	1		
12	13	08/05/09	140	100	140	100	138	100	130	98	1		
12	14	09/04/09	138	90	138	90	136	90	130	90	1		
12	17	09/28/00	150	110	140	100	140	100	140	100		1	
12	N/A	10/09/09	145	100	140	100	145	100	150	105	1		
13	1	11/29/08	120	80	120	80	118	78	110	78	1		
13	2	12/19/08	110	92	110	94	110	82	110	96	1		
13	3	01/04/09	118	80	118	80	118	80	110	78		1	
13	4	01/16/09	112	80	112	80	112	80	100	78		1	
13	5	02/01/09	120	80	118	80	116	80	120	80	2		
13	6	02/17/09	120	80	120	80	118	80	110	78	1		
13	7	03/13/09	120	80	120	80	118	80	110	78	1		
13	8	03/17/09	122	90	122	90	118	88	110	76	1		
13	9	04/17/09	110	80	110	80	110	80	108	80		1	
13	10	05/18/00	110	88	110	88	110	88	110	80		1	
13	11	08/15/09	120	80	115	80	118	80	100	70			
13	12	07/16/09	110	88	110	88	110	88	104	80		1	
13	13	08/17/09	100	78	100	78	100	78	98	70		1	
13	14	09/16/09	110	80	110	80	110	80	110	85		1	
13	15	10/15/09	120	90	115	90	120	90	120	90		1	
13	16	11/13/09	100	80	100	80	100	85	100	80		1	
13	17	12/15/09	110	90	110	95	110	90	110	90		1	
13	e1	03/16/10	110	85	105	80	108	80	110	80			
13	e2	06/09/10	100	80	100	80	100	80	100	80			1
13	e3	09/29/10	100	85	100	80	100	80	100	70		1	
13	e4	12/07/10	100	85	100	80	100	80	90	80		1	
13	e5	03/15/10	110	80	110	80	110	80	100	70		1	
13	e6	08/10/10	120	80	120	80	120	76	120	80		1	
13	tot for e	08/15/09	120	90	120	90	120	86	120	84	1		
16	1	12/08/08	120	100	124	96	122	98	120	96			
16	2	12/30/08	124	90	124	90	124	90	120	80		1	
16	3	01/13/09	120	88	120	88	120	86	110	80	1		
16	4	02/01/08	100	80	100	80	100	86	110	80	1		

Table: Blood Pressure Values

Sub. #	Visit	date	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Standing Diastolic	Standing Systolic	have 2 identical values	have 3 identical values	have 4 identical values
16	5	02/11/09	100	80	100	80	96	78	94	78	1		
16	6	02/27/09	110	80	115	80	115	85	110	90			
16	7	03/13/09	110	70	110	70	108	70	100	70	1		
16	8	03/30/09	108	70	108	70	108	70	100	70		1	
16	9	04/02/09	100	70	100	70	100	70	96	68			1
16	10	05/26/09	98	70	98	70	96	70	96	68	1		
16	11	06/26/09	102	70	102	70	100	70	96	68	1		
16	12	07/27/09	100	70	100	70	100	70	92	68			1
16	13	08/27/09	100	78	100	78	100	78	90	68			1
16	14	09/25/09	110	80	112	82	110	78	110	78	1		
16	15	10/26/09	110	80	105	80	108	80	105	75			
16	16	11/25/09	100	70	100	70	105	70	90	70	1		
16	17	12/23/09	100	70	100	70	100	70	90	70			1
16	e1	03/16/10	110	70	110	70	110	70	90	70			1
16	e2	06/09/10	100	80	100	80	100	80	106	80			1
16	e3	09/20/10	110	80	110	80	110	80	110	80			1
16	e4	12/21/10	110	70	110	70	110	70	100	70			1
16	e5	03/15/11	110	70	110	70	110	70	100	70			1
16	e6	06/10/11	100	70	100	70	100	70	100	70			1
16	and of e	07/07/10	90	60	90	60	60	60	88	60			1
17	1	12/25/08	102	70	102	70	100	70	100	70	2		
17	2	01/08/09	98	70	98	70	98	70	80	66			1
17	3	01/21/09	90	60	90	60	90	60	86	60			1
17	4	02/06/09	90	70	90	70	88	68	80	60	1		
17	5	02/20/09	90	70	90	70	90	68	86	68	1		
17	6	03/09/09	100	80	100	80	100	80	88	68			1
17	7	03/24/09	100	80	100	80	100	80	90	70			1
17	8	04/07/09	110	86	110	86	108	84	100	80	1		
17	9	05/07/09	104	80	104	80	100	78	98	78	1		
17	10	06/05/09	92	70	90	70	88	68	82	68			
17	11	07/06/09	90	68	90	68	90	68	80	66			1
17	12	08/05/09	108	80	108	80	108	80	100	78			1
17	13	09/04/09	110	80	108	80	108	80	106	80	1		
17	14	10/09/09	120	90	115	85	120	85	120	85			
17	15	11/03/09	140	100	145	100	140	100	140	90	1		
17	16	12/03/09	120	80	120	80	120	80	118	70			1
17	17	01/04/10	110	70	110	70	110	70	100	70			1
17	safety flu		128	84	130	80	128	80	124	80			

Table: Blood Pressure Values

Sub. #	Visit	date	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Sitting diastolic	Sitting Systolic	Standing Diastolic	Standing Systolic	have 2 identical values	have 3 identical values	have 4 identical values
20	1	01/24/09	140	100	140	100	140	98	120	80	1		
20	2	02/01/09	130	90	130	90	130	90	122	86		1	
20	3	03/04/09	120	90	120	90	120	90	110	88	1		
20	4	03/19/09	114	90	114	90	110	88	110	88	2		
20	5	04/02/09	110	90	110	90	110	88	109	85	2		
20	6	04/17/09	114	80	114	80	114	80	110	80		1	
20	7	05/04/09	110	82	110	82	110	80	108	78	1		
20	8	05/18/09	120	90	120	90	120	90	106	90		1	
20	9	06/17/09	120	88	120	88	120	88	108	88		1	
20	10	07/17/09	118	88	118	88	118	88	108	84		1	
20	11	08/17/09	110	80	110	80	110	80	100	76		1	
20	12	09/16/09	120	80	115	80	115	80	110	85	1		
20	13	10/15/09	120	90	125	90	120	90	120	90		1	
20	14	11/13/09	120	90	120	90	120	85	110	90	1		
20	15	12/15/09	130	90	130	90	130	90	120	95	1		
20	16	01/13/10	120	100	120	100	120	100	120	100			1
20	17	02/09/10	120	84	120	86	120	84	128	90	1		
20	e1	04/26/10	120	96	120	96	120	98	110	90	1		
20	e2	08/02/10	130	90	130	90	130	90	125	90		1	
20	e3	11/03/10	130	90	130	90	130	90	120	80		1	
20	e4	02/14/11	120	90	125	90	120	90	120	95		1	
20	e5	05/10/11	124	98	120	96	120	96	126	96		1	
20	end of e	07/12/11	120	90	120	90	120	90	120	88		1	
20	safety fl	08/10/11	130	100	130	100	130	100	130	90		1	

173 Total % 86 49.71% 57 32.95% 9 5.20%

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

/s/

JEAN M MULINDE
10/15/2012

JANICE K POHLMAN
10/15/2012

SUSAN D THOMPSON
10/15/2012



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 29, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Jennifer Johnson, DMEP

Subject: QT-IRT Consult to NDA 200677/ (b) (4) / IND 68635

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11 June 2012 regarding sponsor's response to QT-IRT comments issued to the sponsor in a letter dated March 23, 2012 to INDs 68635 and (b) (4). The QT-IRT received and reviewed the following materials:

- Your consult
- An information package that included sponsor's response to Agency's comments and PK/QT modeling report submitted by the sponsor under NDA 200677.

QT-IRT Comments for DMEP

The Sponsor has satisfactorily addressed the QRT-IRT's comments which were sent to the Sponsor dated March 23, 2012. We conclude that the suprathreshold dose of 1950 µg b.i.d dose in the TQT study seems adequate to cover the exposures expected in the worst case scenario of severe hepatic impairment in Cushing's patients.

SPONSOR'S PROPOSED LABEL

5.3 Cardiovascular-related events

Bradycardia has been reported with the use of pasireotide. [see *Adverse Reactions (6)*] Patients with cardiac disease and/or risk factor for bradycardia, such as: history of clinically significant bradycardia or (b) (4)

(b) (4) should be carefully monitored. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control electrolyte balance, may be necessary.

Pasireotide should be used with caution in patients who are at significant risk of developing prolongation of QTc, such as those [see *Pharmacodynamics (12.2)*]:

- with congenital long QT prolongation
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- taking anti-arrhythmic medicinal products or other substances that are known to lead to QT prolongation
- with hypokalemia and/or hypomagnesemia.

Monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with SIGNIFOR and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to SIGNIFOR administration and should be monitored periodically during therapy.

Cardiac Electrophysiology

(b) (4)



QT-IRT'S LABEL RECOMMENDATIONS

QT-IRT's recommendations are suggestions only; we defer final label decisions to the review division.

5.3 Cardiovascular-related events

Bradycardia has been reported with the use of pasireotide. [see *Adverse Reactions (6)*] Patients with cardiac disease and/or risk factor for bradycardia, such as: history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, should be carefully monitored. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control electrolyte balance, may be necessary.

(b) (4) Pasireotide should be used with caution in patients who are at significant risk of developing prolongation of QTc, such as those [see *Pharmacodynamics (12.2)*]:

- (b) (4)
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- (b) (4)
- with hypokalemia and/or hypomagnesemia,

(b) (4)
Hypokalemia or hypomagnesemia must be corrected prior to SIGNIFOR administration and should be monitored periodically during therapy.

12. 5 Cardiac Electrophysiology

QTcI interval was evaluated in a randomized, blinded, crossover study in healthy subjects investigating pasireotide doses of 600 µg b.i.d. and 1950 µg b.i.d. The maximum mean (95% upper confidence bound) placebo-subtracted QTcI change from baseline was 12.7 (14.7) ms and 16.6 (18.6) ms, respectively. Both pasireotide doses decreased heart rate, with a maximum mean (95% lower confidence bound) placebo-subtracted change from baseline of -10.9 (-11.9) bpm observed at 1.5 hours for pasireotide 600 µg bid, and -15.2 (-16.5) bpm at 0.5 hours for pasireotide 1950 µg b.i.d. The suprathreshold dose (1950 µg b.i.d) produced mean steady-state C_{max} values 3.3-fold the mean C_{max} for the 600 µg b.i.d dose in the study. (b) (4)

(b) (4)

(b) (4)

Reviewer's Comment: QT-IRT has not reviewed clinical data related to the Sponsor's claims that no episodes of torsade de pointes were observed in the studies. We defer the decision to include this language to the Division.

1. BACKGROUND

Significant QTc prolongation effect of pasireotide (600 µg b.i.d. and 1950 µg b.i.d) was detected in the TQT study (SOM230B2125). The largest upper bounds of the 2-sided 90% CI for the mean difference between pasireotide (600 µg b.i.d. and 1950 µg b.i.d) and placebo were 14.7 ms and 18.6 ms that are above 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines (for details see QT-IRT review of (b)(4)/IND 68635 dated 7 February 2012). Based on the review of (b)(4)/IND 68635, additional information was requested from the sponsor. The following are the responses from the sponsor to our previous comments:

FDA Comment # 1:

Since a time delay in QTc prolongation is observed while no metabolites of pasireotide have been identified, the underlying mechanism for the delay in QTc prolongation is unclear. You should provide a justification for observing a delay. Furthermore, as your proposed time-lag model under-predicts the QTc prolongation for the 600 mcg twice daily dose, you should also develop an effect compartment model to characterize the exposure-response relationship and for predictions.

Sponsor Response:

Pasireotide has been tested pre-clinically at the relevant cardiac electrophysiological targets and it neither inhibits the delayed potassium rectifier current through hERG at pasireotide concentrations up to 10 µM (equivalent to 10,472 ng/mL) nor prolongs the action potential in the Purkinje fiber at concentrations up to 30 µM (equivalent to 31,416 ng/mL). Based on this evidence, and the temporal lag between maximum plasma concentrations of pasireotide (0.5-0.6 hours), maximal heart rate change (at 0.5-1 hour) and maximal $\Delta\Delta\text{QTcI}$ (at 2 hours), the effect on cardiac repolarization may be explained by pasireotide acting indirectly via centrally mediated autonomic mechanisms (i.e., withdrawal of sympathetic tone and/or enhanced vagal tone) affecting the cardiac sympatho-vagal balance. It would therefore appear likely that the QT prolongation may reflect changes in autonomic regulation.

An effect compartment model has been developed to characterize the exposure-response relationship of QTc prolongation. Notable features of the model were E_{max} dependence of $\Delta\Delta\text{QTcI}$ on the pasireotide concentration in the effect compartment, and a complementary component describing PK-independent diurnal effects. Please refer to “PK/QT Modeling: Response to FDA letter Modeling report”, [SOM230BPopPKQT] included in this submission for more details.

Reviewer’s Comments: The sponsor’s population PK and the effect compartment models are reasonable. For details see reviewer comments in sections 2 and 3.

FDA Comment # 2:

Using the appropriate model, the following scenarios should be simulated and the $\Delta\Delta\text{QTcI}$ predicted at the mean steady state C_{max} .

- a. Predict $\Delta\Delta\text{QTcI}$ at the mean steady state C_{max} of 900 mcg twice daily in the thorough QT study.
- b. As the pharmacokinetics (PK) of pasireotide was different in healthy volunteers compared to patients with Cushing’s disease, you should predict the $\Delta\Delta\text{QTcI}$ at mean steady state C_{max} expected in patients given the highest therapeutic dose of 900 mcg twice daily.

c. Predict $\Delta\Delta QTcI$ at the mean steady state C_{max} expected in patients with severe hepatic impairment taking a dose of 600 mcg twice daily.

Sponsor Response:

As mentioned earlier (see Novartis response to FDA comment #1), an effect compartment model was developed to characterize the exposure-response relationship of QTc prolongation. According to simulations of the PopPK/QTc model, the predicted values of means and confidence intervals (CI) of $\Delta\Delta QTcI$ at times post dose of maximum mean $\Delta\Delta QTcI$ are expected to be as follows for the scenarios specified by the FDA:

- Healthy volunteers, 900 μg b.i.d.: mean: 14.1 msec; 90% CI: 11.4 – 16.8 msec
- Cushing’s patients, 900 μg b.i.d.: mean: 14.6 msec; 90% CI: 11.8 – 17.3 msec
- Cushing’s patients with hepatic impairment, 600 μg b.i.d.: mean: 14.3 msec; 90% CI: 11.6 – 17.0 msec

Please refer to “PK/QT Modeling: Response to FDA letter Modeling report”, [SOM230BPopPKQT] included in this submission for more details.

Reviewer Comments: As stated above, the model predicted values of $\Delta\Delta QTcI$ for healthy subjects and Cushing’s patients at the 900 μg b.i.d dose are 14.1 and 14.6 msec. The maximum mean $\Delta\Delta QTcI$ for Cushing’s patients with severe hepatic impairment at the 600 μg b.i.d dose is predicted to be 14.3 msec. These values are similar to the model predicted $\Delta\Delta QTcI$ at 2 hours post-dose (where the largest upper bound of the $\Delta\Delta QTcI$ was observed in the TQT study). The model predicts that the $\Delta\Delta QTcI$ at 2 hours post-dose for healthy subjects and Cushing’s patients at the 900 μg b.i.d. dose to be 13.9 msec and 14.3 msec (Table 4 and Table 5). The $\Delta\Delta QTcI$ at 2 hours post-dose for Cushing’s patients with severe hepatic impairment at the 600 μg b.i.d dose is 14 msec (Table 6). The predicted C_{max} at steady state for pasireotide at the proposed dose of 600 μg b.i.d dose in Cushing’s patients with severe hepatic impairment (worst case scenario) is 37.8 ng/ml which is lower than the observed C_{max} of 80.6 ng/ml at steady state for the suprathreshold dose of 1950 in TQT study (see QT-IRT review). The predicted steady state C_{max} at 900 μg b.i.d dose in Cushing’s patients with severe hepatic impairment is 56.6 ng/ml. Therefore, the suprathreshold dose of 1950 μg b.i.d dose in the TQT study seems adequate to cover the exposures expected in the worst case scenario of severe hepatic impairment in Cushing’s patients.

FDA Comment # 3a:

You should conduct a central tendency analysis and categorical analysis and submit it to the NDA in a Cardiac Safety Report Format:

- a. The purpose of a central tendency analysis is to provide summary statistics for mean HR, QTc, PR, and QRS interval (together with its 90% two-sided confidence interval) change from baseline stratified by different time points.

Sponsor Response:

Note that Cardiovascular Report “QT/QTc Interval Analysis Report” (CVR) was submitted to the original NDA which addresses some of these requests and the additional analyses requested are presented in this response document.

[B2305 - CSR Table 14.3-2.84x01] displays the Change in ECG parameters (as determined by

central readings) from baseline to time points up to Data cut-off by dose group. This includes descriptive statistics (n, mean, SD, median, min and max, and 90% two-sided confidence interval) for HR, PR, QRS, QT, QTcB and QTcF, as well as the descriptive statistics for the change from baseline in all these parameters.

FDA Comment # 3b:

You should conduct a central tendency analysis and categorical analysis and submit it to the NDA in a Cardiac Safety Report Format:

b. A categorical analysis typically includes the number and percentage of subjects with:

1. Absolute QT/QTc values > 450 ms, > 480 ms, and > 500 ms; as well as
2. With change from baseline > 30 ms and > 60 ms.
3. PR changes from baseline \geq 25% and absolute value over > 200 ms.
4. QRS changes from baseline \geq 25% and absolute value over > 110 ms.
5. Abnormal ECG findings.
6. HR < 60 bpm, > 100 bpm.
7. Adverse events that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.

Sponsor Response:

Note that Cardiovascular Report “QT/QTc Interval Analysis Report” (CVR) was submitted to the original NDA which addresses some of these requests and the additional analyses requested are presented in this response document.

In response to question 3b; 1, 3, and 4, we refer to [B2305 - CSR Table 14.3-2.83] which displays the number and percentage of patients with notable ECG interval values (as determined by central readings) by Data cut-off and dose group, including:

- Absolute QT/QTc values > 450 ms, > 480 ms, and > 500 ms
- PR changes from baseline > 25% and absolute value over > 200 ms
- QRS changes from baseline > 25% and absolute value over > 110 ms

In response to question 3b; 2, newly created [B2305 - CSR Table 14.3-2.83x02] displays the number and percentage of patients with notable ECG interval values (as determined by central readings) by Data cut-off and dose group including:

- Absolute QT/QTc values > 450 ms, > 480 ms, and > 500 ms as well as change from baseline > 30 ms and > 60 ms

In response to request 3b; 5, we refer to [B2305 CSR Listing 16.2.9-1.6] which displays the patients with abnormal ECG evaluation (as determined by central readings) by dose group.

In response to question 3b; 6, newly created [B2305 - CSR Table 14.3-2.85] displays number and percentage of patients with notable ECG heart rate values (as determined by central readings) up to Data cut-off by dose group (HR < 60 bpm, > 100 bpm).

In response to question 3b; 7, we refer to [B2305 CSR Table 14.3.1-1.37] and [B2305 CSR Listing 14.3.2-1.6] which display the adverse events of Special Interest, regardless of study drug relationship, by group name, preferred term and dose group up to Data cut-off.

Adverse events that could be associated with prolongation of cardiac repolarization or proarrhythmia, (e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death) are also presented in Table 6-7 of the QT/QTc Interval Analysis Report [CVR - Table 6-7:

“Adverse events indicative of arrhythmogenic potential, regardless of pasireotide relationship, by preferred term and dose group in Study SOM230B2305”]. The list of preferred terms is presented in [CVR - Section 5.5.2].

Reviewer’s Comments: In study SOM30B 2305 safety analysis was conducted in 162 patients, 82 patients were treated with pasireotide 600 µg b.i.d. and 80 patients with pasireotide 900 µg b.i.d. Table 14.3.2.83 (CSR, page 1756) shows the number and percentage of patients with notable ECG intervals values. No patient treated with the 600-µg dose and two patients (2.7%) under the 900-µg dose experienced a QTcF > 500 ms. Two patients in the 600-µg arm (2.6%) and 3 patients in the 900-µg arm (4.1%) had an increase over baseline > 60 ms. More subjects had an increase over baseline > 30 ms in the higher dose group (47 %) than in the lower dose group (30%).

No subject had an increase over baseline in QRS > 25%. Only one subject in each dose group had an increase in PR > 25% of baseline values (1.3 and 1.4%, 600 µg, 900 µg, respectively). According to table 14.3-2.85, between 71 to 75 % of the subjects had a HR < 60 bpm and 3.8% of the subjects in the lower dose and 9.2 % of the subjects in the higher dose group had HR > 100 bpm.

Grade 1 and 2 QTc prolongation was reported in both dose groups (5 events each). In the majority of cases subjects were bradycardic (CSR, listing 14.3.2-1.6, page 2333). All ten of the ‘Electrocardiogram QT prolonged’ AEs were asymptomatic.

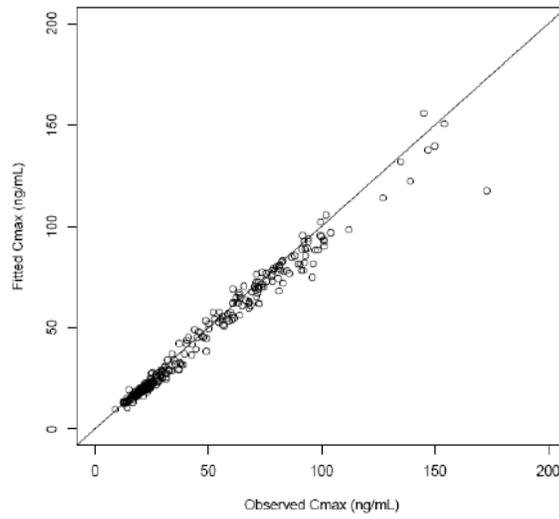
There was a single ‘Electrocardiogram QT prolonged’ SAE leading to study drug discontinuation (B2305-0771-00003). Subject was under 900 µg pasireotide and experienced two episodes of QTc ruled as suspected to be linked to study medication. In both cases local readings were higher than central readings and QTcF was within normal values as follows: 1st episode: local reading QTcB 492 ms and QTcF 454 ms; central reading 358 ms (QTcB) and 427 ms (QTcF). 2nd episode: local reading QTcB 485 ms and QTcF 447 ms; central reading 335ms (QTcB) and 396 ms (QTcF). (Source: SOM230B, cardiovascular report, page 1055).

Data reported suggest that there is a small QTc signal with pasireotide, which seems to be related to changes in HR in the majority of cases. No SAEs of concern were reported.

2. SPONSOR’S POPULATION PK ANALYSIS

A population PK model was used to describe the data from Study B2125 with 2990 pasireotide concentration observations from 105 subjects. The model that best described the data was a 3 compartment disposition model with first order absorption, linear elimination, and covariate relationships of body weight on central volume of distribution and age on clearance and central volume of distribution. The FOCE method with interaction was used for parameter estimation. Figure 1 shows the plot for model predicted C_{max} of individual versus observed C_{max}.

Figure 1: Sponsor's Plot of Model Predicted C_{max} of Individual versus Observed C_{max} .



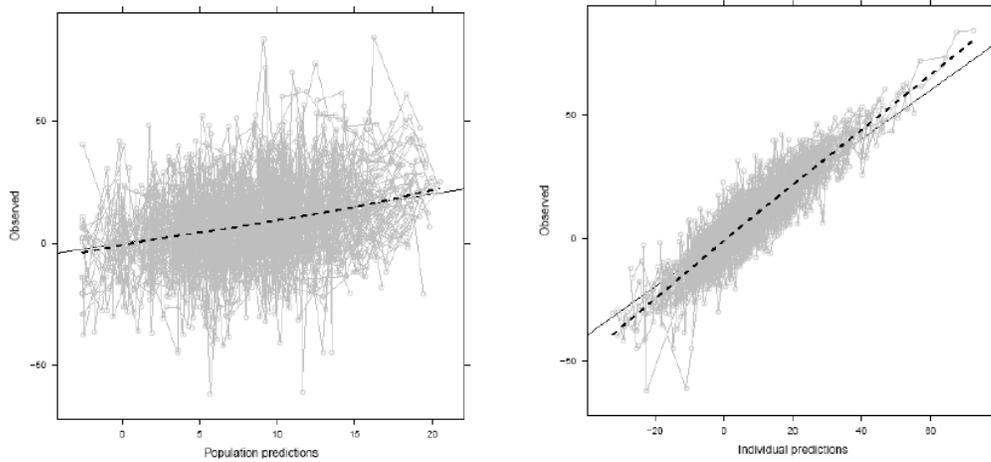
Source: Figure 5-2 from PK/QT modeling report.

Reviewer Comments: The sponsor's population PK model is reasonable. Within the exposures achieved in study B2125, the model predicts the C_{max} of the drug reasonably well as observed in Figure 1. The parameter estimates of the sponsor's model are provided in Table 7. Stand errors for parameters could not be obtained from NONMEM.

3. SPONSOR'S EFFECT COMPARTMENT MODEL FOR $\Delta\Delta QTcI$

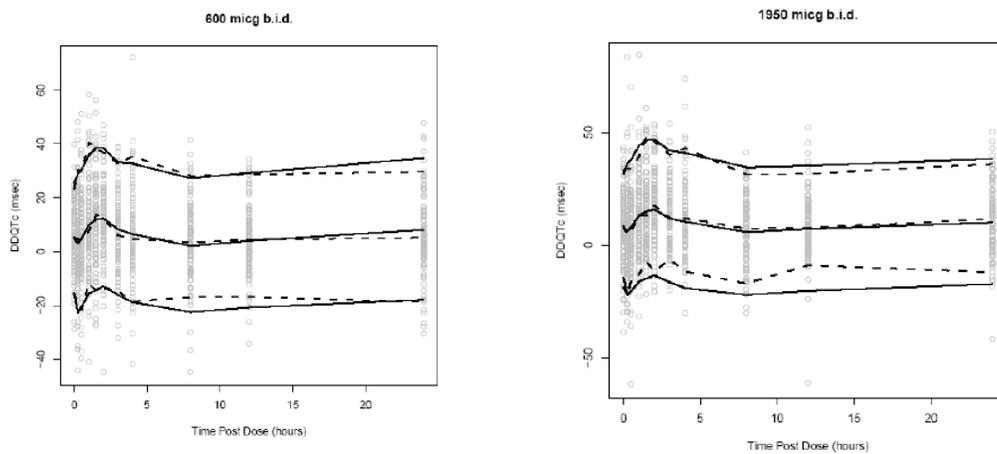
The data is described by an effect-compartment model with E_{max} dependence of $\Delta\Delta QTcI$ on the pasireotide concentration in the effect compartment and with a complementary component describing PK-independent diurnal effects. The FO method in NONMEM was used for parameter estimation. The plot of observed $\Delta\Delta QTcI$ versus population predicted $\Delta\Delta QTcI$ and observed $\Delta\Delta QTcI$ versus individual predicted $\Delta\Delta QTcI$ are shown in Figure 2. Figure 3 shows the visual predictive check of the model based on observed values of $\Delta\Delta QTcI$ for 600 and 900 μg b.i.d dose group. Table 1 and Table 2 show the mean and 90% CI for observed $\Delta\Delta QTcI$ and mean model fitted $\Delta\Delta QTcI$ by time post dose for 600 and 1950 μg b.i.d. dose group.

Figure 2: Sponsor’s Plot of Observed versus Population and Individual Predicted $\Delta\Delta QTcI$ values



Source: Figure 5-3 from PK/QT modeling report.

Figure 3: Sponsor’s Visual Predictive Check of the Model Based on Observed Values of $\Delta\Delta QTcI$ for 600 and 1950 μg b.i.d Dose Groups



Points are the observed values and dashed lines are the 5th, 50th, and 95th percentile of the observed $\Delta\Delta QTcI$ by time point. Solid lines the 5th, 50th, and 95th percentile of the simulated data set by time point. Source: Figure 5-4 from PK/QT modeling report.

Table 1: Sponsor’s Mean and 90% CI for Observed $\Delta\Delta QTcI$ and Mean Model Fitted $\Delta\Delta QTcI$ by Time Post-Dose for 600- μg b.i.d. Dose Group

Time post dose (hours)	Observed 90% Confidence Interval (msec)	Observed Mean (msec)	Individual Predictions’ Mean (msec)
0	4 – 8	6	5
0.25	1 – 7	4	2
0.5	2 – 8	5	4
1	7 – 12	10	9
1.5	9 – 15	12	11
2	10 – 14	12	12
3	4 – 9	7	8
4	3 – 8	6	7
8	1 – 6	3	3
12	3 – 7	5	4
24	4 – 8	6	8

Source: Table 5-7 from PK/QT modeling report.

Table 2: Sponsor’s Mean and 90% CI for Observed $\Delta\Delta QTcI$ and Mean Model Fitted $\Delta\Delta QTcI$ by Time Post-Dose for 1950 μg b.i.d. Dose Group

Time post dose (hours)	Observed 90% Confidence Interval (msec)	Observed Mean (msec)	Individual Predictions’ Mean (msec)
0	5 – 10	8	9
0.25	2 – 8	5	7
0.5	4 – 10	7	9
1	10 – 16	13	14
1.5	12 – 18	15	16
2	14 – 20	17	17
3	12 – 16	14	13
4	10 – 16	13	12
8	5 – 10	7	7
12	6 – 11	8	8
24	9 – 14	12	10

Source: Table 5-8 from PK/QT modeling report

Reviewer Comments: The sponsor’s effect compartment model for $\Delta\Delta QTcI$ is reasonable. The diagnostic plot (Figure 2) and the visual predictive check (Figure 3) provided by the sponsor show that the model fits the data reasonably well. Similarly Table 1 and Table 2 show that the model predicts the mean $\Delta\Delta QTcI$ for the 600 and 1950 μg b.i.d dose group reasonably.

3. SPONSOR’S EFFECT COMPARTMENT MODEL FOR $\Delta\Delta QTcI$

Using the model described above, Study B2125 was simulated 100 times to predict $\Delta\Delta QTcI$ for the 900 μg b.i.d dose. For the prediction of $\Delta\Delta QTcI$ in Cushing’s patients, the PK parameter

estimates from a population PK model developed for Cushing's patients was used. In particular, clearance value for patients with Cushing's disease was 3.8 L/h, which is lower than the clearance of 5.79 L/h for healthy volunteers in Study 2125. For Cushing's disease patients with severe hepatic impairment, the clearance was reduced by 44% from 3.80 L/h to 2.13 L/h based on the results of the dedicated study. The model predicted values of means and confidence intervals (CI) of $\Delta\Delta QTcI$ at times post dose of maximum mean $\Delta\Delta QTcI$ for healthy subjects and Cushing's patients at the 900 μg b.i.d dose and Cushing's patients with severe hepatic impairment at the 600 μg b.i.d dose, are shown in is shown in Table 3.

The model predicted individual $\Delta\Delta QTcI$ by time point for the various scenarios are provided in Table 4, Table 5, and Table 6

Table 3: Sponsor's Summary Statistics of Times Post-Dose of Maximum Mean $\Delta\Delta QTcI$, and of Means and Confidence Limits at Those Times, in Healthy Volunteers, Cushing's Patients and Cushing's Patients with Severe Hepatic Impairment

Healthy Volunteers					
Dose	Time post dose (hours) ^a	Mean $\Delta\Delta QTcI$ (msec)	Lower 90% CI (msec)	Upper 90% CI (msec)	
900 μg b.i.d.	1: 4%	Min. : 11.0	Min. : 8.4	Min. : 13.7	
	1.5: 34%	1st Qu.: 13.0	1st Qu.: 10.4	1st Qu.: 15.7	
	2: 62%	Median :14.0	Median :11.3	Median :16.6	
		Mean : 14.1	Mean : 11.4	Mean : 16.8	
		3rd Qu.: 15.2	3rd Qu.: 12.6	3rd Qu.: 17.8	
		Max. : 18.5	Max. : 15.6	Max. : 21.4	
Cushing's Patients					
Dose	Time post dose (hours) ^a	Mean $\Delta\Delta QTcI$ (msec)	Lower 90% CI (msec)	Upper 90% CI (msec)	
900 μg b.i.d.	1: 4.4%	Min. : 10.8	Min. : 7.9	Min. : 13.6	
	1.5: 30.8%	1st Qu.: 13.5	1st Qu.: 10.8	1st Qu.: 16.2	
	2: 64.6%	Median :14.6	Median :11.8	Median :17.3	
	3: 0.2%	Mean : 14.6	Mean : 11.8	Mean : 17.3	
		3rd Qu.: 15.5	3rd Qu.: 12.8	3rd Qu.: 18.3	
		Max. : 19.0	Max. : 16.2	Max. : 21.7	
Cushing's Patients with Severe Hepatic Impairment					
Dose	Time post dose (hours) ^a	Mean $\Delta\Delta QTcI$ (msec)	Lower 90% CI (msec)	Upper 90% CI (msec)	
600 μg b.i.d.	1: 4.8%	Min. : 9.3	Min. : 7.1	Min. : 11.6	
	1.5: 37.8%	1st Qu.: 13.3	1st Qu.: 10.6	1st Qu.: 16.0	
	2: 57.4%	Median :14.3	Median :11.6	Median :17.0	
		Mean : 14.3	Mean : 11.6	Mean : 17.0	
		3rd Qu.: 15.3	3rd Qu.: 12.6	3rd Qu.: 18.0	
		Max. : 20.0	Max. : 17.8	Max. : 22.3	

Source: Tables 5-9, 5-11 and 5-13 in PK/QT modeling report

Table 4: Sponsor’s Summary Statistics for Simulated Individual $\Delta\Delta$ QTcI following 900 μ g b.i.d sc Dose by Time Point in Healthy Volunteers

Dose	Time post dose (hours)	$\Delta\Delta$ QTcI (msec)					SOM230 concentration (ng/mL)
		1st Qu.	Median	Mean	3rd Qu.	SD	
900 μ g b.i.d.	0	-0.3	5.6	5.8	11.9	9.1	6.5
	0.25	-5.2	4	4	13	13.6	26.1
	0.5	-3.1	5.9	6	15	13.6	31.4
	1	1.9	11.1	11.4	20.5	14	31.4
	1.5	3.5	13.1	13.2	22.5	14.4	28.1
	2	4.6	13.6	13.9	22.9	14	24.8
	3	1	9.5	9.8	18.4	13	19.4
	4	-1.3	7.9	8	17.4	13.9	15.7
	8	-5.5	3.2	3.3	12	12.9	8.9
	12	-3.6	5	5	13.6	12.8	6.5
	24	-0.5	8.8	8.8	18	13.8	3.7

Source: Table 5-10 in PK/QT modeling report

Table 5: Sponsor’s Summary Statistics for Simulated Individual $\Delta\Delta$ QTcI following 900 μ g b.i.d sc Dose by Time Point in Cushing’s Patients

Dose	Time post dose (hours)	$\Delta\Delta$ QTcI (msec)					SOM230 concentration (ng/mL)
		1st Qu.	Median	Mean	3rd Qu.	SD	
900 μ g b.i.d.	0	-0.6	5.6	5.6	11.7	9.2	5.6
	0.25	-5.1	4.3	4.5	13.9	14.2	45.6
	0.5	-2.8	6.5	6.7	16	14.2	48.3
	1	2.2	11.6	11.9	21.4	14.6	41.4
	1.5	3.6	13.4	13.6	23.4	15	34.5
	2	4.7	14	14.3	23.6	14.4	29
	3	1	9.9	10.1	18.9	13.4	21.2
	4	-1.1	8.3	8.4	17.7	14.1	16.3
	8	-5.6	3	3.1	11.9	13	8.3
	12	-3.9	4.8	4.8	13.4	12.9	5.7
	24	-0.5	8.6	8.7	18	13.6	2.7

Source: Table 5-12 in PK/QT modeling report

Table 6: Sponsor’s Summary Statistics for Simulated Individual $\Delta\Delta QTcI$ following 600 and 900 μg b.i.d sc Doses by Time Point in Cushing’s Patients with Severe Hepatic Impairment

Dose	Time post dose (hours)	$\Delta\Delta QTcI$ (msec)					SOM230 concentration (ng/mL)
		1st Qu.	Median	Mean	3rd Qu.	SD	
600 μg b.i.d.	0	-0.4	5.9	6	12.3	9.6	8.3
	0.25	-5.1	4.3	4.5	13.9	14.3	35.3
	0.5	-2.9	6.3	6.5	15.6	14	37.8
	1	1.9	11.2	11.6	20.9	14.4	34.3
	1.5	3.3	13.1	13.3	23.1	14.8	30.2
	2	4.4	13.8	14	23.2	14.2	26.8
	3	0.8	9.8	9.9	18.7	13.5	21.7
	4	-1.3	8.2	8.3	17.8	14.3	18.2
	8	-5.3	3.4	3.6	12.5	13.3	11.3
	12	-3.7	5.1	5.2	14	13.1	8.5
900 μg b.i.d.	24	-0.4	8.9	9	18.2	13.9	4.7
	0	0.1	6.8	7.1	13.8	10.5	12.2
	0.25	-4.5	5.4	5.7	15.7	15.2	52.9
	0.5	-2.4	7.4	7.7	17.4	15	56.6
	1	2.4	12.4	12.8	22.8	15.4	51.2
	1.5	3.8	14.2	14.5	24.9	15.8	45.2
	2	4.9	14.9	15.2	25.2	15.3	40.1
	3	1.4	10.9	11.2	20.6	14.7	32.4
	4	-0.7	9.4	9.6	19.7	15.3	27.1
	8	-4.7	4.6	4.8	14.2	14.2	16.7
12	-3.1	6.2	6.3	15.4	13.8	12.5	
24	0.1	9.7	9.7	19.1	14.2	6.9	

Source: Table 5-14 in PK/QT modeling report

Reviewer Comments: The model predicts that the $\Delta\Delta QTcI$ at 2 hours post-dose (where the largest upper bound of the $\Delta\Delta QTcI$ was observed in the TQT study) for healthy subjects and Cushing’s patients at the 900 μg b.i.d. dose to be 13.9 msec and 14.3 msec. The $\Delta\Delta QTcI$ at 2 hours post-dose for Cushing’s patients with severe hepatic impairment at the 600 μg b.i.d dose is predicted to be 14 msec. The predicted C_{max} at steady state for pasireotide at the proposed dose of 600 μg b.i.d dose in Cushing’s patients with severe hepatic impairment (worst case scenario) is 37.8 ng/ml which is lower than the observed C_{max} at steady state for the supratherapeutic dose of 1950 μg at steady state (80.6 ng/ml) in TQT study. The predicted steady state C_{max} at 900 μg b.i.d dose in Cushing’s patients with severe hepatic impairment is 56.6 ng/ml. Therefore, the supratherapeutic dose of 1950 μg b.i.d dose in the TQT study seems adequate to cover the exposures expected in the worst case scenario of severe hepatic impairment in Cushing’s patients.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Appendix A

Table 7 : Sponsor's Parameter Estimates for the Population PK Model of Study 2125

Parameter	[PopPKHV]		Model 6 ^a
	Estimate	(Standard Error)	Estimate
Θ_{02} CL/F (L/h)	7.65	(0.562)	5.79
Θ_{01} V_2/F (L)	37.7	(1.02)	37.0
Θ_{03} k_a (h^{-1})	7.30	(0.905)	3.65
Θ_{04} k_{23} (h^{-1})	0.192	(0.0110)	0.155
Θ_{05} k_{32} (h^{-1})	0.179	(0.00906)	0.103
Θ_{06} k_{24} (h^{-1})	0.0452	(0.00796)	0.0476
Θ_7 k_{42} (h^{-1})	0.00497	(0.00217)	0.00131
Θ_{11} $V_2 \sim$ age	0.0159	(0.00727)	0.00688
Θ_{12} $V_2 \sim$ weight	0.00679	(0.00392)	0.0102
Θ_{13} CL \sim age	-0.0108	(0.00871)	-0.00764
Θ_{14} Empirical bias adjustment	--	--	1.10
Θ_{15} Power of proportional error	2.0 (Fixed)	--	1.76
Ω_2 BSV CL/F	0.0979	(0.0150)	0.0718
Ω_1 BSV V_2/F	0.0660	(0.00855)	0.0195
Ω_{2-3} BSV CL/F $\sim V_2/F$	0.0324	(0.00790)	0.0244
Ω_3 BSV k_a	0.502	(0.103)	0.120
Ω_4 BSV k_{23}	0.136	(0.0337)	0.036
Ω_5 BSV k_{32}	0.0779	(0.0139)	0.0395
Ω_6 BSV k_{24}	0.125	(0.0396)	0.0783
Ω_7 BSV k_{42}	0.299	(0.0933)	0.0395
Ω_8 BOV CL/F	--	--	0.0166
Ω_{8-9} BOV CL/F $\sim V_2/F$	--	--	0.00231
Ω_9 BOV V_2/F	--	--	0.0143
Ω_{10} BOV k_a	--	--	0.102
Θ_8 proportional residual error SD (σ_{prop})	0.161	(0.00639)	0.197
Θ_9 additive residual error SD (σ_{add}) (pg/mL)	16.4	(3.96)	6.32

^a Standard Errors could not be estimated by NONMEM

Source: Table 5-3 in PK/QT modeling report

Table 8: Sponsor’s Parameter Estimates for the Effect Compartment (PK/QTc) Model of Study 2125

Parameter	Estimate	Standard Error
Θ_1 TVM (msec), expected $\Delta\Delta$ /QTcI absent sex, diurnal, period, and drug effects	4.40	1.48
Θ_2 β_M (msec), addition to TVM for females	-4.31	1.80
Θ_3 Per2 (msec), effect of Period 2	2.07	1.46
Θ_4 Per3 (msec), effect of Period 3	1.17	1.43
Θ_5 Per4 (msec), effect of Period 4	1.06	1.63
Θ_6 (msec), diurnal effect 0.25 hour post dose	-2.65	1.40
Θ_7 (msec), diurnal effect 0.5 hour post dose	-1.13	1.36
Θ_8 (msec), diurnal effect 1 hour post dose	3.58	1.67
Θ_9 (msec), diurnal effect 1.5 hours post dose	5.28	1.84
Θ_{10} (msec), diurnal effect 2 hours post dose	5.99	1.96
Θ_{11} (msec), diurnal effect 3 hours post dose	2.13	1.95
Θ_{17} (msec), diurnal effect 4 hours post dose	0.839	1.84
Θ_{18} (msec), diurnal effect 8 hours post dose	-3.10	1.47
Θ_{19} (msec), diurnal effect 12 hours post dose	-0.857	1.42
Θ_{20} (msec), diurnal effect 24 hours post dose	3.77	1.61
Θ_{12} k_{eq} (1/h), rate constant of equilibration between central and effect compartments	0.215	0.09
Θ_{13} E_{max} (msec), maximum effect of drug in effect compartment	9.41	2.56
Θ_{14} additive residual error SD (σ)(msec)	8.67	0.31
Θ_{15} C_{50} (pg/mL), concentration of half-maximal effect	19.9	2.63
Θ_{16} a , Hill coefficient	1.76	0.28
Ω_1 BSV of TVM	68.1	13.2
Ω_2 BSV of diurnal effect 0.25 hour post dose	88.4	26.8
Ω_3 BSV of diurnal effect .5 hour post dose	70.6	17.9
Ω_4 BSV of diurnal effect 1 hour post dose	72.7	16.9
Ω_5 BSV of diurnal effect 1.5 hours post dose	84.4	16.3
Ω_6 BSV of diurnal effect 2 hours post dose	71.0	20.7
Ω_7 BSV of diurnal effect 3 hours post dose	55.4	16.8
Ω_{10} BSV of diurnal effect 4 hours post dose	84.6	21.9
Ω_{11} BSV of diurnal effect 8 hours post dose	76.1	18.5
Ω_{12} BSV of diurnal effect 12 hours post dose	80.0	19.7
Ω_{13} BSV of diurnal effect 24 hours post dose	109.	23
Ω_8 BSV of $\log(k_{eq})$	10.7	5.68
Ω_9 BSV of E_{max}	226.	54.8

Source: /nmpkpd/run508/run508.mod

Source: Table 5-5 in PK/QT modeling report

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ANSHU MARATHE
08/29/2012

MONICA L FISZMAN
08/29/2012

KEVIN M KRUDYS
08/29/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 200677

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

Applicant: Novartis Pharmaceuticals Corporation

Labeling Reviewed

Submission Date: February 17, 2012

Receipt Date: February 17, 2012

Background and Summary Description

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)

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

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 has submitted 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 submitted efficacy data from its proof-of-concept Study B2208, entitled, "A Phase II POC, 15-day, open-label, single-arm, non-randomized, multi-center study to assess the safety, efficacy and PK of 600 µg administered s.c. b.i.d. SOM230 administered in patients with Cushing's disease", and its study extension phase, B2208E1.

The sponsor submitted its related 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.

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 submitted to (b) (4) requests for review of its proposed proprietary name Signifor on (b) (4) a conditionally acceptable letter issued. The sponsor submitted a request for review of the proprietary name again with the NDA submission.

A Pre-NDA meeting was held with the sponsor on August 30, 2010, and minutes issued on January 27, 2011.

The sponsor originally submitted NDA 200677 on June 21, 2011. On August 19, 2011, the sponsor submitted information pertaining to the recent observation of (b) (4) particulates discovered in historical and intended commercial drug batches for the to-be-marketed presentation of pre-filled syringes. FDA held a teleconference with the sponsor on August 19, 2011, to discuss and clarify the prevalence of this trend with regards to the number of syringes that had particulates, the number, size, identity and origin of the particulates, and time of onset for particulate formation. The sponsor was not able to completely answer these questions during the teleconference and stated that a root cause analysis was ongoing. Several approaches to remedy this (refuse-to-file) issue were discussed. The sponsor withdrew NDA 200677 on this same day. (Refer to the RPM Filing Review dated August 19, 2011.)

Since the product quality concerns with the pre-filled syringes identified above did not extend to the ampoule form of the drug product (used in the completed and ongoing clinical trials with pasireotide), the sponsor resubmitted NDA 200677 on February 17, 2011, using the ampoule presentation. (For further information on this issue, refer to the CMC review by Olen Stephens and Ali Al-Hakim on August 26, 2011.)

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during

labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)

• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.

- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”
- **Indications and Usage**
 - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
 - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
 - All contraindications listed in the FPI must also be listed in HL.
 - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
 - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
 - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
 - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.
- **Patient Counseling Information Statement**
 - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and

other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”

- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

In addition, the following labeling issues were identified:

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, “Patient Information.”
- 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

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by May 18, 2012. The resubmitted labeling will be used for further labeling discussions.

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
04/30/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 200677 BLA#	NDA Supplement #:S- N/A BLA Supplement #	Efficacy Supplement Type SE- N/A
Proprietary Name: Signifor Established/Proper Name: pasireotide Dosage Form: Injection (s.c.) Strengths: 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A		
Date of Application: February 17, 2012 Date of Receipt: February 17, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: December 17, 2012	Action Goal Date (if different):	
Filing Date: April 17, 2012	Date of Filing Meeting: April 10, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with Cushing's disease who require medical therapeutic intervention		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 068635 and (b)(4) (Division of Oncology Products 2)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th data-bbox="203 1451 495 1486">Application No.</th> <th data-bbox="495 1451 773 1486">Drug Name</th> <th data-bbox="773 1451 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1451 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>																				

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>				
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA # N/A</p>				
Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	X			
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</p>	X			
Financial Disclosure	YES	NO	NA	Comment
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	X			
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p>	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	All-electronic submission

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		X		

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Orphan indication
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>	X			Risk management plan (not REMS) submitted
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT Interdisciplinary Review Team and epidemiology consults to issue soon; SEALD Team consult sent
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date: May 15, 2006	X			

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date: August 30, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			Clinical SPA No Agreement letter issued on November 22, 2006; Final ECAC reports for carcinogenicity SPAs faxed on October 19, 2006 and on December 20, 2004; Stability SPA No Agreement letter issued on August 12, 2004

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 10, 2012

BLA/NDA/Supp #: NDA 200677

PROPRIETARY NAME: Signifor

ESTABLISHED/PROPER NAME: pasireotide

DOSAGE FORM/STRENGTH: Injection (s.c.)

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with Cushing's disease who require medical therapeutic intervention

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)

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 has submitted 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 submitted efficacy data from its proof-of-concept Study B2208, entitled, "A Phase II POC, 15-day, open-label, single-arm, non-randomized, multi-center study to assess the safety, efficacy and PK of 600 µg administered s.c. b.i.d. SOM230 administered in patients with Cushing's disease", and its study extension phase, B2208E1.

The sponsor submitted its related 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. The sponsor submitted a request for review of the proprietary name again with the NDA submission.

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 on July 22, 2010, 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 final study reports for both this study (submitted on October 7, 2011) and the previously submitted QT study (see above) were consulted to the QT Interdisciplinary Review Team for review on October 21, 2011. A letter issued to the sponsor (to both INDs 068635 (b) (4)) on March 23, 2012.

A Pre-NDA meeting was held with the sponsor on August 30, 2010, and minutes issued on January 27, 2011.

The sponsor originally submitted NDA 200677 on June 21, 2011. On August 19, 2011, the sponsor submitted information pertaining to the recent observation of (b) (4) particulates discovered in historical and intended commercial drug batches for the to-be-marketed presentation of pre-filled syringes. FDA held a teleconference with the sponsor on August 19, 2011, to discuss and clarify the prevalence of this trend with regards to the number of syringes that had particulates, the number, size, identity and origin of the particulates, and time of onset for particulate formation. The sponsor was not able to completely answer these questions during the teleconference and stated that a root cause analysis was ongoing. Several approaches to remedy this (refuse-to-file) issue were discussed. The sponsor withdrew NDA 200677 on this same day. (Refer to the RPM Filing Review dated August 19, 2011.)

Since the product quality concerns with the pre-filled syringes identified above did not extend to the ampoule form of the drug product (used in the completed and ongoing clinical trials with pasireotide), the sponsor resubmitted NDA 200677 on February 17, 2011, using the ampoule

presentation. (For further information on this issue, refer to the CMC review by Olen Stephens and Ali Al-Hakim on August 26, 2011.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Johnson	Y
	CPMS/TL:	Lina AlJuburi	Y
Cross-Discipline Team Leader (CDTL)	Dragos Roman		Y
Clinical	Reviewer:	Naomi Lowy	Y
	TL:	Dragos Roman	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Sang Chung	Y
	TL:	Jaya Vaidyanathan	Y
Biostatistics	Reviewer:	Lee Ping Pian	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Karen Davis-Bruno	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Olen Stephens	Y
	TL:	Suong Tran	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	N
	TL:	Stephen Langille	N
CMC Labeling Review	Reviewer:	Olen Stephens	Y
	TL:	Suong Tran	N
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jamie Wilkins Parker	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Jennie Chang (until 4/30) Amarilys Vega	Y
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	Jean Mulinde	Y
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers	Houda Mahayni (ONDQA Biopharm) Shawna Hutchins (Patient Labeling) Steven Hertz (Office of Compliance)		Y Y Y
Other attendees	Amy Egan (Division Director Safety) Mehreen Hai (Safety RPM) Marina Zemskova (Clinical Reviewer)		Y Y Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the</i></p>	<input checked="" type="checkbox"/> YES Date if known: TBD <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Curtis Rosebraugh, M.D., MPH</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

JENNIFER L JOHNSON
04/30/2012

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2012-037
APPLICATION NUMBER	NDA 200677 / IND 068635
LETTER DATE/SUBMISSION NUMBER	February 17, 2012 / SDN5
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	March 23, 2012
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	Naomi Lowy
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	James P. Stansbury
REVIEW COMPLETION DATE	August 23, 2012
ESTABLISHED NAME	pasireotide injection
TRADE NAME	Signifor
APPLICANT	Novartis Pharmaceuticals
ENDPOINT(S) CONCEPT(S) MEASURE(S)	Health-Related Quality-of-Life (HRQL) Cushing Quality-of-Life (CushingQoL) Questionnaire
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
INDICATION	treatment of Cushing's disease
INTENDED POPULATION(S)	adults with persistent or recurrent Cushing's disease, or adults with <i>de novo</i> disease who would not be eligible for surgery
NOTE	This review examines an endpoint and instrument used in a pivotal trial that is complete as part of a New Drug Application. The retrospective review has been requested because the sponsor finds HRQL results to be supportive of treatment benefit from the product in the absence of a full demonstration of instrument content validity, established clinical meaning for levels of change, statistically significant results, or a sustained trend in results.

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology Products regarding NDA 200677. The sponsor used the Cushing's Syndrome Quality-of-Life (CushingQoL) Questionnaire to measure *health-related quality-of-life* (HRQL) in a Phase 3 trial assessing the efficacy and safety of 2 different doses of pasireotide. The CushingQoL total score was a secondary endpoint in pivotal Trial CSOM230B2305, which included adult patients with persistent or recurrent Cushing's disease following pituitary resection and patients with de novo disease who were not candidates for surgery.

The review concludes that the evidence submitted by the sponsor does not demonstrate a clear measurable benefit in HRQL despite the sponsor's assertion of "improvement in the patients' perception of their health status." No dossier for the CushingQoL was submitted in line with FDA guidance. (b) (4)

Content validity for the CushingQoL remains in doubt.

An additional concern relates to design. Trial SCOM230B2305 included no comparator and it was determined that a placebo controlled trial would be unethical. Thus, it is unclear how much of the observed improvement in patient-perceived HRQL might be an artifact of the trial situation (i.e. the unmeasured placebo effect). No analyses clarifying the clinical meaning of changes were provided.

Finally, HRQL results were tabulated using descriptive statistical comparisons. The suggestive mean percent changes in HRQL scores at Month 6 (31.3% for 600 µg vs. 73.0% for 900 µg) were clearly inflated due to outliers and had broadly overlapping 95% confidence intervals, thus reflecting statistically non-significant difference between arms. The clinical meaning of the more modest median changes (13.2% vs. 30.0%) was unclear, and the apparent 'dose-response' difference in HRQL was not consistent through the open label period to Month 12 (median 26.0% for 600 µg vs. 20.6% for 900 µg).

Overall, the results showing HRQL benefit are not compelling, and derived using an instrument for which content validity remains uncertain.

B. PRELIMINARY RESPONSES TO DIVISION QUESTIONS

The following comments are revised versions of our initial responses discussed in the Division's Signifor Mid-Cycle Review Meeting held July 2, 2012.

- 1) Is there any relevance of the QoL questionnaire for Cushing's disease?

Yes, the questionnaire likely measures some concerns of importance to Cushing's disease patients. However, we cannot determine if these items are a comprehensive elaboration of

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Cushing's HRQL concerns, or if they include elements that are most important in measuring quality-of-life for these patients.

(b) (4)

[REDACTED] we have insufficient information to adequately assess the content validity of the Cushing's Syndrome Quality-of-Life Questionnaire (CushingQoL). Webb et al's (2008) article remains the sole source of information on preliminary work completed with Cushing's patients. The reference tells us that 10 patients were interviewed in the concept elicitation study, with no evidence that a cognitive debriefing regarding proposed items was carried out. There is no additional information allowing us to assess the qualitative analysis, the degree of concept saturation achieved, nor ultimately determine if the CushingQoL is an optimal set of items for measuring HRQL.

The authors of the published study mention a factor analysis and Rasch analysis to explore latent structure and dimensionality in their abstract. The manuscript fails to elaborate this work further. However, the authors go on to describe correlations that the authors present as evidence for construct validation.

The four-week recall assessing general status is typical of HRQL instruments designed for use in clinical practice conditions or apt for observational health services studies. Whether this level of precision is fit for assessment of treatment benefit in a specific drug trial context remains a review issue.

We can describe the content of the CushingQoL roughly as follows:

- four relatively proximal symptom impact items (trouble sleeping, pain interfering with daily life, slow wound healing, and bruising easily)
- four items about CS-related affective attributes (irritability, mood swings, etc.; self-confidence; worries about appearance; and worries about health)
- three items touching on personal and social constraints imposed by CS (feeling less like going out; having to give up leisure activities; and effects on everyday work or study)
- one item about cognitive impacts (difficulty remembering things)

Again, these items are likely of importance to patients but we do not have the evidence that these are the most significant impacts or HRQL concerns.

2) Can any of the QoL data be included in the eventual package insert?

No. In the absence of evidence for content validity for the CushingQoL, data that allow for interpretation of the clinical meaning of improvements in HRQL, or statistically significant results, we do not recommend incorporating CushingQoL results in labeling. A health-related quality-of-life claim cannot be supported because the CushingQoL has not been demonstrated to capture the most important physical, psychological/mental, and social impacts of Cushing's disease on daily life, a convincing impact of treatment on identified signs and symptoms of Cushing's disease is not demonstrated, and the results, even were the first two conditions met, are not statistically significant or sustained.

On the positive side, the changes reported in the HRQL measure at least fall in the direction of patient improvement.

C. STUDY ENDPOINT REVIEW

Preliminary response to DMEP questions about use of the CushingQoL in Trial CSOM230B2305 were prepared for a mid-cycle review meeting held July 2, 2012. Continued discussion for planning a forthcoming Advisory Council meeting was held August 7, 2012. The Division observes that the sponsor finds the HRQL results supportive of high-dose pasireotide use, despite inconsistent and inconclusive results. As a result, we provide the following review discussing issues with the instrument, trial design, and the trial results.

1 CONTEXT OF USE

1.1 Target Population

Trial CSOM230B2305 included male and female patients, 18 years of age or older, with persistent or recurrent Cushing's disease, post-pituitary resection, who had not received pituitary irradiation within the last ten years and who were appropriate candidates for medical treatment. Patients with *de novo* Cushing's disease were included if they were not considered candidates for pituitary surgery if they were poor surgical candidates, had surgically unapproachable tumors, or refused to have surgery in favor of medical treatment. Because surgery is the primary treatment choice for Cushing's disease patients and given that it has a relatively high success rate, patients who were candidates for surgery were not considered eligible for the study.

Cushing's disease was fully defined. An additional key inclusion criterion was that patients have mean urinary free cortisol at least 1 1/2 times the upper-limit of normal ($mUFC \geq 1.5 \times ULN$).

Of 165 patients randomized, 66% participated through the Month 6 primary efficacy assessment, with about 48% completing participation through Month 12 at the end of the open-label phase. Nearly 43% of patients withdrew due to either adverse events or unsatisfactory results. Tables showing patient disposition, demographic information, and clinical characteristics of study participants are displayed in Appendix A.

1.2 Target Product Profile

No TPP was part of the material reviewed here. (b) (4)

1.3 Endpoint Model

The endpoint structure for Trial CSOM230B2305 is as follows:

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Primary efficacy endpoint:

Month 6 responders defined as the proportion of responders in each of the pasireotide dose groups at Month 6. A Month 6 responder was defined as a patient with Month 6 mUFC \leq ULN and no dose increase (relative to the randomized dose) prior to Month 6 UFC assessment. If Month 6 mUFC was missing then it was imputed by the last available mUFC (of at least 3 specimens) between (and including) Month 3 and Month 6. Primary analysis of this endpoint was performed on the full analysis set.

Secondary efficacy endpoints:

- Proportion of patients with mUFC \leq ULN at Months 3, 6 and 12 (mUFC based on 4 UFC samples) and at intermediate visits (mUFC based on 2 UFC samples).
- Time to first UFC response
- Plasma ACTH and serum cortisol
- UFC responders at Month 6 based on median UFC response
- Clinical signs
- Clinical symptoms
- Tumor volume
- Response rates at Month 6 after pooling dose groups
- Quality of Life

2 CONCEPT OF MEASUREMENT AND CONCEPTUAL FRAMEWORK

The CushingQoL is described by the sponsor as a “novel single-domain 12 item Cushing’s disease health related quality of life (HRQL) questionnaire.” HRQL appears to be the sole intended concept of measurement. No conceptual framework for the instrument was included in the review materials, nor was one provided earlier in a patient-reported outcomes (PRO) dossier.

3 CLINICAL OUTCOME ASSESSMENT MEASURE(S)

The Cushing’s Syndrome Quality-of-Life (CushingQoL) Questionnaire is composed of 12 items that touch on outcomes thought to be of concern to patients with Cushing’s disease (see Appendix B). The item attributes fall into four identifiable categories:

- four relatively proximal symptom impact items (trouble sleeping, pain interfering with daily life, slow wound healing, and bruising easily)
- four items about CS-related affective attributes (irritability, mood swings, etc.; self-confidence; worries about appearance; and worries about health)
- three items touching on personal and social constraints imposed by CS (feeling less like going out; having to give up leisure activities; and effects on everyday work or study)
- one item about cognitive impacts (difficulty remembering things)

The single published reference on the instrument mentions a latent structure involving “sub-components referent to daily life, emotional or physical aspects domains [sic]” although the factor analysis demonstrating the proposed structure is not presented.^{1, p.626}

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The items are framed negatively (i.e. ask about problems) but scoring is positive, with a higher score indicating better health-related quality-of-life. Thus, a value of ‘1’ is given to responses ‘Always’ or ‘Very much,’ while ‘5’ corresponds to ‘Never’ or ‘Not at all.’ Raw scores can range from 12-60 and are standardized on a 100 pt. scale.

The time-frame or recall given for evaluating items is “in the past 4 weeks.” The framing of the patient explanation states the goal of “help[ing] us to know how you feel and how much your illness has interfered in your usual activities.”

The CushingQoL was developed during the year prior to study initiation by Dr. Susan Webb and Dr. Xavier Badia working in Spain. The initial version included 34 items which were subsequently reduced to the 12-item questionnaire. Verification of some of instrument’s measurement properties was subsequently documented by Web et al.¹ with a sample of 125 patients from Spain, France, Germany, the Netherlands and Italy.

Webb and colleagues noted that the score is interpretable only if the number of unanswered items does not exceed 3 or 25% of the questions. The statistical plan for CSOM230B2305 likewise stipulated that a complete form would require responses to 9 items. HRQL data were collected at baseline, Months 3, 6, and 12 (or final study visit) and tabulated by dose groups. Standardized scores and their changes from baseline were descriptively summarized.

4 CONTENT VALIDITY

Webb et al’s article remains the sole source of information on preliminary work completed with Cushing’s patients. The authors’ literature review indicates that the effort is the first instrument specific to use with Cushing’s syndrome. Generic health status questionnaires including the SF-36, the Hospital Anxiety and Depression Scale (HADS), the General Health Questionnaire-28, the WHO quality of life-BREF, and the Social Adjustment Scale were used in previous studies.

A total of 10 patients were interviewed in the concept elicitation study, although there is no evidence that cognitive debriefing about proposed items was subsequently carried out. We do not have information allowing us to assess the qualitative analysis, the degree of concept saturation achieved, nor a basis on which to determine if the CushingQoL presents an optimal set of items for measuring HRQL.

The authors also mention a factor analysis and Rasch analysis to explore latent structure, dimensionality, and item hierarchy among 125 patients included in the main study, although data and summaries of these analyses are not provided. The 12-item CushingQoL is simply described as unidimensional on the basis of the Rasch analysis. The authors also refer to sub-components including “daily life, emotional, and physical aspects domain,” although evidence for a factor structure supporting this as a latent structure is not provided. The article better documents additional measurement properties of the instrument (see Section 5 below).

Examining face validity of the instrument reveals the following issues in questionnaire content:

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- Some of the items of the instrument may be confusing to the patient, e.g., “I bruise easily,” has the response options of “always, often, sometimes, rarely, never.” Do patients pick “never” because they avoid getting bruises effectively or because they observe that they don’t bruise easily, understanding the item in the way it was intended? Cognitive debriefing was not performed to answer this concern about how items are understood.
- The CushingQoL uses a four-week time frame for assessing HRQL status. This is typical of HRQL instruments designed for use in clinical practice conditions or apt for observational health services studies. More frequently, FDA Divisions prefer the use of 24-hour recalls of specific symptoms and impacts for drug development trials when appropriate.
- We also have concerns when patients are asked to summarize their experience over time. Do patients pick “sometimes” because their bruising experience varies over the course of a month or because they are not sure when or how many times they have bruised over the last month (i.e. does long recall encourage satisficing that is inaccurate)?
- The questionnaire has at least two items that reflect more distal affective or social patient characteristics. These items may not clearly reflect treatment benefit or be expected to respond to changing health status.
 - 6. I have less self-confidence, I feel more insecure.
 - 8. I feel less like going out or seeing relatives or friends.The latter question also ‘double-barrels’ different kinds of relationships, in turn combining these with “going out,” which could create considerable ambiguity in the item.

Otherwise, the instrument appears to capture HRQL concerns that could vary with changing severity in the patient’s condition.

Reviewer note: Overall, the evidence does not favor strong endorsement of the content validity of the CushingQoL for use as a tool in drug development trials in its current form.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Internal consistency reliability and construct validity were demonstrated for the CushingQoL in Web et al’s study in 5 European countries. Cronbach’s α was 0.87, reflecting strong internal consistency. Construct validation was demonstrated in moderate to strong correlation with all subscales of the SF-36. The associations by dimension were reported as physical 0.670, role physical 0.708, bodily pain 0.602, general health 0.597, vitality 0.716, social functioning 0.676, role emotional 0.638, and mental health 0.706.

Longitudinal validation tests were to have been demonstrated in Trial CSOM230B2305. In particular, the protocol suggested that the ability to detect change would be reviewed. However,

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there is no data presented that clarifies the clinical meaning of changes in the CushingQoL in the Final Report. Demonstrations of test-retest reliability seem not to have been conducted in this study or elsewhere.

Reviewer note: Given the sponsor's assertion that the HRQL data are supportive of an increased sense of well being, it would be critical to know what level of change in score exceeds what might be expected simply as a result of trial participation. This would be more easily demonstrated in a placebo-controlled trial, although it could conceivably be demonstrated through an anchor-based approach using a global estimate of perceived change or perhaps the association of HRQL with individual patient changes in signs and symptoms. However, we do not recommend such analyses without first establishing content validity of the instrument in the context of use represented here.

6 INTERPRETATION OF SCORES

The scoring of the CushingQoL is positive, a higher score indicating better health-related quality-of-life. This occurs despite the fact that items ask about the frequency or severity of negative impacts on HRQL. Items are scored on a Likert-type scale of 1-5. A value of '1' is given to responses 'Always' or 'Very much,' while '5' corresponds to 'Never' or 'Not at all.' Raw scores range from 12-60, but are standardized and reported on a 100 pt. scale.

No attempt to explain clinical relevance of the HRQL results, either using a benchmark or cumulative distribution function, is made in study reporting.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The CushingQoL has been translated from its original Spanish into a total of 16 languages with 6 additional versions to accommodate national dialects:

Translations and cultural adaptations were produced ... from the initial Spanish version into German, Italian, French, and Dutch, and later to 11 further languages (English, Danish, Polish, Norwegian, Finnish, Turkish, Flemish, Greek, Bulgarian, Mandarin Chinese, and Portuguese – with an additional cultural adaptation for Brazil; further cultural adaptations were also performed for Argentinean Spanish, for Belgian and Canadian French, as well as for USA and Canadian English).^{1, p.624}

Translations were presented to 5 native-speaking patients who were debriefed to correct comprehension, clarity, cultural relevance and suitable wording (retrospective debriefing). Recommended practices of dual review of first translation, back-translation, and revision to ensure linguistic equivalence prior to debriefing with native-speaking patients were not followed.*

* Wild D, Eremenco S, Mear I, Martin M, Houchin C, Gawlicki M, Hareendran A, Wiklund I, Chong LY, von Maltzahn R, Cohen L, Molsen E. Multinational trials—recommendations on the translations required, approaches to using the same language in in different countries, and the approaches to support pooling the data: The ISPOR

Trial CSOM230B2305 was conducted at 36 sites in 13 countries, covering 11 languages. The locations were in Belgium, Brazil, Canada, France, Denmark, Finland, Germany, the Netherlands, Norway, Poland, Portugal, and the United States.

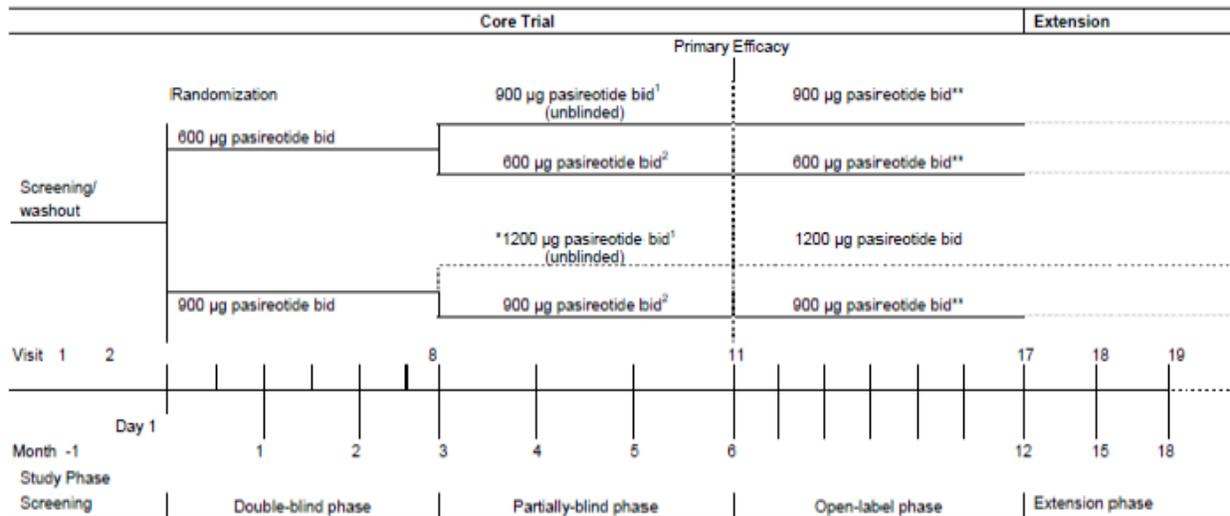
8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Paper-and-pencil administration of the questionnaire was apparently the only mode employed.

9 PROTOCOL AND ANALYSIS PLAN

Patients were randomized to either a twice-daily, 600 µg dose or a 900 µg per injection regimen. An option to increase dosage at 3 months was built in to the design, and following the primary efficacy assessment at 6 months, the trial continued through an open-label phase through Month 12. The schematic for this design is found below.

Figure 9-1 Study design



¹ For patients who had a baseline mUFC ≥ 2 x ULN with a Month 3 mUFC > 2 x ULN or who had a baseline mUFC < 2 x ULN with a Month 3 mUFC > baseline mUFC

² For patients who had a baseline mean UFC ≥ 2 x ULN with a Month 3 mUFC ≤ 2 x ULN or who had a baseline mUFC < 2 x ULN with a Month 3 mUFC ≤ baseline mUFC

* Permitted dose increase only if patient had tolerated 900 µg

** During open-label phase doses could be increased by 300 µg at any time during the study if response was lost

All doses were allowed to be reduced by 300 µg at any time during the study if the doses were not tolerated

China only: patients did not receive doses higher than 900 µg s.c. b.i.d. at anytime during the study

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The rationale for the design stems from the fact that there is no approved medical therapy for the treatment of Cushing's disease. Alternative therapies are judged to be suboptimal. The use of a placebo would not be deemed ethical given the time required for a clinical trial, and the morbidity associated with extended hypercortisolism and the clinical symptoms associated with Cushing's disease.

Reviewer note: A key concern about the HRQL endpoint in Trial CSOM230B2305 results from the fact that there was no comparator for pasireotide in the trial, and that half the trial period was conducted as an open-label study. The clinical meaning of modest average improvement in HRQL scores is difficult to interpret.

Overall, the CushingQoL was appropriately included in the hierarchy of secondary outcomes given the sponsor's assumptions that the instrument was sufficiently comprehensive and appropriate to measure patients' perceived HRQL. The scoring was adequate, and the frequency and timing of administration (i.e. single administration at key visits) was in line with the one-month recall period (see Section 4 discussion of content validity). Detail about the specifics of questionnaire administration at specified visits was not provided.

Reviewer note: Although the HRQL was placed correctly in the hierarchy of secondary endpoints following symptoms measures, efficacy for the symptoms was not demonstrated. (b) (4)

While framed as a secondary endpoint, the analysis plan proposed descriptive tabulation with calculation of 95% confidence intervals for the distributional means. Values were tabulated at baseline, Months 3, 6, and 12 (or final study visit) by dose groups and overall. The SAP made no provision for examination of a cumulative distribution function to compare treatment arms, nor alternatively were HRQL results used to define clinically meaningful response based on a benchmark.

The results for the HRQL analyses can be viewed in Appendix C. As noted previously, mean percent changes in HRQL scores at Month 6 (31.3% for 600 µg vs. 73.0% for 900 µg) were clearly inflated due to outliers and had broadly overlapping 95% confidence intervals. The observed difference between arms was not statistically significant. The clinical meaning of the more modest median changes (13.2% vs. 30.0%) was unclear, and this apparent 'dose-response' in HRQL was not consistent through the open label period to Month 12 (median 26.0% for 600 µg vs. 20.6% for 900 µg).

Reviewer note: Beyond issues of instrument content validity, results showing HRQL benefit are not compelling. A subgroup analysis comparing patients on the basis of clinician rated status ("controlled," "partially controlled," and "uncontrolled") was also uninformative.

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10 KEY REFERENCE FOR MEASURE

1. Webb SM, Badia X, Barahona MJ, Colao A, Strasburger CJ, Tabarin A, van Aken MO, Pivonello, Stalla G, Lamberts SWJ, Glusman, JE. Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. *European Journal of Endocrinology*. 2008; 158:623-30.

D. APPENDICES

Appendix A

Demographic and Clinical Characteristics of Patient Population

Trial CSOM230B2305

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Signifor (pasireotide injection)

Table 10-1 Patient disposition up to data cut-off by randomized dose group (All randomized set)

Disposition Reason	Pasireotide 600 µg b.i.d. N=83 n (%)	Pasireotide 900 µg b.i.d. N=82 n (%)	Overall N = 165 n (%)
Randomized	83 (100.0)	82 (100.0)	165 (100.0)
Randomized but not treated	1 (1.2)	2 (2.4)	3 (1.8)
Randomized and treated	82 (98.8)	80 (97.6)	162 (98.2)
Discontinued at any time*	49 (59.8)	48 (60.0)	97 (59.9)
Reason for discontinuation			
Adverse event(s)	13 (15.9)	15 (18.8)	28 (17.3)
Unsatisfactory therapeutic effect	19 (23.2)	22 (27.5)	41 (25.3)
Subject withdrew consent	13 (15.9)	11 (13.8)	24 (14.8)
Protocol deviation	4 (4.9)	0	4 (2.5)
Discontinued at or prior to Month 6	28 (34.1)	27 (33.8)	55 (34.0)
Discontinued prior to Month 12 but after Month 6	15 (18.3)	14 (17.5)	29 (17.9)
Completed Month 12	39 (47.6)	39 (48.8)	78 (48.1)
Completed Month 12 and did not enter Extension phase*	14 (17.1)	7 (8.8)	21 (13.0)
Completed Month 12 and entered Extension Phase	25 (30.5)	32 (40.0)	57 (35.2)
Ongoing in Extension phase	19 (23.2)	25 (31.3)	44 (27.2)
Discontinued study in Extension phase	6 (7.3)	7 (8.8)	13 (8.0)

Note: % for the first three rows based on N. % for the remaining rows based on randomized and treated subjects. *Patients who completed Month 12 and did not enter extension phase are not counted as discontinuations.

Source: [Table 14.1-1.3](#).

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Signifor (pasireotide injection)

Table 11-2 Baseline demographics by randomized dose group (Full analysis set)

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N = 162
Age (years)			
n	82	80	162
Mean	40.5	39.9	40.2
SD	12.97	10.77	11.90
Median	39.0	41.0	39.0
Min	18	19	18
Max	67	71	71
Age – n (%)			
< 65 years	78 (95.1)	79 (98.8)	157 (96.9)
≥ 65 years	4 (4.9)	1 (1.3)	5 (3.1)
Sex – n (%)			
Male	20 (24.4)	16 (20.0)	36 (22.2)
Female	62 (75.6)	64 (80.0)	126 (77.8)
Race – n (%)			
Caucasian	65 (79.3)	62 (77.5)	127 (78.4)
Black	2 (2.4)	1 (1.3)	3 (1.9)
Asian	10 (12.2)	10 (12.5)	20 (12.3)
Native American	2 (2.4)	2 (2.5)	4 (2.5)
Other	3 (3.7)	4 (5.0)	7 (4.3)
Missing	0 (0.0)	1 (1.3)	1 (0.6)
Ethnicity – n (%)			
Hispanic/Latino	29 (35.4)	22 (27.5)	51 (31.5)
Chinese	10 (12.2)	10 (12.5)	20 (12.3)
Mixed ethnicity	0 (0.0)	1 (1.3)	1 (0.6)
Other	43 (52.4)	46 (57.5)	89 (54.9)
Missing	0 (0.0)	1 (1.3)	1 (0.6)

Source: [Table 14.1-3.1.](#)

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Signifor (pasireotide injection)

Table 11-3 Disease history and baseline characteristics by randomized dose group (Full analysis set)

		Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Time (months) to first pasireotide dose since diagnosis				
n		82	80	162
Mean (SD)		53.38 (63.79)	54.70 (62.79)	54.03 (63.11)
Median		35.48	29.70	33.99
Min –Max		0.10-341.78	0.10-372.14	0.10-372.14
Cushing's Disease Status – n (%)	De novo	15 (18.3)	12 (15.0)	27 (16.7)
	Persistent/recurrent	67 (81.7)	68 (85.0)	135 (83.3)
Any previous surgery – n (%)	No	18 (22.0)	16 (20.0)	34 (21.0)
	Yes	64 (78.0)	64 (80.0)	128 (79.0)
Any previous pituitary irradiation – n (%)	No	79 (96.3)	76 (95.0)	155 (95.7)
	Yes	3 (3.7)	4 (5.0)	7 (4.3)
Any previous medication – n (%)	No	46 (56.1)	38 (47.5)	84 (51.9)
	Yes	36 (43.9)	42 (52.5)	78 (48.1)
Baseline mean UFC				
n		77	76	153
Mean (SD)		1155.94 (2629.779)	781.90 (926.384)	970.14 (1979.020)
Median		730.00	487.00	564.50
Min-Max		219.50-22943.75	195.00-6122.75	195.00-22943.75

Time to first pasireotide dose since diagnosis = (First pasireotide dose date – date of diagnosis of Cushing's disease +1)*12/365.25.

Source: [Table 14.1-3.2](#).

Appendix B

The Cushings Syndrome Quality of Life (CushingsQoL) Questionnaire

3 Pages Have Been Withheld In Full As Copyright Material

Appendix C

Analysis of Changes in HRQL Score

By Time of Instrument Completion

Trial CSOM230B2305

STUDY ENDPOINT REVIEW

CSOM230B2305 Month 12

Table 14.2-2.9 (Page 1 of 2)
Change from baseline in HRQL score at time points up to Month 12 by randomized dose group
(Full analysis set)

Visit	Statistics	Pasireotide 600 ug bid N=82			Pasireotide 900 ug bid N=80		
		Actual	Change from baseline: Actual	Change from baseline: Percent	Actual	Change from baseline: Actual	Change from baseline: Percent
Baseline	n	81			78		
	Mean	41.6			40.5		
	SD	20.41			20.11		
	Median	41.7			37.5		
	Min	6.3			4.2		
	Max	87.5			87.5		
Month 3	n	67	66	66	66	65	65
	Mean	50.0	6.3	32.0	48.7	8.8	54.2
	SD	20.41	14.88	85.87	18.07	14.44	142.14
	Median	52.1	6.3	9.1	47.9	10.4	22.6
	Min	4.2	-20.8	-75.0	16.7	-31.3	-47.1
	Max	91.7	52.1	425.0	89.6	47.9	1050.0
Month 6	n	56	56	56	56	55	55
	Mean	48.7	6.2	31.3	52.0	12.9	73.0
	SD	21.08	16.02	79.99	19.11	14.80	181.06
	Median	50.0	7.3	13.2	54.2	8.3	30.0
	Min	0.0	-35.4	-100.0	16.7	-10.4	-21.4
	Max	85.4	52.1	400.0	91.7	52.1	1250.0
	95% CI*			(10.4, 52.3)			(25.2, 120.9)

Note: Patients were randomized to Pasireotide 600 ug or 900 ug bid at baseline.
*95% CI shown are on the mean percentage change from baseline.

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(Production version)

CSOM230B2305 Month 12

Table 14.2-2.9 (Page 2 of 2)
 Change from baseline in HRQL score at time points up to Month 12 by randomized dose group
 (Full analysis set)

Visit	Statistics	Pasireotide 600 ug bid N=82			Pasireotide 900 ug bid N=80		
		Actual	Change from baseline: Actual	Change from baseline: Percent	Actual	Change from baseline: Actual	Change from baseline: Percent
Month 12	n	37	36	36	39	38	38
	Mean	50.0	9.4	38.9	54.8	12.8	91.8
	SD	20.32	17.38	77.87	18.87	20.44	221.94
	Median	50.0	10.4	26.0	58.3	9.4	20.6
	Min	2.1	-31.3	-66.7	18.8	-25.0	-37.5
	Max	93.8	58.3	311.1	89.6	66.7	1200.0
	95% CI*			(13.5, 64.4)			(21.2, 162.4)

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/s/

JAMES P STANSBURY
08/23/2012

LAURIE B BURKE
08/23/2012

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: February 29, 2012

To: Tejashri Purohit-Sheth, M.D., Acting Division Director, DGCPC
Constance Cullity, M.D., M.P.H., Branch Chief, GCPEB
Susan Leibenhaut, Acting Team Leader, GCPAB
CDEROCDSIPMOs@fda.hhs.gov
Jean Mulinde, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Naomi Lowy, M.D., Clinical Reviewer, Division of Metabolism and
Endocrinology Products (DMEP)
Dragos Roman, M.D., Team Leader, Division of Metabolism and
Endocrinology Products (DMEP)

From: Jennifer Johnson, Regulatory Health Project Manager, DMEP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA #200677

IND#:68635

Applicant: Novartis Pharmaceuticals Corp.

Regulatory Contact: Sandip Roy, Ph.D.

Phone: 862-778-0015

Email: sandip.roy@novartis.com

Drug Proprietary Name: Signifor

Generic Drug Name: pasireotide

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): TBD

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of Cushing's Disease

PDUFA: TBD

Action Goal Date: TBD

DGCPC/OSI Consult

version: 09/28/2011

Inspection Summary Goal Date: TBD

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
204 Van Gaal, Luc U.Z. Antwerpen, Wilrijkstraat 10 Edegem, 2650 BE Western Europe phone:+ 32 3 821 38 85 fax:+ 32 3 821 41 85 email:	CSOM23 0B2305	5	A Randomized, Double-blind Study to Assess the Safety and Efficacy of Different Dose Levels of Pasireotide (SOM230) sc Over a 6 Month Treatment Period in Patients With de Novo, Persistent or Recurrent Cushing's Disease
704 Colao, Annamaria Policlinico II Università degli Studi di Napoli, via Pansini, 5 Napoli, NA 80131 IT Western Europe phone:+39 081 7462132-7464285 fax:+39 081 5465443 email:	CSOM23 0B2305	14	A Randomized, Double-blind Study to Assess the Safety and Efficacy of Different Dose Levels of Pasireotide (SOM230) sc Over a 6 Month Treatment Period in Patients With de Novo, Persistent or Recurrent Cushing's Disease
771 Jin, Zimeng Peking Union Medical College Hospital, No.1 Shuai Fu Yuan Wang Fu Jing.Dongcheng District Beijing, 100730 CH Asia/Pacific phone:+86 10 6529 5006 fax:+86 10 65296872 email:	CSOM23 0B2305	15	A Randomized, Double-blind Study to Assess the Safety and Efficacy of Different Dose Levels of Pasireotide (SOM230) sc Over a 6 Month Treatment Period in Patients With de Novo, Persistent or Recurrent Cushing's Disease

III. Site Selection/Rationale

Site Information

STUDY:	CSOM230B2305	SITEID:	204
---------------	--------------	----------------	-----

NAME	Van Gaal, Luc
LOCATION	U.Z. Antwerpen, Wilrijkstraat 10 Edegem, , BE 2650
PHONE/FAX	+ 32 3 821 38 85 / + 32 3 821 41 85
EMAIL	

RANK	8	FINLDISC	0	COMPLAINT	0
SITE RISK	7.2	OAI	0	TSLI	3

(b) (5)

Site Information

STUDY:	CSOM230B2305	SITEID:	704
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NAME	Colao, Annamaria
LOCATION	Policlinico II Università degli Studi di Napoli, via Pansini, 5 Napoli, IT NA 80131
PHONE/FAX	+39 081 7462132-7464285 / +39 081 5465443
EMAIL	0

RANK	1	FINLDISC	0	COMPLAINT	0
SITE RISK	13.4	OAI	0	TSLI	3

(b) (5)

Site Information

STUDY:	CSOM230B2305	SITEID:	771
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NAME	Jin, Zimeng
LOCATION	Peking Union Medical College Hospital, No.1 Shuai Fu Yuan Wang Fu Jing Dongcheng District Beijing, , CH 100730
PHONE/FAX	+86 10 6529 5006 / +86 10 65296872
EMAIL	0

RANK	2	FINLISC	0	COMPLAINT	0
SITE RISK	12.8	OAI	0	TSLI	3



(b) (5)

Summarize the reason for requesting OSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for OSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for OSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study). Foreign sites drive efficacy benefit.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Jennifer Johnson at 301-796-2194 or Naomi Lowy at 301-796-0692 .

Concurrence: (as needed)

- Medical Team Leader
- Medical Reviewer

_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

*****Things to consider in decision to submit request for OSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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
02/29/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 200677 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE- N/A
Proprietary Name: Signifor Established/Proper Name: pasireotide Dosage Form: Injection Strengths: 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A		
Date of Application: June 21, 2011 Date of Receipt: June 21, 2011 Date clock started after UN: N/A		
PDUFA Goal Date: April 21, 2012	Action Goal Date (if different): April 20, 2012	
Filing Date: August 20, 2011	Date of Filing Meeting: August 9, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of Cushing's Disease		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): IND 068635				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	X			
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Wrong NDA # included on form (user fee staff informed)

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th data-bbox="203 1451 495 1486">Application No.</th> <th data-bbox="495 1451 771 1486">Drug Name</th> <th data-bbox="771 1451 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1451 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>		<p>Pasireotide also has orphan designation for treatment of acromegaly (8/25/09)</p>																

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		If approved, application will receive 7 years orphan drug exclusivity.
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	This product is an NME but does not have abuse potential.

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Product has orphan designation for the proposed indication.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>	X			Risk management plan submitted
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		X		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		X		Color mock-ups of carton and container labeling needed.
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			IRT-QT consult sent August 12, 2011
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): May 15, 2006 <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 30, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): See notes section <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			Clinical SPA No Agreement letter issued on November 22, 2006; Final ECAC reports for carcinogenicity SPAs faxed on October 19, 2006 and on December 20, 2004; Stability SPA No Agreement letter issued on August 12, 2004

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 9, 2011

BLA/NDA/Supp #: NDA 200677

PROPRIETARY NAME: Signifor

ESTABLISHED/PROPER NAME: pasireotide

DOSAGE FORM/STRENGTH: Injection; 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of Cushing's Disease

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)

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 submitted 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 submitted efficacy data from its proof-of-concept Study B2208, entitled, "A Phase II POC, 15-day, open-label, single-arm, non-randomized, multi-center study to assess the safety, efficacy and PK of 600 µg administered s.c. b.i.d.SOM230 administered in patients with Cushing's disease", and its study extension phase, B2208E1.

The sponsor submitted its related 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. The sponsor submitted a request for review of the proprietary name again with the NDA submission.

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 on July 22, 2010, 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 final study reports for both this study and the previously submitted QT study (see above) are being consulted to the QT Interdisciplinary Review Team for review.

A Pre-NDA meeting was held with the sponsor on August 30, 2010, and minutes issued on January 27, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Johnson	Y
	CPMS/TL:	Julie Marchick	Y
Cross-Discipline Team Leader (CDTL)	Dragos Roman		Y
Clinical	Reviewer:	Naomi Lowy	Y
	TL:	Dragos Roman	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Zhihong Li	Y
	TL:	Jayabharathi Vaidyanathan	Y
Biostatistics	Reviewer:	Lee Ping Pian	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Karen Davis Bruno	Y
Statistics (carcinogenicity)	Reviewer:	Matthew Jackson	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Olen Stephens	Y

	TL:	Suong Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	John Metcalfe	Y
	TL:	Jim McVey	N
CMC Labeling Review	Reviewer:	Olen Stephens	Y
	TL:	Suong Tran	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Rick Abate	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	TBD	
	TL:	TBD	
OC/DCRMS (REMS)	Reviewer:	TBD	
	TL:	TBD	

Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Houda Mahayni – ONDQA Biopharm Amy Egan – Deputy Director for Safety Mary Parks – Director, DMEP		Y Y Y
Other attendees	Steven Hertz – Office of Compliance John Bishai – DMEP Safety RPM Marina Zemskova – Clinical Reviewer Ermias Zerislassie – OSE RPM		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>If yes, list issues:</p> <ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

Quality Microbiology (for sterile products)		<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
Comments:		
Facility Inspection		<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Establishment(s) ready for inspection? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
Comments:		
Facility/Microbiology Review (BLAs only)		<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:		<input type="checkbox"/> Review issues for 74-day letter
CMC Labeling Review		
Comments: None		<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT		
Signatory Authority: Curtis Rosebraugh (ODE II)		
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):		
Comments:		
REGULATORY CONCLUSIONS/DEFICIENCIES		
X	The application is unsuitable for filing. Explain why: At the time of the filing meeting, the application was found suitable for filing by all disciplines. However, on August 18, 2011, the applicant informed FDA of newly discovered quality issues with its stability program. The clinical and CMC reviewers discussed the issues internally and with the applicant via teleconference on August 19, 2011, and the determination was made that these issues would be serious enough to warrant a refuse-to-file decision. The applicant submitted an	

	NDA withdrawal request submission on August 19, 2011, and will work with FDA to resolve these issues and re-submit its application. See “Other” in Action Items below.
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input checked="" type="checkbox"/>	Other: The comments intended for the 74-day filing letter will be conveyed in a withdrawal acknowledgment request letter to the applicant during the week of August 22, 2011. Any consults sent (DSI, IRT-QT) will be cancelled.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

JENNIFER L JOHNSON
08/19/2011

DSI CONSULT: Request for Clinical Inspections

Date: August 5, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Leibenhaut, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Naomi Lowy, M.D., Clinical Reviewer*
Dragos Roman, M.D., Clinical Team Leader
Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

From: *Jennifer Johnson, Regulatory Health Project Manager/DMEP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 200677

Applicant/ Applicant contact information (to include phone/email):

Leslie Bennett
Senior Associate Director, Drug Regulatory Affairs
862-778-6364
leslie.bennett@novartis.com

Alternate contact:

Michelle Hack
Associate Director, Drug Regulatory Affairs
862-778-3534
michelle.hack@novartis.com

Drug Proprietary Name: Signifor (pasireotide) Injection, 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): TBD

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

DSI Consult
version: 5/08/2008

Proposed New Indication(s): Treatment of Cushing’s Disease

PDUFA: TBD

Action Goal Date: TBD

Inspection Summary Goal Date: TBD

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
701 Prof. Marco Boscaro Ospedali Riuniti Umberto I- GM Lancisi-G. Salesi S.O.D. Clin. Di Endocrinologia e Malattie del Metabolismo Via Conca, 71 Torrette di Ancona AN 60126 Italy 328 2667636-3331762542	2305	6	Cushing’s disease
704 Prof. Annamaria Colao Policlinico II Universita degli Studi di Napoli Dip. Endocrin. E Onc. Molecol. Via Pansini, 5 Napoli NA 80131 Italy +3908174621-32328 5390000	2305	14	Cushing’s disease
771 Dr. Zimeng Jin No. 1 Shuai Fu Yuan Wang Fu Jing. Dongcheng District Beijing 100730 China +86 10 6529 5006	2305	15	Cushing’s disease

III. Site Selection/Rationale

These 3 sites are among the highest enrolling sites. Specifically, they are 3 of the 5 highest enrollers. This is a new molecular entity for the treatment of Cushing's disease, an indication for which no drug is currently approved.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Jennifer Johnson* at 301-796-2194 or *Naomi Lowy* at 301-796-0692.

Concurrence: (as needed)

Dragos Roman Medical Team Leader

Naomi Lowy Medical Reviewer

Mary Parks Division Director (for foreign inspection requests or requests for 5 or more sites only)

*****Things to consider in decision to submit request for DSI Audit**

- Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?
- Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?
- Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?
- Are there concerns that the data may be fraudulent or inconsistent?
 - Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action
 - Expected commonly reported AEs are not reported in the NDA
- Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?
- Is this a new molecular entity or original biological product?
- Is the data gathered solely from foreign sites?
- Were the NDA studies conducted under an IND?

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/s/

JENNIFER L JOHNSON
08/05/2011