CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203255Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	December 12, 2014
To:	Jean-Marc Guettier, M.D. 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)** Robin Duer, MBA, BSN, RN Acting Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kendra Jones Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	SIGNIFOR LAR (pasireotide)
Dosage Form and Route:	For injectable suspension, for intramuscular use
Application Type/Number:	NDA 203-255
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On November 15, 2013, Novartis Pharmaceuticals Corporation submitted for the Agency's review a New Drug Application (NDA 203255) for SIGNAFOR LAR (pasireotide) injectable suspension, for intramuscular use. SIGNAFOR LAR (pasireotide) is indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.

Revised labeling for SIGNAFOR LAR (pasireotide) was submitted to the Agency on February 14, 2014.

On September 2, 2014, the Agency granted the Applicant a review extension until December 15, 2014 due to a major amendment submission to this NDA.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on January 2, 2014 and January 6, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for SIGNAFOR LAR (pasireotide) injectable suspension, for intramuscular use.

2 MATERIAL REVIEWED

- Draft SIGNAFOR LAR (pasireotide) PPI received on February 14, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on December 10, 2014.
- Draft SIGNAFOR LAR (pasireotide) PPI received on February 14, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on December 10, 2014.
- Draft SIGNAFOR LAR (pasireotide) Prescribing Information (PI) received on November 15, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on December 10, 2014.
- Draft SIGNAFOR LAR (pasireotide) Prescribing Information (PI) received on November 15, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on December 10, 2014.
- SIGNAFOR (pasireotide diaspartate) DMPP PPI review provided to DMEP on December 07, 2012.
- Draft SOMATULINE DEPOT (lanreotide) injection labeling dated December 4, 2014.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. The PPI document id formatted using the Verdana font, size 11.

In our collaborative review of the PPI we have:

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

/s/

SHAWNA L HUTCHINS
12/12/2014

KENDRA Y JONES
12/12/2014

ROBIN E DUER
12/12/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Office of Compliance (OC), Division of Manufacturing & Quality (DMQ)
Respiratory, ENT, General Hospital, and Ophthalmic Devices Branch (REGO)

DATE: December 1, 2014

TO: Jennifer Johnson, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, CDER

Jennifer.Johnson@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Jennifer Johnson

Through: Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH

Francisco Vicenty -S
2014.12.04 22:10:39 -05'00'

From: Viky Verna, REGO, DMQ, OC, CDRH

Applicant: Novartis Pharmaceuticals Corporation

One Health Plaza,

East Hanover, NJ 07936-1080

FEI# (b) (4)

Application # NDA 203255

Consult # ICC1400030

Product Name: SIGNIFOR LAR

Consult Instructions: Please assist with the CDRH review of the device (syringe and syringe-vial adapter) for this product as it pertains to necessary regulatory requirements for design, purchasing controls, manufacturing validations, acceptance tests for products or any required device facilities inspections.

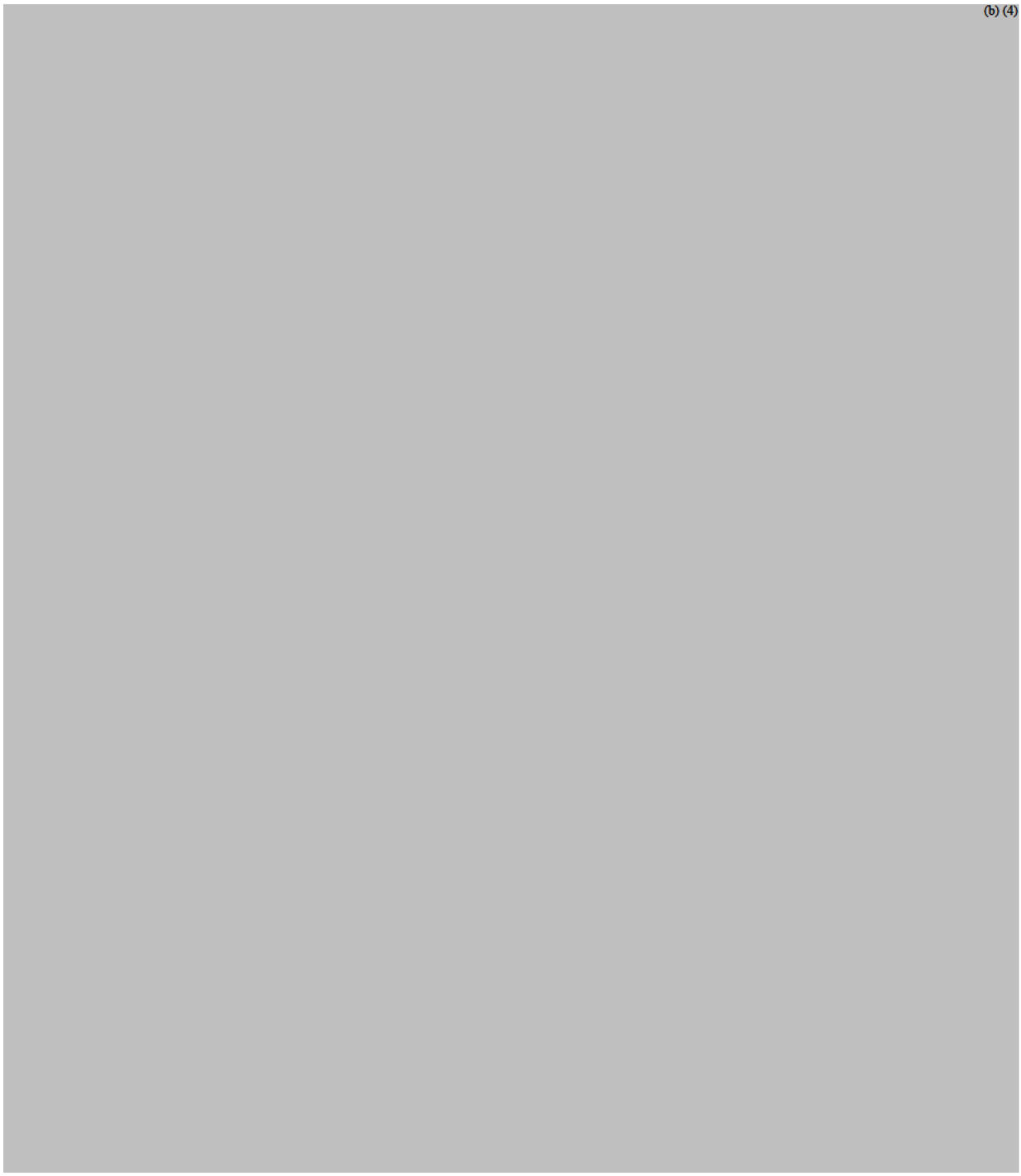
Inspection Needed: No - Date: 11/17/2014

Desk Review: Additional Information required

Final Recommendation: APPROVAL

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Signifor LAR, NDA 203255.

(b) (4)



In addition, along with the vehicle prefilled syringe and [redacted] drug product

- a vial adapter (polycarbonate) and
- a 20G x 1.5'' safety injection needle (stainless steel with safety shield/protective cap (polypropylene)), each packed [redacted], is provided.

The firm noted that the current [redacted]

[redacted]

Device Constituent

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. [redacted]

[redacted]

An analysis of the firm's inspection history over the past 2 years showed that a drug inspection which also covered applicable Quality System Requirements, was conducted

on [redacted]. The inspection revealed multiple deficiencies and was classified VAI. The firm issued several responses which described the corrections to the FDA 483 observations. A Close-Out Letter (FMD-145) was issued to the firm on [redacted].

DESK REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

Per the application documentation provided including the FDA form 356h, several firms are involved in the manufacturing of the Signifor LAR finished product. However the firm did not specify which firm has ultimate responsibility over the overall combination product. The firm did not describe the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements).

FIRM RESPONSE:

The firm response dated November 25, 2014, appears to be adequate. The firm confirmed that Novartis has ultimate responsibility for the combination product including the final release. The sponsor described the responsibilities of each manufacturing site and how Novartis controls all levels of the structure. The firm explained that all Novartis group companies (Novartis Pharma AG, Novartis Pharma Stein AG, [redacted]) have quality systems implemented that are derived from the Novartis Quality Manual, and the applicable external quality system requirements (e.g. 21 CFR part 820). The effective implementation and maintenance of the quality system are verified by elements such as management review, internal audits and health authority inspections. Quality agreements are in place between Novartis group companies and contract manufacturers [redacted] which lay down the individual roles and responsibilities between the contract giver and acceptor for the specific manufacturing steps.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm provided information covering the activities performed to verify and validate the design of the combination product. The activities included:

- Biocompatibility testing of [redacted] Syringe system performed by [redacted]
- Stability and compatibility data generated on the final combination product
- Rubber selection study
- In-use compatibility study
- Leachables/extractables

- BET and pyrogenicity testing
- Break out and sliding force evaluation for the (b) (4) system.

However, the firm did not describe its design control system covering requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. The firm did not provide the plan used for the design development of the combination product. The firm did not describe how it implemented the plan develop the combination product.

FIRM RESPONSE:

The firm response dated November 25, 2014, appears to be adequate. The firm confirmed that Novartis has established a design control process derived from the Novartis Quality Manual and the applicable external requirements under which medical devices and combination products such as the Signifor LAR injection kit are developed and maintained. This procedure covers design planning, design input, design output, design verification, design validation, design review, design transfer, design history file and also design changes for the overall finished combination products and medical devices.

The sponsor also confirmed that a design and development plan was established for the Signifor microparticle injection kit. The design control activities for the Signifor LAR injection kit was applied for the individual components and integrated use (safety and performance related to proper functionality and compatibility) of the injection kit (powder for suspension for injection in vial, vehicle in prefilled syringe, vial adapter and safety injection needle) and its overall secondary packaging and labeling.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

Per the application, multiple materials including device constituent components will be supplied by contractors. The firm listed the suppliers involved with their responsibilities described. For example:

- The components are supplied from (b) (4) the manufacturing site of the drug product diluent (b) (4)
- The front Stopper and the Plunger stopper are manufactured by (b) (4).

However, the sponsor firm did not summarize its procedure(s) for purchasing controls. The procedure(s) should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers. The procedure(s) should define how the firm maintains records of acceptable suppliers and

how it addresses the purchasing data approval process. The procedure(s) should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use. The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product. The firm should describe how it applied the purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product or provide evidence of the application (i.e. supplier agreement).

FIRM RESPONSE:

The firm response dated November 25, 2014, appears to be adequate. The sponsor confirmed that Novartis has established procedures in place for the evaluation, selection and approval of suppliers and contractors. Audits are performed to demonstrate compliance with the corresponding requirements, including those for medical devices. Quality agreements are implemented defining the roles and responsibilities, applicable standards, notification of changes, audit rights, involvement in case of deviations, complaints, recalls.

Listing of approved suppliers is maintained by the quality unit. Procedures are in place determining that purchase can only be performed from approved suppliers. Procedures are implemented for control of the incoming products. The extent of incoming control testing is based on audit and performance history of the suppliers. Processes and procedures for quality oversight and control of suppliers and contractors are implemented and include periodic audits and monitoring of quality performance.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm did not provide any information pertaining to its Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions.

FIRM RESPONSE:

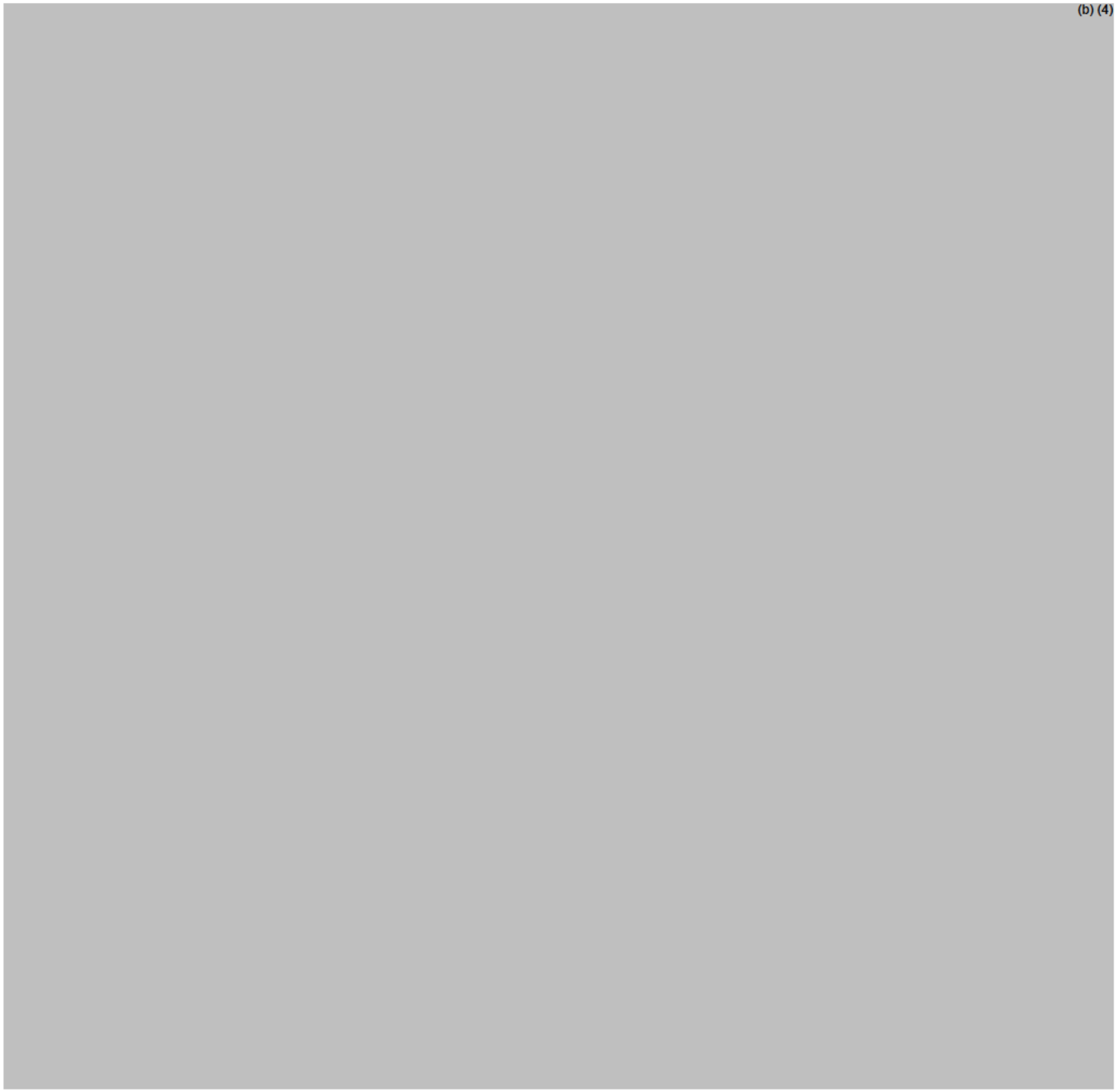
The firm response dated November 25, 2014, appears to be adequate. The sponsor confirmed that all Novartis group companies (Novartis Pharma AG, Novartis Pharma Stein AG, (b) (4)) have quality systems implemented that are derived from the Novartis Quality Manual. Novartis has procedures and processes in place governing CAPAs. These procedures consist of Deviation, Complaints, Quality Events, CAPAs, and Management Review. Novartis uses software (b) (4)) for the handling of Deviation, Quality Event, Complaints and CAPAs, the same applies to Audits and

corresponding CAPAs (internal, external and 3rd party). In terms of manufacturing operations (including environmental, calibration and maintenance) each individual Deviation is tracked, investigated to identify the root cause and Corrective and/or Preventative Actions are applied accordingly, as defined in local procedures.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

MANUFACTURING

(b) (4)



Additional testing on sterility and bacterial endotoxins will be performed annually in all upcoming stability studies (e.g. annual stability).

Documentation Review Recommendation

This application was deficient overall. Additional information is required for an adequate desk review.

UPDATE 12/1/2014

The firm response dated November 25, 2014, appears to be adequate. No additional information is required for the documentation review.

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application NDA 203255 and has the following recommendations:

The application for NDA 203255 is approvable from the perspective of the applicable Quality System Requirements.

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

(2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

Viky Verna -S

Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2014.12.01 15:38:00 -05'00'

Viky Verna, MS BME, MS Pharm

Prepared: VVerna: 11/16/2014; 12/1/2014

Reviewed: FMLast name: Month/Day/Year

CTS No.: ICC1400030

NDA 203255

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

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/s/

JENNIFER L JOHNSON

12/08/2014

CDRH/OC final review memo completed and sent to RPM Jennifer Johnson via email on 12/5/14, in response to 1/3/14 consult request. No deficiencies remaining, approval recommended.

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: September 26, 2014
From: Keith Marin, Combination Product Team Lead, GHDB, WO66, RM 2567
General Hospital Devices Branch, DAGRID, ODE, CDRH

To: Jennifer Johnson, Regulatory Health Program Manager,
CDER/OMPT/CDER/OND/ODEII/DMEP

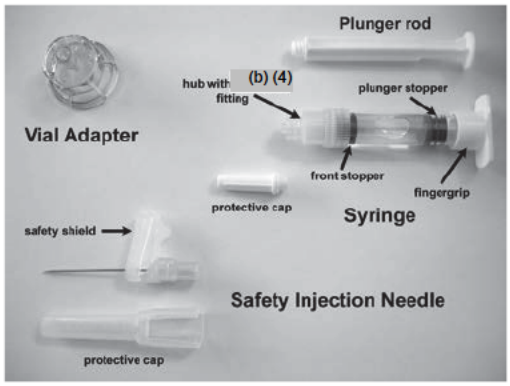
Subject: CDRH Consult NDA 203255/ICC1300623, Final Review, Syringe and syringe-vial adapter for Signifor LAR (pasireotide) intramuscular injection

Subject: Dr. Bifeng Qian, Biologist, CDRH/ODE/DAGRID/ICDB

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 203255. The device constituent of this combination product consists of a syringe and syringe-vial adapter for use with Signifor LAR (pasireotide) intramuscular injection.

2. Device Description



The primary container closure system for the vehicle for powder for suspension for injection, 2ml solution (Figure 1-1) is a pre-filled syringe which consists of the following components:

- a 3ml colorless glass syringe which is closed at both ends with grey rubber stoppers (a front and a plunger stopper)

Additionally the syringe contains administration features/accessories, i.e.:

- a hub with a (b) (4) fitting
- a cap to protect the (b) (4) end of the hub
- a finger-grip, and
- a plunger rod

In addition, along with the pre-filled syringe and drug product a vial adapter and a safety injection needle will be provided.

The (b) (4) syringe barrel used is compliant with (b) (4). It does not correspond to the ISO 11040-4 design by concept as the tip and the flange are plastic components assembled onto the barrel and consequently the syringe cannot comply with the dimensional requirements of this standard. The hydrolytic resistance grain corresponds to type I according to USP 660 and Ph.Eur. 3.2.1, as alternatively required of the ISO 11040-4. The 3ml glass is not annealed, consequently the annealing requirement of ISO 11040-4 is not applicable.

3. Documents Reviewed

K963583
K012736
DMF (b) (4)
DMF
DMF
NDA 203255, 3.2.P.7

Reviewer Notes: *The DMF holder has indicated that they correspond to ISO 11040-4 and comply with (b) (4) As the (b) (4) tip is plastic, the issues of tip breakage in glass syringes should not be a concern.*

4. CDRH Review and Comments

The sponsor has stated in their submission that they are proposing to use the Medimop vial adapter (K963583). The proposed vial adaptor is a needle free device (b) (4) transfer liquid drug product (DP) from the primary container (vial) to a delivery syringe. Based on a past review of this 510(k) on November 14, 2013, it appears that complete performance, biocompatibility and sterility testing have been done on this device component. There are no additional concerns related to the vial adapter at this time.

The sponsor has stated in their submission that they are proposing to use the Monoject® safety needle with the syringe and vial adapter. This device has been cleared under K012736. The needle is a manually operated safety hypodermic needle that is designed to reduce the potential for inadvertent needle sticks.

Drug Master File (b) (4) contains information regarding the (b) (4) syringe system. The (b) (4) syringe system is composed of the syringe barrel with

or without the needle, elastomeric closures (front and plunger stoppers), and plunger rod. The syringe barrel consists of the glass barrel, needle, needle hub, needle guard, and finger grips.

Drug Master File (b) (4) contains information about the front stopper and plunger stopper. As these are in contact with the drug, CDRH will defer to CDER on evaluation of this component.

Drug Master File (b) (4) contains information about the front stopper and plunger stopper. As these are in contact with the drug, CDRH will defer to CDER on evaluation of this component.

5. CDRH Comments for Review Team

Sterilization
Sterilization testing will be evaluated by CDER.

Biocompatibility
Biocompatibility testing was assessed for the syringe component of the device. However, CDRH was unable to locate biocompatibility testing for the plunger rod, finger grips, and cap on the syringe.

Functional Performance
The syringe appears to be the same as the (b) (4) syringe that is described in DMF (b) (4). However, breakloose and glide force testing for the final finished combination product (with needle) and the actual drug product could not be located. Additionally, air and liquid leakage and torque testing of the needle and (b) (4) connector could not be located. Finally, the DMF Holder mentioned that the 3ml glass syringe is not annealed and thus does not follow ISO 11040-4. However, it is not clear what process they have used to ensure the syringe does not shatter.

Human Factors
Human Factors Usability studies will be reviewed under a separate consult by CDRH Human Factors Team LCDR Quynh Nguyen.

Additional Consults Needed
Please ensure that a separate consult has been sent to CDRH Office of Compliance to assist with any necessary regulation requirements for design, purchasing controls, manufacturing validations, acceptance tests for products, or device facilities inspections that may be required for approval of this NDA.

6. CDRH Recommendations for Master File Holder

Based on our review, the following deficiencies should be conveyed to the NDA Holder:

Bench Performance Testing

1. In NDA 203255, you have stated that the you intend to use the Medimop Medical Projects Mixject Dispensing pin/with detachable vial holder/with preattached needle (K963583) with the (b) (4) syringe sytem. However, not all of the testing has been provided to demonstrate the safety of this device with your drug. Provide a complete test report (protocol, acceptance criteria, results, and conclusion) for the following testing:
    a. Demonstrate that the vial adaptor/syringe doesn't result in air or liquid leakage
    b. Provide torque testing force necessary to disconnect syringe's (b) (4) connection from vial adapter

DMF Holder Response: The vial adapter and the (b) (4) syringe are connected through standard (b) (4) connections, i.e. (b) (4) Air and liquid leakage as well as the torque force testing have been investigated by the suppliers as part of (b) (4) testing for both (b) (4) connections. They are both compliant with the international standard (b) (4). The corresponding supplier statements are provided in [Appendix 1] for the vial adapter and [Appendix 2] for the syringe.

CDRH Reviewer Response: RESPONSE ACCEPTABLE. The sponsor has provided in Appendix 5 functionality and deliverable dose testing. The tip of the syringe is plastic and conforms with (b) (4) Furthermore, based on the results of the testing, all function testing complied with (b) (4) and demonstrated that adaptor/syringe did not have air/liquid leakage and torque testing to remove connection of vial and adapter was acceptable.

    c. Provide force necessary to draw up Signifor LAR (pasireotide) in syringe
    d. Provide break loose and glide force of syringe for injection

DMF Holder Response: The operating force data generated during stability correspond to the initial movement done by the user to transfer the vehicle from the syringe to the vial. No specific data have been generated on the forces needed to draw up Signifor LAR® (Pasireotide suspension) back in the syringe as well as the forces being applied to inject the suspension. They are, however, not expected to alter significantly from the operating force data generated during stability of diluent. The initial vehicle transfer break loose force data generated, i.e. well below the (b) (4) limit, are considered worst case, as being much higher compared to the break loose force needed to draw up Signifor LAR® (Pasireotide suspension) back in the syringe as well as to inject. This is due to two factors, (b) (4) Also the sliding force data generated to transfer the vehicle into the vial, i.e. well below the defined (b) (4) limit, are not expected

to change significantly compared to the sliding force needed to draw up Signifor LAR® (Pasireotide suspension) back in the syringe as well as to inject due to the (b) (4)

Table 6-1 Test results

	Break-out force (N)	Minimum sliding force (N) (after break-out)	Maximum sliding force (N) (includes the over-pressure effect in vial)
Number of samples	n=60	n=60	n=60
Mean	11.6	1.7	5.1
Max	16.5	2.4	6.7
Min	7.5	0.3	1.2
Compliance*	C	C	C

*: Requirements: Break-out force (mean) ≤ (b) (4) N and (individual) ≤ (b) (4) N as well as sliding force ≤ (b) (4) N

The forces required to transfer the vehicle from the (b) (4) syringe into the vial meet the acceptance criteria for break out force (mean) ≤ (b) (4) N, break out force (individual) ≤ (b) (4) N and sliding force ≤ (b) (4) N.

Table 6-3 Withdrawal test results

	Automatic plunger displacement (mm) induced by the overpressure in the vial (no force applied at any time)	Whole suspension in the vial has been transferred in the syringe (Yes/No) during the automatic plunger displacement (no force applied at any time)
Number of samples	n=60	n=60
Mean	36.5	Yes (force remains negative during the whole suspension withdrawal as no force is required
Max	41.4	
Min	30.3	

The forces required to withdraw the Signifor suspension from the vial back into the syringe remain well within the defined comfortable and acceptable operating limits of break out force (mean) ≤ (b) (4) N, break out force (individual) ≤ (b) (4) N and sliding force ≤ (b) (4) N.

6.3 Injecting the suspension

6.3.1 Test results

Table 6-4 Test results

	Break-out force (N)	Maximum sliding force (N) (correspond to suspension expelling)
Number of samples	n=60	n=60
Mean	1.6	2.4
Min	1.0	1.9
Max	2.9	4.6
Compliance*	C	C

*: Requirements: Break-out force (mean) ≤ (b) (4) N and (individual) ≤ (b) (4) N as well as sliding force ≤ (b) (4) N

The forces required to expel the suspension from the (b) (4) syringe for injection remain well within the defined comfortable and acceptable operating limits of break out force (mean) ≤ (b) (4) N, break out force (individual) ≤ (b) (4) N and sliding force ≤ (b) (4) N.

CDRH Reviewer Response: RESPONSE ACCEPTABLE. The sponsor has provided break loose and glide force testing for their syringe with use of the drug. The testing proved that the forces required to transfer the vehicle from the (b) (4) syringe into the vial remain well within the defined comfortable and acceptable operating limits of break out force (mean) ≤ (b) (4) N, break out force (individual) ≤ (b) (4) N and sliding force ≤ (b) (4) N.

2. ***You have indicated that the 3ml glass is not annealed and consequently the annealing requirement of ISO 11040-4 is not applicable. It is not clear how you have addressed the risk of your device shattering inadvertently. Please provide rationale on why you have deviated from the ISO requirement and how you have addressed the risk of breakage of the syringe.***

CDRH Reviewer Response: RESPONSE NOT ACCEPTABLE. The sponsor has not responded to this question. The question will need to be asked again. On March 31, 2014 the following IR was sent to the DMF holder:

1. ***In our letter on February 28, 2014, we asked you to provide the following: "You have indicated that the 3ml glass is not annealed and consequently the annealing requirement of ISO 11040-4 is not applicable. It is not clear how you have addressed the risk of your device shattering inadvertently. Please provide rationale on why you have deviated from the ISO requirement and how you have addressed the risk of breakage of the syringe." You have not responded to this question. Please provide rationale on why you have deviated from the ISO requirement and how you have addressed the risk of breakage of the syringe.***

CDRH Reviewer Response: RESPONSE ACCEPTABLE. The DMF holder states that ISO 11040-4 does not apply to the (b) (4) because the product is a result of an assembly of the glass barrel with two plastic hubs where ISO 11040-4 applies to glass syringes. (b) (4) mitigates breakage risk by implementing inspectiosn to eliminate devices that could impact glass integrity. (b) (4) performs inspections for chips, cracks, and splits and scratches on the outside of the barrel and clink inclusions between (b) (4) mm. Additionally, (b) (4) implemented camera inspections on the glass barrel during manufacturing. For the final inspection, (b) (4) inspects for cracked, chipped, shock, and scratches of the barrel. It is our belief that the sponsor has provided their plan on how they mitigate the risk of breakage for their device. Their mitigation seems reasonable as it addresses the common causes of breakage. I have no further concerns.

Biocompatibility

Based on our review, the following deficiencies should be conveyed to the DMF Holder:

(b) (4)

3. No biocompatibility data were found in the master file or in the NDA for the plunger rod, finger grip, and cap. You should submit applicable biocompatibility data for the autoinjector using a risk analysis framework according to ISO 10993-1: 2003, Biological evaluation of medical devices—Part 1: Evaluation and testing. If you will submit materials data safety sheets for the materials of construction in lieu of testing recommended by the standard for a device with limited contact duration with intact skin, you should provide a rationale as to why testing was not conducted. Additionally, it is not clear based on the information that you have provided on whether the kit components for your device have been sterilized once or twice. If the kit components are supplied sterile and are re-sterilized, you will need to provide biocompatibility according to ISO 10993, not just the material safety data sheets.

Sponsor Response: The (b) (4) syringe barrels are provided to customers either, (b) (4) (b) (4)). The syringe barrels provided to the customer were (b) (4)

For your reference, please see enclosed Biocompatibility I Toxicology Summary reports for the Needle Guard and Finger grip and Plunger Rod enclosed in Attachment 1 and 2, respectively.

- ***(b) (4) Biocompatibility I Toxicology Summary report for Needle Guard and Finger grip (Attachment 1).***

- (b) (4) ***Biocompatibility I Toxicology Summary report for Plunger Rod (Attachment 2).***

CDRH Reviewer Response: <u>RESPONSE NOT ACCEPTABLE</u>. The sponsor has provided a certification that they provided cytotoxicity, hemolysis, and irritation testing. However, they haven't provided any details of the testing, simply that they have complied with the standards. The sponsor will need to provide the complete test reports so they can be evaluated. On March 31, 2014, the following IR was sent to the DMF Holder:

1. ***In your February 28, 2014 response, you provided a compliance certification for your biocompatibility testing. However, you have not provided any details on the testing such as the protocol, acceptance criteria, test results, or conclusion for the biocompatibility testing. Please provide the complete test report so we can evaluate the safety of your device.***

Sponsor Response: The sponsor references DMF (b) (4)

CDRH Reviewer Response: <u>RESPONSE NOT ACCEPTABLE</u>. On April 16, 2014, the sponsor provided the biocompatibility for our review. Dr. Bifeng Qian was consulted to review this information. Based on her evaluation, the information provided in the DMF holder's supplement response is insufficient to address the biocompatibility concerns on the subject device. It is recommended that additional information be acquired in order to complete the review of this submission.

<u>On June 5, 2014, the following IR deficiencies were sent to the DMF holder</u> (b) (4)

1. Please clarify if the (b) (4) syringe system has been previously cleared by the FDA. If yes, please provide the 510(k) number. If not, please address the following concerns regarding the biocompatibility of the device:

    1) The biocompatibility testing provided in your (b) (4) supplement response regarding the (b) (4) syringe system is outdated, which was all conducted 6-16 years ago. Please provide recent testing data for review.

        a) For the device components that will contact drug/fluid path or blood path, please provide complete biocompatibility study reports of the following based on the nature, degree, and duration of exposure, using the final finished subject device:
            - *In vitro* cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for *in vitro* cytotoxicity;
            - Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;

- Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
- Acute systemic toxicity testing based on ISO 10993 Biological evaluation of medical device, Part 11 Tests for systemic toxicity;
- Haemocompatibility testing based on ISO 10993 Biological evaluation of medical devices, Part 4 Selection of tests for interactions with blood.

b) For the device components that have only limited skin contact, please provide the following biocompatibility study reports:
   - *In vitro* cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for *in vitro* cytotoxicity;
   - Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
   - Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization.

2) Your hemolysis testing provided contains the following issues. Please address and provide a revised study report which includes the recent testing data:
   a) Your hemolysis testing provided was based solely on extract test method. Hemolysis testing using direct contact test method is not provided. According to your referenced ISO 10993-4:2002 Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood and the FDA recognized ASTM F756-08 Standard Practice for Assessment of Hemolytic Properties of Materials, both the extract test and the direct contact test should be performed unless the material application or contact time justifies the exclusion of one of the tests. Based on the intended use, the subject device will contact drug and blood path. Please provide hemolysis testing using both the direct contact and the extract test methods or provide an appropriate scientific justification for not performing either one of the tests.

   b) You state that hemolysis of rabbit blood cells was determined after incubation 0.2 mL freshly diluted blood samples with 10 mL of the test extracts for 60 minutes at 37°C. The significantly reduced blood volume (0.2 mL vs. 10 mL test extracts) and incubation time (60 min) used shows a major deviation from your referenced ISO 10993-4:2002 and the FDA recognized ASTM F756-08. Please provide an appropriate scientific justification for the adequacy and

appropriateness of your test method used for analysis of the hemolytic property of the subject device or please provide a revised testing report based on ISO 10993-4:2002 and ASTM F756-08.

3) You have not provided any testing for evaluation of particulate matters on the device. Particulates that may be present on medical devices pose potential health risks to patients when introduced into drug delivery pathway and/or blood path. Please provide a particulate matter assessment based on USP <788> Particulate Matter in Injections.

CDRH Reviewer Response: <u>RESPONSE NOT ACCEPTABLE</u>. CDER was contacted by (b) (4) on June 18, 2014 and based on the message, the MAF holder is not finishing the device, but providing the components to the drug company". It appears that the MAF holder only serves as a "raw material supplier". As a result, it will be the drug company's responsibility to address the biocompatibility deficiencies if (b) (4) doesn't have testing on the final finished device. If the biocompatibility testing provided was based on the DMF holder's unfinished device components, it is not acceptable. In addition, the testing was conducted 6-16 years ago, there could be one or more changes as listed above, occurred during these years. In particular regarding the manufacturing materials used, change in the source or in the specification is often seen. That is why we generally request recent testing data for review. If the sponsor claims that there have been no changes made to the device during these over 10 years, they need to provide solid evidence to support. As a result, we sent the IR to the NDA holder (Novartis).

<u>On June 5, 2014 and June 30, 2014, the following IR deficiencies were sent to the NDA holder (Novartis):</u>

1. ***Please clarify if the (b) (4) syringe system has been previously cleared by the FDA. If yes, please provide the 510(k) number. If not, please address the following concerns regarding the biocompatibility of the device:***

    a. ***The biocompatibility testing provided in your (b) (4) supplement response regarding the (b) (4) syringe system is outdated, which was all conducted 6-16 years ago. Please provide recent testing data for review:***

        i. For the device components that will contact drug/fluid path or blood path, please provide complete biocompatibility study reports of the following based on the nature, degree, and duration of exposure, using the final finished subject device:
            - ***In vitro cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for in vitro cytotoxicity;***

- ***Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;***
- ***Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;***
- ***Acute systemic toxicity testing based on ISO 10993 Biological evaluation of medical device, Part 11 Tests for systemic toxicity;***
- ***Haemocompatibility testing based on ISO 10993 Biological evaluation of medical devices, Part 4 Selection of tests for interactions with blood.***

ii. For the device components that have only limited skin contact, please provide the following biocompatibility study reports:

- ***In vitro cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for in vitro cytotoxicity;***
- ***Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;***
- ***Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization.***

Sponsor's Response: (b) (4) has clarified the following:

- ***The (b) (4) syringe system is not covered under any 510(k) and has not been cleared by the FDA.***
- ***The (b) (4) syringe system is being used as a container closure system of the combination product diluent, i.e. Vehicle for powder for suspension for injection 2ml solution being manufactured at (b) (4)***
- (b) (4)
- ***In response to FDA questions on biocompatibility testing, Novartis would like to refer to the results of the biocompatibility studies performed by the supplier (b) (4) on each component of the (b) (4) syringe system.***

- *It is acknowledged that the (b) (4) biocompatibility testing has been performed on the individual component items and not on the final combination product. However, the processing steps performed at (b) (4) are considered to have a negligible impact on the biocompatibility of the (b) (4) syringe system, see enclosed assessment from an external company (b) (4) (having expertise in biocompatibility testing).*

Reviewer Comments: <u>RESPONSE NOT ACCEPTABLE</u>. *(b) (4) has clarified that (b) (4) will not be providing the final finished devices but simply the components to Novartis. Therefore, we consider that it is the responsibility of the NDA holder (Novartis) to address the biocompatibility concerns for the final finished subject device - (b) (4) syringe system. In the supplement response, Novartis states that the processing steps performed in their manufacturing facility, including the (b) (4), have a negligible impact on the biocompatibility of the (b) (4) syringe system. However, they have not provided any biocompatibility testing for the final finished sterilized subject device. This is not acceptable. For medical devices, biocompatibility testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization), as recommended in ISO 10993 Biological evaluation of medical devices, Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2009). Risk analysis or biocompatibility testing based on raw materials, or unfinished device components, or device components which were sterilized by a different sterilization method may have limitations and may not represent the final finished sterilized subject device in the submission. FDA believes that safety assessments need to be done based on the final finished subject device which has processed using the same sterilization procedures as proposed. We request again that the sponsor provide biocompatibility testing based on the nature, degree, and duration of exposure, using the final finished and sterilized subject device.*

2) *Your hemolysis testing provided contains the following issues. Please address and provide a revised study report which includes the recent testing data:*
   a) *Your hemolysis testing provided was based solely on extract test method. Hemolysis testing using direct contact test method is not provided. According to your referenced ISO 10993-4:2002 Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood and the FDA recognized ASTM F756-08 Standard Practice for Assessment of Hemolytic Properties of Materials, both the extract test and the direct contact test should be performed unless the material application*

or contact time justifies the exclusion of one of the tests. Based on the intended use, the subject device will contact drug and blood path. Please provide hemolysis testing using both the direct contact and the extract test methods or provide an appropriate scientific justification for not performing either one of the tests.

b) You state that hemolysis of rabbit blood cells was determined after incubation 0.2 mL freshly diluted blood samples with 10 mL of the test extracts for 60 minutes at 37°C. The significantly reduced blood volume (0.2 mL vs. 10 mL test extracts) and incubation time (60 min) used shows a major deviation from your referenced ISO 10993-4:2002 and the FDA recognized ASTM F756-08. Please provide an appropriate scientific justification for the adequacy and appropriateness of your test method used for analysis of the hemolytic property of the subject device or please provide a revised testing report based on ISO 10993-4:2002 and ASTM F756-08.

Sponsor's response: The sponsor provided bacterial endotoxin and rabbit pyrogenicity testing. Novartis has conducted the material and bacterial mediated pyrogenicity testing for the final finished sterilized (b) (4) syringe system.

(b) (4)

(b) (4)

CDRH Reviewer Comments: RESPONSE ACCEPTABLE.

3) ***You have not provided any testing for evaluation of particulate matters on the device. Particulates that may be present on medical devices pose potential health risks to patients when introduced into drug delivery pathway and/or blood path. Please provide a particulate matter assessment based on USP <788> Particulate Matter in Injections.***

Sponsor's response: The sponsor states that the following studies have been performed following the principles of the ISO guidance 10993-12 to investigate leachables from the (b) (4) syringe system:

- ***Study 1: (b) (4) syringe stopper selection studies to ensure selection of the stopper with lowest leaching potential***
- ***Study 2: Long term leachable studies performed during registration stability of the vehicle prefilled syringes following storage at 5°C/ambient RH (long term storage condition), 25 °C/60% RH and 30 °C/75% RH up to 60 months***
- ***Study 3: In-use compatibility study simulating the instructions of use***

- ***The expelled vehicle is analyzed (b) (4). The leachable compounds were determined (b) (4) HPLC on a C18 column with UV detection at a wavelength of 220 nm.***

- (b) (4)

- ***In line with the outcome of the stopper selection study (study 1), the 60 months registration stability study of the vehicle prefilled syringes (study 2) confirmed the absence of leachable compounds in the expelled diluent from the (b) (4) syringe system at the detection limit of (b) (4) µg/ml. This is equivalent to (b) (4) µg/day or (b) (4) µg/device (= (b) (4) syringe system) based on a 2 ml vehicle volume used to reconstitute Signifor LAR® powder for suspension.***

- ***The (b) (4) content is considered to remain unchanged, i.e. ≤ (b) (4) mg/l (≤ (b) (4) mg/device), following storage at 5 °C/ambient RH (long term storage conditions). At higher temperatures, an (b) (4) content with time is observed, reaching a maximum of (b) (4) mg/l (30 mg/device) following 60 months storage at 30 °C/75% RH.***

- ***The in-use compatibility study (study 3) was performed simulating instructions for use. For all storage time intervals examined, no leachable could be detected***

above the detection limit of (b) (4) µg/ml equivalent to (b) (4) µg/day and (b) (4) µg/device after 1, 2 and 24 hours storage time.

- *In summary of all studies, no leachable compounds have been observed at levels above (b) (4) µg/day, which is considered to be a worst case limit as (b) (4) times lower than the Threshold of Toxicological Concern (TTC) of 1.5 µg/day*

- *As no leachables were found above the suggested safety limits (1.5 µg/day), no specific toxicological evaluation on leachables was necessary, and thus ISO 10993 Part 17 and Part 18 are deemed to be not applicable in the case of the (b) (4) syringe system.*

CDRH Reviewer Comments: <u>RESPONSE NOT ACCEPTABLE</u>. The chemical leachability testing provided contains the following issues. The sponsor will need to address the issues and provide revised testing for the (b) (4) syringe system:

a) *The leachable studies were performed under the following storage conditions: 5°C/ambient RH, 25 °C/60% RH, and/or 30 °C/75% RH. Concerns on the leachable chemicals at higher temperatures under the worst case conditions (e.g. summer time while the storage room is not air conditioned), have not been adequately addressed. Please provide chemical leachable and extractable analysis for the worst case conditions and provide your recommended risk mitigation procedure.*

b) *Please clearly identify the list of chemical compounds screened and justify for the adequacy.*

c) *Please clearly identify the list of chemical compounds detected and specify the concentrations of all leachables / residues per device component (wt/wt). Please provide a risk assessment for all identified leachable chemicals based on the target population and a worst case scenario.*

d) *You state that at higher temperatures, an (b) (4) content with time is observed, reaching a maximum of (b) (4) mg/L ((b) (4) µg/device) following 60 months storage at 30°C/75% RH. Please provide a risk assessment on the leachable (b) (4) based on the target population and a worst case scenario.*

<u>On August 11, 2014, the following IR deficiencies were sent to the NDA holder (Novartis):</u>

1. (b) (4). Therefore, we consider that it is the responsibility of the NDA holder (Novartis) to address the biocompatibility concerns for the final finished subject device - (b) (4) syringe system. In the supplement response, you state that the processing steps performed in your manufacturing facility, including the (b) (4)

procedures, have a negligible impact on the biocompatibility of the (b) (4) syringe system. However, you have not provided any biocompatibility testing for the final finished sterilized subject device that have not been previously FDA cleared or approved. This is not acceptable. For medical devices, biocompatibility testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization), as recommended in the FDA-recognized standard ISO 10993 Biological evaluation of medical devices, Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2009). Risk analysis or biocompatibility testing based on raw materials, or unfinished device components, or device components which were sterilized by a different sterilization method may have limitations and may not represent the final finished sterilized subject device in the submission. FDA believes that safety assessments need to be done based on the final finished subject device which has processed using the same sterilization procedures as proposed. As we have previously requested, please provide biocompatibility testing based on the nature, degree, and duration of exposure, using the final finished and sterilized subject device.

2. The chemical leachability testing provided contains the following issues. Please address the issues and provide revised testing for the (b) (4) syringe system:

   - The leachable studies were performed under the following storage conditions: 5°C/ambient RH, 25 °C/60% RH, and/or 30 °C/75% RH. Concerns on the leachable chemicals at higher temperatures under the worst case conditions (e.g. summer time while the storage room is not air conditioned), have not been adequately addressed. Please provide chemical leachable and extractable analysis for the worst case conditions and provide your recommended risk mitigation procedure.

   - Please clearly identify the list of chemical compounds screened and justify for the adequacy.

   - Please clearly identify the list of chemical compounds detected and specify the concentrations of all leachables / residues per device component (wt/wt). Please provide a risk assessment for all identified leachable chemicals based on the target population and a worst case scenario.

   - You state that at higher temperatures, an (b) (4) content with time is observed, reaching a maximum of (b) (4) mg/L ((b) (4) µg/device) following 60 months storage at 30 °C/75% RH. Please provide a risk assessment on the leachable (b) (4) based on the target population and a worst case scenario.

3. In response to the FDA request for the USP <788> particulate matter testing, you state that the vehicle solution in the (b) (4) syringe system is tested routinely for the particulate matters at each time of batch release and after 60 months of storage and that all the results comply with the test requirements. However, the test reports are not provided for review. In order to determine if the testing provided is appropriate and adequate, please provide complete particulate matter testing reports which include the following information: a clear and detailed description of the test device and sample preparation, description of the test methods used, summary of the test results, the test criteria and rationale, and the conclusion.

Sponsor Comments: In the response by Novartis on August 18, 2014, the sponsor confirmed that the container closure system for Signifor LAR diluent (b) (4) ***in a tabular overview:***

Container closure components	***Signifor LAR diluent (NDA 203255)***	(b) (4)
(b) (4) ***syringe (glass barrel, hub, fingergrip, cap)***	***ü***	
Plungerrod	***ü***	
Front stopper	***ü*** (b) (4) ***rubber)***	
Plunger stopper	***ü*** (b) (4) ***rubber)***	

CDRH Review Comments: <u>RESPONSE NOT ACCEPTABLE</u>. During the interactive communications with the CDER, the sponsor has clarified that the current (b) (4) ***As the device constituent of the combination product proposed in NDA 203255 has already been approved, I believe***

that no new biocompatibility testing and particulate matter testing on the device shall be requested. However, the 2 mL solution "vehicle for powder for suspension for injection", which will be pre-filled in the syringes and proposed for Signifor LAR (pasireotide) intramuscular injection in NDA 203255, (b) (4) The current vehicle solution has introduced new chemicals which may raise additional device-drug material compatibility issues. In the June-30-2014 supplement response, Novartis states that chemical leachability testing has been conducted. However the testing information provided in the supplement response is not clear and adequate. As a result, we recommend that the sponsor address the following issues and provide the revised chemical leachability testing report and the associated risk assessment for the (b) (4) syringe system.

On August 18, 2014, the following IR deficiency was sent to the NDA holder (Novartis):

1. During the interactive communications with the CDER, Novartis has clarified that the current (b) (4) However, based on the FDA database, the 2 mL solution "vehicle for powder for suspension for injection", which will be pre-filled in the syringes and proposed for Signifor LAR (pasireotide) intramuscular injection in NDA 203255, (b) (4) The current vehicle solution has introduced new chemicals which may raise additional device-drug material compatibility issues. In the June-30-2014 supplement response, Novartis states that chemical leachability testing has been conducted. However the testing information provided in your supplement response is not clear and adequate. Please address the following issues and provide the revised chemical leachability testing report and the associated risk assessment for the (b) (4) syringe system:

    a) Please confirm that the chemical leachable studies were performed using the same pre-filled syringes as proposed for Signifor LAR (pasireotide) intramuscular injection in NDA 203255.

Sponsor's Comments Dated August 25, 2014:

- (b) (4)
- Three types of leachable studies have been described in our response dated June 30, 2014 (Sequence #0015), i.e.

a) Study 1: (b) (4) syringe stopper selection studies

b) Study 2: Long term leachable studies performed during registration stability of the vehicle prefilled syringes following storage at 5°C/ambient RH (long term storage condition), 25 °C/60% RH and 30 °C/75% RH up to 60 months
c) Study 3: In-use compatibility study simulating instructions of use reported in the submitted Drug product section 3.2.P.2 'Pharmaceutical Development'

- It is confirmed that the leachable studies Study 2 and Study 3 have been performed using the finally proposed formulation and prefilled syringe of Signifor LAR diluent outlined in NDA 203255.

- In the stopper selection study (Study 1) also the finally proposed formulation of Signifor LAR diluent has been used. As per intention of the study, different rubber stoppers including the finally selected one for Signifor LAR diluent have been investigated.

- It is noted that Study 2 and Study 3 are considered the main leachable studies as supporting the finally proposed formulation and prefilled syringe considering long term storage as well as in-use.

CDRH's Review Comments: The sponsor has adequately addressed our concerns. RESPONSE ADEQUATE.

b) Please clearly identify the list of chemical compounds screened in the leachability testing and justify for the adequacy.

Sponsor's Comments Dated August 25, 2014:

- The long term leachables study (Study 2) was a screening study, performed using HPLC-Diode Array Detection (DAD). The method was used to screen quantitatively for all potentially occurring leachables with the aid of an external reference, i.e (b) (4) . To show system suitability 3 reference compounds (b) (4)) were injected down to concentrations of 0.1 µg/mL. The validated analytical method [Appendix 2] is able to detect those 3 reference compounds as well as other potential leachables (examples: (b) (4) with a reporting limit of (b) (4) µg/mL. Quantification at the concentration level of (b) (4) µg/mL would indicate potential leachables at a level of (b) (4) µg/2 mL, i.e. (b) (4) µg per syringe.

- The in use compatibility study (Study 3) was also a screening leachables study, performed with the aid of HPLC-DAD. Quantification of all potential leachables was performed with the

external reference (b) (4) with a lower reporting limit of (b) (4) µg/mL and the ability to detect the potential leachables to the concentration level of (b) (4) µg/mL. Quantification at the concentration level of (b) (4) µg/mL would indicate potential leachables at a level of (b) (4) µg/ 2 mL, i.e. (b) (4) µg per syringe.

CDRH's Review Comments: We have discussed the sponsor procedure internally and confirmed that the analytical technique used is considered acceptable in measuring the chemical residues. The response has adequately addressed our concerns. RESPONSE ADEQUATE.

c) Please clearly identify the list of chemical compounds detected and specify the concentrations of all leachables / residues per device component (wt/wt). Please provide a risk assessment for all identified leachable chemicals based on the target population and a worst case scenario.

Sponsor's Comments Dated August 25, 2014:

- As no compounds were detected at the reporting limit of the method, it is not possible for us to list any chemical compounds as leachables, as requested. The concentration of all potential leachables/residues from the entire device is < (b) (4) µg/day corresponding to the Safety Concern Threshold (SCT) for an individual unknown compound. By injecting into a patient the maximum volume of 2 mL per day (corresponding to the vehicle volume in the device), the results are below the maximum permitted daily intake.

- We would like to clarify that the study was designed to determine the potential leachable content in the volume which is in contact with the entire CCS (container closure system), therefore we are not in the position to specify the concentrations of all leachables/residues per device component (wt/wt).

- The risk assessment, as requested, was not formally issued for a specific leachable compound because no leachable was detected above the reporting limit, which implies a (b) (4) fold safety margin, as discussed in the answer to question 2. The safety of patients with regard to leachables from the CCS is guaranteed, because the safety concern threshold (SCT) of (b) (4) µg was endorsed by independent toxicologists, amongst those toxicologists from Novartis Preclinical Safety. In a memorandum from Novartis Preclinical Safety toxicologists [Appendix 4] it is even endorsed that the parenteral SCT of (b) (4) µg is applicable for the assessment of leachables when administering into children; this should certainly cover a worst case scenario regarding patient population.

CDRH's Review Comments: The response has adequately addressed our concerns. RESPONSE ADEQUATE.

d) You state that at higher temperatures, an (b) (4) content with time is observed, reaching a maximum of (b) (4) mg/L ((b) (4) µg/device) following 60 months storage at 30 °C/75% RH. Please provide a risk assessment on the leachable (b) (4) based on the target population and a worst case scenario.

Sponsor's Comments Dated August 25, 2014:

- The drug product is to be stored at refrigerated conditions. This is clearly indicated on the label, i.e. store at 2 to 8°C. Thus, the (b) (4) observed at higher temperature is not considered a concern. As can be seen in submitted registration stability report, see Table 3-9, Table 3-10 and Table 3-11 of [RSR2387 Data-1C], there is no increase in (b) (4) at 5°C long term storage conditions compared to initial value.

CDRH's Review Comments: The response has adequately addressed our concerns. RESPONSE ADEQUATE.

e) The chemical leachable studies were performed under the following storage conditions: 5°C/ambient RH, 25 °C/60% RH, and/or 30 °C/75% RH. Concerns on the leachable chemicals at higher temperatures under the worst case conditions (e.g. summer time while the storage room is not air conditioned), have not been adequately addressed. Please provide chemical leachable and extractable analysis for the worst case conditions. Alternatively, please provide your recommended risk mitigation procedure and appropriate caution/warning statement in the labeling.

Sponsor's Comments Dated August 25, 2014:

- The drug product is to be stored at refrigerated conditions. This is clearly indicated on the label, i.e. store at 2 to 8°C. Thus, no leachable testing has been performed at higher temperatures than 30°C/75% RH.

CDRH's Review Comments: The response has adequately addressed our concerns. RESPONSE ADEQUATE.

Conclusion: The sponsor has addressed both performance and biocompatibility concerns. CDRH/ODE does not have any additional questions.

If you have any questions, please contact LCDR Keith Marin at 301-796-2462.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Keith G. Marin -S 2014.10.08 10:30:01 -04'00'
Team Lead Sign-Off	Ryan J. Mcgowan -S Digitally signed by Ryan J. Mcgowan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000352462, cn=Ryan J. Mcgowan -S Date: 2014.10.06 15:24:26 -04'00'
Branch Chief Sign-Off	Digitally signed by Richard C. Chapman -S Date: 2014.10.08 13:33:02 -04'00'

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

10/08/2014

CDRH device review by Bifeng Qian, with concurrence from Keith Marin, Ryan McGowan and Richard Chapman

9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

SEALD CONSULT REVIEW

SEALD TRACKING NUMBER	AT 2014-013
NDA NUMBER	203255 (IND 74642)
LETTER DATE/SUBMISSION NUMBER	SDN 1
PDUFA GOAL DATE	September 15, 2014
DATE OF CONSULT REQUEST	January 17, 2014
REVIEW DIVISION	Division of Metabolism and Endocrinology Products
MEDICAL REVIEWER	Smita Abraham
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER	Yasmin Choudhry
STUDY ENDPOINTS ASSOCIATE DIRECTOR (ACTING)	Elektra Papadopoulos
REVIEW COMPLETION DATE	August 19, 2014
ESTABLISHED NAME	Pasireotide
TRADE NAME	Signifor
SPONSOR	Novartis Pharmaceuticals
CLINICAL OUTCOME ASSESSMENT TYPE	Patient Reported Outcome
ENDPOINT CONCEPT	Quality of life
MEASURE	Acromegaly Quality of Life (ACRO QoL) Questionnaire
INDICATION	Treatment of patients with acromegaly (b) (4)
INTENDED POPULATION	Adults

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 (DMEP) regarding NDA 203255 for pasireotide for the treatment of adult patients with acromegaly submitted by Novartis on November 15, 2013.

The Sponsor has utilized the Acromegaly Quality of Life (ACRO QoL), a 38-item questionnaire to measure health-related quality of life (HRQoL) impacts i.e., *physical well-being* and *psychological well-being* in patients with acromegaly in the completed phase 3 clinical trials. Note that of the 38 items, the sponsor chose to score only 22 items.

(b) (4) See Section 1.4 of this review for details.

While the instrument's name, AcroQoL, implies that this instrument is a measure of overall quality of life (QoL), QoL is a general concept that implies an evaluation of the effect of all aspects of life on general well-being. Many elements of QoL do not relate directly either to disease states or therapy, therefore, QoL is not an appropriate outcome for evaluating treatment benefit. (b) (4).

(b) (4)

SEALD defers to the biostatistics and clinical review staff whether the ACRO QoL endpoint(s) were pre-specified with appropriate adjustment for multiplicity. (b) (4)

B. STUDY ENDPOINT REVIEW

Materials Reviewed:

- DMEP consult dated January 17, 2014
- NDA 203255 received on November 15, 2013 containing the following PRO-related documents in Section 5.3.5.3:
    - 6853-a-b-combined-acroqol-assessment report
    - Study 2305-acroqol-additional-analysis report
    - Study 2402-acroqol-additional-analysis report

Background:

According to the sponsor, acromegaly is a rare disease that most commonly affects middle-aged adults; it is caused by abnormal production of growth hormone usually due to a benign tumor of the pituitary. It is estimated that about 3 out of every million people develop acromegaly each year and that 40 to 60 out of every million people suffer from the disease at any time. Symptoms are often disfiguring, with skin changes and larger than normal facial features, hand/fingers, feet and toes predominating. Subjects affected by acromegaly can suffer from fatigue, weakness, joint swelling/pain, headache, paresthesia, excessive sweating/body odor and cardiovascular symptoms which can significantly affect the HRQoL.

The sponsor is developing pasireotide, a novel somatostatin analog, for long-term maintenance therapy in patients with acromegaly, and has completed three phase 3 studies; the proposed ACRO QoL was utilized as a secondary endpoint measure in 2 of the 3 studies.

1 CONTEXT OF USE (COU)

1.1 Target Study Population and Clinical Setting

The targeted population will be adult patients with documented acromegaly based on growth hormone levels and with diagnosis of pituitary micro- or macro-adenoma.

1.2 Clinical Trial Design

The ACRO QoL was studied in two randomized, double-blind, placebo controlled and multicenter phase 3 clinical trials: Study CSOM230C2305, and Study CSOM230C2402. The HRQoL was assessed at Visit 2 (baseline), 4, 5, 6, 8, 9, and 10 using the ACRO QoL.

1.3 Endpoint Positioning

The primary objective was: *To compare the proportion of patients achieving biochemical control (defined as mean GH levels <2.5 µg/L and normalization of sex- and age adjusted IGF-1) at 24 weeks with pasireotide LAR 40 mg and pasireotide LAR 60 mg separately versus continued treatment with octreotide LAR 30 mg or lanreotide autogel (ATG) 120 mg.*

Secondary variables: The proportion of patients achieving:

- Biochemical control defined as mean GH levels < 2.5 µg/L and normalization of sex- and age-adjusted IGF-1 at 12 weeks
- The proportion of patients achieving GH levels < 2.5 µg/L at 12 and 24 weeks
- The proportion of patients achieving normal IGF-1 (sex- and age-adjusted) at 12 and 24 weeks
- The proportion of patients achieving GH levels < 1 µg/L and normal, sex- and age-adjusted IGF-1 at 12 and 24 weeks
- The proportion of patients achieving GH levels < 1 µg/L at 12 and 24 weeks
- The proportion of patients achieving a tumor size reduction > 25% at 24 weeks
- The percent change in tumor volume from baseline to 24 weeks
- Time to response (for responders only), defined as the time from the date of first injection to the first evaluation the patient achieves mean GH < 2.5 µg/L and normalization of IGF-1 (age- and sex-adjusted)
- Change from baseline in clinical symptoms of acromegaly (ring size; headache, fatigue perspiration, paresthesias and osteoarthralgia according to a five-point score scale)
- **Change from baseline in health related QoL assessed by the Acro QoL instrument**
- PK levels of pasireotide LAR 40 mg and pasireotide LAR 60 mg

Reviewer comment: The PRO-related secondary endpoints listed above occupied a much lower position and were listed under "Additional secondary objectives" indicating that the ACRO QoL was studied as an exploratory endpoint.

(b) (4)

- (b) (4)


2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The COI is the HRQoL and the conceptual framework is depicted below in the table below (taken from page 22 of the combined-acroqol-assessment report). Note that the in phase 3 clinical trials, the 38-item ACRO QoL was administered, and the final scale consisted of 22 items:

The ACRO QoL instrument is comprised of 22 questions divided into two scales: one evaluating physical aspects (8 items) and the second addressing psychological aspects (14 items). The psychological scale was further divided into a subscale evaluating physical appearance and a subscale focusing on the impact of the disease on personal relationships of the patient (7 items each). Each of the questions had a 5-item Likert scale.

Table 2: Summary of final 22-item AcroQoL

Subscale	Item	Item wording	Response options
Physical	1	My legs feel weak	5-point Likert scale, 1='always' and 5='never'
	3	I get depressed	5-point Likert scale, 1='always' and 5='never'
	9	I have problems carrying out my usual activities	5-point Likert scale, 1='always' and 5='never'
	13	The illness affects my performance at work or in my usual tasks	5-point Likert scale, 1='always' and 5='never'
	14	My joints ache	5-point Likert scale, 1='always' and 5='never'
	15	I feel tired	5-point Likert scale, 1='always' and 5='never'
	19	I feel like a sick person	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	22	I feel weak	5-point Likert scale, 1='always' and 5='never'
Psychological: Appearance	2	I feel ugly	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	4	I look awful in photographs	5-point Likert scale, 1='completely agree'

Subscale	Item	Item wording	Response options
			and 5='completely disagree'
	7	I look different in the mirror	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	11	Some parts of my body (nose, feet, hands,...) are too big	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	12	I have problems doing things with my hands, for example, sewing or handling tools	5-point Likert scale, 1='always' and 5='never'
	16	I snore at night	5-point Likert scale, anchored at 1='always' and 5='never'
	17	It is hard for me to articulate words due to the size of my tongue	5-point Likert scale, anchored at 1='always' and 5='never'
Psychological: Personal relations	5	I avoid going out very much with friends because of my appearance	5-point Likert scale, anchored at 1='always' and 5='never'
	6	I try to avoid socialising	5-point Likert scale, anchored at 1='always' and 5='never'
	8	I feel rejected by people because of my illness	5-point Likert scale, anchored at 1='completely agree' and 5='completely disagree'
	10	People stare at me because of my appearance	5-point Likert scale, anchored at 1='completely agree' and 5='completely disagree'
	18	I have problems with sexual relationships	5-point Likert scale, anchored at 1='always' and 5='never'
	20	The physical changes produced by my illness govern my life	5-point Likert scale, anchored at 1='completely agree' and 5='completely disagree'
	21	I have little sexual appetite	5-point Likert scale, anchored at 1='always' and 5='never'

3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

The ACRO QoL is a 38-item, paper and pen instrument that was utilized in phase 3 studies to assess the HRQoL in patients with acromegaly. Of the 38 items, 22 items (shown in the table in Section 2 above and also in Appendix B of this review) were used in the final scale covered

under the two domains: Physical Well-being (8 items) and the Psychological Well-being: Appearance (7 items), and Personal Relations (7 items). The sponsor states that the reduction of the questionnaire was based on the Rasch analyses of the items.

Scoring algorithm: Each of the 22 items of the ACRO QoL is rated on a 1 to 5 Likert scale measuring either the frequency of occurrence (always, most of the time, sometimes, rarely, or never) or the degree of agreement with the items (completely agree, moderately agree, neither agree nor disagree, moderately disagree, completely disagree). A global score is obtained by summing the scores from the 22 items and converting the score on each subscale and the global score to a 0 (worst) -100 (best) score. Scores for each of the three subscale scores are calculated in the same manner, and thus all four scale scores range from 0 (worst possible HRQoL) to 100 (best possible HRQoL).

The instrument properties are summarized in the table below taken from page 19/151 of the combined-acroqol-assessment report:

Table 1: Summary of AcroQoL instrument properties

AcroQoL Property	

Number of items, domain and subscale structure	22 items assessing health related quality of life in two domains:
	• Physical well-being (8 items)
	• Psychological well-being
	  ○ Appearance (7 items)
	  ○ Personal relations (7 items)

Response format	14 items are responded to on a 5-point Likert scale, anchored at 1='always' and 5='never' (Items: 1, 3, 5, 6, 9, 12, 13, 14, 15, 16, 17, 18, 21, 22) 8 items are responded to on a 5-point Likert scale, anchored at 1='completely agree' and 5='completely disagree' (Items: 2, 4, 7, 8, 10, 11, 19, 20)
Recall period	None: patients rate their current HRQoL
Scoring procedure	A global score is obtained by summing the scores from the 22 items and converting to a 0-100 score using the following formula: $(\frac{(X)-22}{(110-22)})\times 100$ where X is the sum of the item responses (between 1 and 5 for each answer). Thus scores on each subscale and the global score range from 0 (indicating worst possible HRQoL) to 100 (indicating the best possible HRQoL.[2]
Mode of administration	Self-administered pen and paper questionnaire

See Appendix A: The Acromegaly Quality of Life Questionnaire (ACRO QoL) - 38-item; and Appendix B: ACRO QoL-the final 22-item questionnaire.

Reviewer comment: The ACRO QoL does not comprehensively capture the patient's experiences with acromegaly. Certain symptoms (e.g., paresthesias, headaches) are omitted. The domain names, (b) (4) *, do not appear to reflect the item content in some cases. For example, the item "I snore at night" and "It is hard for me to articulate words due to the size of my tongue" are not psychological- or appearance-related impacts of acromegaly and yet these items are included within the "Psychological: Appearance" domain of the ACRO QoL. The instrument domains include varied concepts of symptoms, signs and disease impact making it difficult to clearly define what is being measured. For example: Item # 4: I look horrible in photographs; and Item #12: I look different in the mirror may be influenced by a variety of external factors unrelated to acromegaly and such items are ill-defined and therefore inadequate* (b) (4)

4 CONTENT VALIDITY

The sponsor referenced literature publications to support the initial develop of the ACRO QoL. No details of Instrument development were provided. The ACRO QoL was initially developed in Spanish. The table (taken from page 20/151 of the combined-acroqol-assessment report) below summarizes the sponsor's development process of the ACRO QoL for use in pasireotide clinical trials:

Figure 2: AcroQoL development process[2]

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See Section 2 of this review for the sponsor's table (Table 2: Summary of the final 22-item ACROQoL. The reduction of the questionnaire was based on successive and independent Rasch analyses of all the 38 initial items of ACRO QoL. The sponsor states that the analyses were performed using WINSTEPS, version 2.96, following the model known as "Rating Scale" (given that the analyzed items contain more than two response options). Items were considered for deletion based on evidence of redundancy and overlap, taking into account information from the Rasch analysis regarding item in-fit (items with in-fit MNSQ indicates values of 1.3 were considered to have poor fit) and from principle components analysis regarding the factor loadings of each of the 38 items on the first factor.

According to the sponsor, the distribution of the 22 items across the evaluated continuum on the Rasch distribution map, as well as the distribution of individuals, was satisfactory; the separation of individuals (2.87) and reliability (0.89) were excellent; and the separation of the items (5.18) and their reliability (0.96) was also more than satisfactory. The sponsor stated that there were still some items with in-fit values above 1.3; this was considered to be due to the bidimensionality of the items which constitute the questionnaire; and that the division of the 22 items in two scales, one Physical (8 items), the other Psychological (14 items) was felt to adequately accommodate this dimensionality. In view of the content of the items of the psychological scale, it was proposed (by the sponsor's scale development team) that the scale be divided into two additional Psychological subscales: Appearance (7 items) and Personal Relations (7 items).

Reviewer comment: It seems that the sponsor has relied mostly on the literature and expert input in the development of the ACRO QoL for evidence of content validity. The PRO guidance also emphasizes the importance of adequate patient input in the instrument development process, as well as literature review and expert input. The instrument is not comprehensive with respect to symptoms and the instrument domains include items that do not appear appropriate or relevant to the concept measured (b) (4) .

(b) (4)

(b) (4)

As noted above, Novartis's ACRO QoL does not capture certain relevant symptoms of acromegaly such as paresthesias, loss of memory, severe headaches, vision problems, tremors, excessive sweating etc. (see Appendix D of the sponsor's combined-acroqol-assessment report: Full list of initial expressions used as a basis for ACRO QoL items).

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

The sponsor provided results of the two completed phase 3 studies in support of the evaluation of the other measurement properties (including construct validity and reliability) and concluded that these data provide substantial evidence that the ACRO QoL has strong psychometric measurement properties and is an adequate measure of HRQoL in acromegaly.

Reviewer comment: We are not commenting on these findings and other measure because the assessment is not well-defined with evidence of content validity. Other measurement properties (reliability, construct validity and ability to detect change) are not reviewed until the instrument's content validity has been established.

6 INTERPRETATION OF SCORES

See the scoring algorithm in Section 3 of this review.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The ACRO QoL was originally developed in Spanish. The sponsor states that the following language versions of Acro QoL were used in the phase 3 study CSOM230C2305: English, French, German, Italian, Spanish (Spain), Spanish (US), Spanish (Argentina), Spanish (Chile), Spanish (Colombia), Spanish (Mexico), Danish, Norwegian, Swedish, Dutch, Greek, Hebrew, Czech, Korean, Polish, Portuguese (Brazil) and Turkish. The standard methodology was employed involving 'two forward one backwards' translations followed by cognitive debriefing in the target language (see page 79/151 of the combined-acroqol-assessment report).

Reviewer comment: It seems that the sponsor took this information from the article by S.M. Web et al Acromegaly Quality of Life Questionnaire (ACRO QOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties, published

in Clinical Endocrinology in 2002. The translation into different languages was not conducted by the sponsor.

8 REVIEW USER MANUAL

A user manual for the ACRO QoL was not provided.

9 CLINICAL TRIAL PROTOCOL AND ANALYSIS PLAN

Study design: The two phase 3 clinical studies (C2305 and C2402) were randomized, double-blind, and placebo controlled studies.

The sponsor's statistical analysis plan is (taken from som230c2402-legacy-clinical study report) includes:

- The change from baseline in the ACRO QoL total score and sub-scores at week 24 will be analyzed using an ANCOVA model with treatment group as the fixed effect and baseline scores and randomization stratum as covariates. The changes in scores for the ACRO QoL will be examined from baseline to study end and between visits.
- *Multiplicity adjustments:* It is unclear whether the sponsor has specified appropriate adjustments for multiplicity for the ACRO QoL-related endpoint. (b) (4)
- *Handling of missing data*: If a patient had less than 3 samples for the assessment of 5-point mean GH from the 2-hour profile, the mean GH was considered to be missing. If GH and IGF-1 measurements were taken more than 35 days after the LAR injection, the GH (and mean GH) and/or IGF-1 at the corresponding visit were considered to be missing. Missing mean GH and/or imputed using data obtained at or after Month 6 by the LOCF method for the primary efficacy variable; otherwise, patients were considered as non-responders. If one of the two values (mean GH or IGF-1) was missing at Month 12, and if the available value did not meet the response criteria for that parameter, the patient was considered a non-responder. If, however, the available value met the response criteria, then both GH and IGF-1 were imputed using LOCF from the same visit closest to Month 12.

Reviewer comment: The ACRO QoL does not occupy a higher position on the hierarchy of the secondary endpoints.

APPENDIX A

The Acromegaly Quality of Life Questionnaire (ACRO QoL)
A 38-item questionnaire used in phase 3 clinical trials
(Taken from Appendix F page 111/151of the combined-acroqol-assessment report)

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APPENDIX B

The ACRO QoL – The final 22-item questionnaire

Table 2: Summary of final 22-item AcroQoL

Subscale	Item	Item wording	Response options
Physical	1	My legs feel weak	5-point Likert scale, 1='always' and 5='never'
	3	I get depressed	5-point Likert scale, 1='always' and 5='never'
	9	I have problems carrying out my usual activities	5-point Likert scale, 1='always' and 5='never'
	13	The illness affects my performance at work or in my usual tasks	5-point Likert scale, 1='always' and 5='never'
	14	My joints ache	5-point Likert scale, 1='always' and 5='never'
	15	I feel tired	5-point Likert scale, 1='always' and 5='never'
	19	I feel like a sick person	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	22	I feel weak	5-point Likert scale, 1='always' and 5='never'
Psychological: Appearance	2	I feel ugly	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	4	I look awful in photographs	5-point Likert scale, 1='completely agree'

Subscale	Item	Item wording	Response options
			and 5='completely disagree'
	7	I look different in the mirror	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	11	Some parts of my body (nose, feet, hands,...) are too big	5-point Likert scale, 1='completely agree' and 5='completely disagree'
	12	I have problems doing things with my hands, for example, sewing or handling tools	5-point Likert scale, 1='always' and 5='never'
	16	I snore at night	5-point Likert scale, anchored at 1='always' and 5='never'
	17	It is hard for me to articulate words due to the size of my tongue	5-point Likert scale, anchored at 1='always' and 5='never'
Psychological: Personal relations	5	I avoid going out very much with friends because of my appearance	5-point Likert scale, anchored at 1='always' and 5='never'
	6	I try to avoid socialising	5-point Likert scale, anchored at 1='always' and 5='never'
	8	I feel rejected by people because of my illness	5-point Likert scale, anchored at 1='completely agree' and 5='completely disagree'
	10	People stare at me because of my appearance	5-point Likert scale, anchored at 1='completely agree' and 5='completely disagree'
	18	I have problems with sexual relationships	5-point Likert scale, anchored at 1='always' and 5='never'
	20	The physical changes produced by my illness govern my life	5-point Likert scale, anchored at 1='completely agree' and 5='completely disagree'
	21	I have little sexual appetite	5-point Likert scale, anchored at 1='always' and 5='never'

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/s/

YASMIN A CHOUDHRY
08/19/2014

ELEKTRA J PAPADOPOULOS
08/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

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

CDRH Human Factors Review

DATE: August 5, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Jennifer Johnson, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA203255**
Applicant: Novartis Pharmaceuticals
Device Constituent: delivery system (prefilled syringe, vial, vial adapter, safety injection needle)
Drug Constituent: Signifor LAR (pasireotide)
Intended Treatment: for patients with acromegaly
CDRH CTS Tracking No. 1300073

Digitally signed by Quynhnhu T. Nguyen -S
Date: 2014.08.13 10:58:39 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist
(Human Factors Premarket Evaluation Team - HFPMET)

Ronald D. Kaye -S
Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald D. Kaye -S, 0.9.2342.19200300.100.1.1=1300110677
Date: 2014.08.13 11:03:35 -04'00'

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

CDRH Human Factors Review

Overview and Recommendation

The Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drug Evaluation and Research requested a consultative review from Center for Devices and Radiological Health's Human Factors Premarket Evaluation Team on the human factors study report submitted in the original NDA, 203255, for the SOM230C delivery system (prefilled syringe, vial, vial adapter, safety injection needle) to deliver Signifor LAR (pasireotide).

Novartis stated that Human Factors Engineering activities for the proposed delivery product included (1) use-related risk analyses (2) two formative user studies; and (3) human factors validation study, which was conducted with 44 participants. This consultant is concerned with the following results:

- 2 participants (5%) were observed to have difficulties on the step of keeping plunger pressed, shake vial moderately for minimum of 15s. One participant experienced minor leakage between the vial adapter and the vial while shaking. The volume of fluid that leaked is estimated to be vehicle only and less than (b)(4)% of the total volume. Novartis reported that the leaking experienced by one participant was minor and would not have resulted in a less effective dose. This consultant defers to the review team to verify that if the leakage volume of (b)(4)% of total drug delivery is considered clinically acceptable.
- 18 participants (41%) failed to state the intent to wait for 30 minutes for the product to reach to room temperature. Novartis stated injecting cold drug product may cause patient discomfort. As a result, this step in the Instructions For Use (IFU) has been modified to include an image of 30 minutes and an "attention" section to call the user's attention to this step.
- 7 participants (16%) failed to clean the rubber stopper with an alcohol swab. This can lead to the stopper not being disinfected and can cause contamination to the drug product. That is why Novartis recommends to disinfect the stopper before attaching the vial adapter in the IFU. This consultant defers to the review team to determine whether injecting contaminated product is considered clinically acceptable.
- 7 participants (16%) failed to gently tap syringe to remove any visible bubbles and expel from syringe. Novartis indicated that this is within normal variation of standard clinical practice for intramuscular injections. This consultant differs to the review team to determine whether it is clinically acceptable to inject visible bubbles in the intramuscular space.

As a result of the validation study, Novartis implemented modifications to the IFU which included a red attention box to call out the two critical steps: (1) waiting for 30 minutes for the drug product to reach room temperature prior to reconstitution and (2) shaking the vial moderately after adding the diluent to ensure a uniform mixture. The first critical step now includes an image of 30 seconds, and an attention section to call out the user's attention for the 30 minute wait time. The second critical step now includes an attention section to call out the user's attention for the 30 seconds shake time. In addition, other IFU changes included the cartoon depiction of the injection site and the injection angle of 90 degree, and clarifications on the steps of activating safety needle and vial adapter attachment.

Recommendation: The IFU modifications were made on the steps of waiting for 30 minutes for the drug product to reach room temperature prior to reconstitution and shaking the vial moderately after adding the diluent to ensure a uniform mixture are critical information that the user needs to be aware when using this device. However, this consultant does not believe that the IFU changes need to be retested. The consultant would caution that if the clinical team determines that the use errors that could result in delivering less than (b)(4)% of the drug volume and in delivering a contaminated product are clinically significant for this particular drug product, then the consultant would recommend that the Sponsor implement additional mitigations to address those use errors.

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA203255
Applicant: Novartis Pharmaceuticals
Device Constituent: delivery system
(prefilled syringe, vial, vial adapter, safety injection needle)
Drug Constituent: Signifor LAR (pasireotide)
Intended Treatment: for patients with acromegaly

CDRH Human Factors Involvement History

- 1/16/2014: CDRH HFPMET received a request to review the human factors study report included in the original NDA.
- 4/9/2014: CDRH HFPMET provided a mid-cycle review update
- 8/6/2014: CDRH HFPMET provided recommendation to CDER.

CDRH Human Factors Review and Evaluation

Within the human factors study report ((b) (4) Consultant, P1208-R-003 v1.0, dated 28 November 2012), Novartis stated Human Factors Engineering activities for the proposed delivery product included:

- Use-related risk analyses were performed using Failure Mode and Effects Analysis (FMEA). These analyses according to Novartis did not identify any critical tasks. Therefore, the tasks involved with using the device are either essential and non-essential. This consultant does not agree that there are no critical tasks associated with the use of the proposed product. However, it should be noted that as a direct response to the human factors validation study results, Novartis indicated that there are two critical tasks associated with product use, and implemented a change in the Instructions for Use to include a warning box that describes those two critical tasks. Please see Appendix 2 for more details.
- Two formative user studies, which informed the design of the delivery system and IFU and packaging. The first formative study was conducted with the SOM230C delivery system with the (b) (4) safety needle. The second study was a survey-based study using rating scales to obtain user's ratings on the proposed system and comparable products that are currently on the market.
- A human factors validation study, which was conducted with 44 participants. Of these, 21 were secondary care doctors who specialize in the fields of endocrinology (b) (4), and 23 secondary care nurses who specialize in the fields of endocrinology (b) (4). None participants were trained in the use of the delivery system to represent the worst-case no training scenario. Participants were given the IFU and asked to prepare an injection using the delivery system and administer it into an injection pad. Participants were permitted to refer to the IFU at any time, but were not required to use it. The study results were recorded using one of the following three categorizations: (A) Correct performance; (D) Performance with difficulties; and (F) Failed performance. This consultant is concerned with the following results:
  - 2 participants (5%) were observed to have difficulties on the step of keeping plunger pressed, shake vial moderately for minimum of 15s. One participant experienced minor leakage between the vial adapter and the vial while shaking. This participant held the

syringe plunger in one hand and the vial in the other hand, which appeared to cause the vial adapter to separate slightly from the vial while shaking. Accurate measurement of leakage was not possible during the study. However, the volume of fluid that leaked is estimated to be vehicle only and less than (b) (4)% of the total volume. Novartis reported that the leaking experienced by one participant was minor and would not have resulted in a less effective dose.

- 18 participants (41%) failed to state the intent to wait for 30 minutes for the product to reach to room temperature. Novartis stated that acclimatization has no effect on the deliverable dose [Novartis Report PHAD001707A]. However, injecting cold drug product may cause patient discomfort. As a result, this step in the IFU has been modified to include an image of 30 minutes and an "attention" section to call the user's attention to this step.
- 7 participants (16%) failed to clean the rubber stopper with an alcohol swab. This can lead to the stopper not being disinfected and can cause contamination to the drug product. Novartis reported that the stopper is sterilized before being placed on the vial. It is then capped before the vial is placed in secondary packaging. The cap and secondary packaging will protect the outer surface of the stopper, but do not constitute a sterile barrier. For this reason, it is recommended to disinfect the stopper before attaching the vial adapter.
- 7 participants (16%) failed to gently tap syringe to remove any visible bubbles and expel from syringe. Novartis indicated that this is within normal variation of standard clinical practice for intramuscular injections.

Subsequent to the human factors validation study, Novartis reported that slight modifications have been made to the wording in the IFU to improve clarity. The changes include a new warning box on the front page indicating important steps for effective dosing and a rationale for completing these steps. This emphasis was also added in the text for the corresponding steps. Two pictures in the IFU were changed to emphasize the acclimatization time and the potential injection sites. The labeling on the packaging was modified to give more emphasis to the information about important steps. Please see Appendix 2.

Appendix 1: Device Related Information

The SOM230C delivery system is a self-contained package consisting of:

- One SOM230C 60 mg powder for suspension for injection in a vial
- One vehicle for SOM230C 2 ml solution in a prefilled syringe
- One vial adapter
- One safety injection needle (20G x 1.5")

A Package Insert (PI), including Instructions for Use (IFU), would be included with each delivery system.

Figure 1 – Components of the delivery system

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Appendix 2: Post-validation Study Modifications to Instructions for Use

Table 1 – Modifications to the IFU

Version used for validation testing	Updated version after validation testing
Warning box	
(b) (4)	**Attention** There are 2 critical steps in the reconstitution of Signifor LAR. **Not following** (b) (4) **could result in failure to deliver the drug appropriately.** • **The injection kit must reach room temperature**. Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours. • After adding the diluent solution, **shake the vial moderately** in a horizontal direction for a minimum of 30 seconds **until uniform suspension is formed**.
30 minutes acclimatization	
(b) (4)	 **Step 1** Remove the Signifor LAR injection kit from refrigerated storage. ATTENTION: **It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.** Note: The injection kit can be re-refrigerated if needed.
Vial adapter attachment	
(b) (4)	Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging. Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, (b) (4) audible "click".

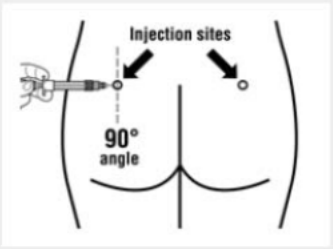
30 seconds shaking

(b) (4)

ATTENTION: Keep the plunger pressed and shake the vial **moderately** in a horizontal direction **for a minimum of 30 seconds** so that the powder is completely suspended. **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**

Injection site depiction

(b) (4)



Activating safety needle

(b) (4)

Activate the safety guard over the needle in one of the 2 methods shown:

- either press the hinged section of the safety guard down onto a hard surface (figure A)

- or push the hinge forward with your finger (figure B).

An audible "click" confirms the proper activation.

Dispose of syringe immediately (in a sharps container)

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

08/19/2014

CDRH Human Factors study report review (completed on 8/13/14 and sent to CDER RPM on 8/15/14) in response to consult request on 1/16/14

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 21, 2014

TO: Smita Abraham, M.D., Clinical Reviewer
Dragos Roman, M.D., Clinical Team Leader
Jennifer Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

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

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 203255

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: Pasireotide (SIGNIFOR® LAR)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of patients with acromegaly [redacted] (b) (4)

CONSULTATION REQUEST DATE: January 17, 2014
CLINICAL INSPECTION SUMMARY GOAL DATE: July 21, 2014
DIVISION ACTION GOAL DATE: September 15, 2014
PDUFA DATE: September 15, 2014

I. BACKGROUND

Novartis is seeking approval of three dose strengths of SIGNIFOR® LAR (pasireotide) injection for the treatment of patients with acromegaly [redacted] (b) (4) This is a new indication for this drug product. SIGNIFOR formulation was approved by the FDA in December 2012 for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

This submission is primarily based on two large Phase 3 studies: CSOM230C2305 (further abbreviated **C2305**) entitled, "A Multicenter, Randomized, Blinded Study to Assess Safety and Efficacy of Pasireotide LAR vs Octreotide LAR in Patients with Active Acromegaly" and CSOM230C2402 (further abbreviated **C2402**) entitled, "A Phase III, Multicenter, Randomized, Parallel-Group Study to Assess the Efficacy and Safety of Double-Blind Pasireotide LAR 40 Mg and Pasireotide LAR 60 Mg Versus Open-Label Octreotide LAR or Lanreotide ATG in Patients with Inadequately Controlled Acromegaly".

For study **C2305**, the study began February 11, 2008 and patients have enrolled across 27 countries at 84 study centers. The study consists of two study phases: a 12-month core phase and an optional extension. There have been 358 patients enrolled, of whom 176 and 182 were randomized to receive pasireotide and octreotide, respectively. From the pasireotide group, 74 patients continued the same treatment in the extension and 38 crossed over to octreotide, whereas from the octreotide group 46 patients continued the same treatment in the extension and 81 crossed over to pasireotide. The study is still ongoing. The data analyses presented in the current clinical study report are based on the May 3, 2012 database lock.

Due to the different appearance of the LAR formulations, a true double-blind treatment was not feasible. To ensure blinding of the patient and the investigator, all injections of pasireotide LAR and octreotide LAR were to be prepared and given by an independent unblinded nurse/study coordinator. The dedicated independent nurse/coordinator was to call the IVRS, administer the LAR treatment and complete the Dosage Administration Record CRF. This document was to remain concealed from the patient, the investigator and the sponsor's clinical monitor. The investigators wishing to continue treating a patient in the extension treatment period were allowed to unblind the patient's treatment after all End of Study assessments have been completed and recorded. Novartis personnel and groups performing central assessments were to remain blind to treatment until the database is locked.

For study **C2402**, the study consisted of a core and extension phase. Patients were enrolled

across 18 countries at 72 study centers. The study began July 19, 2010 and the core phase was completed January 22, 2013. The study is currently ongoing. There have been 198 patients randomized (65 patients in each of the pasireotide arms and 68 patients in the active control arm). Six did not receive study treatment. The application includes data from the 24-week core phase.

This is a study with an open-label, active control arm and with blinding of the dose in the pasireotide LAR treatment arms. The identity of the treatments in the pasireotide LAR treatment arms have been concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 203255 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	**Protocol # and # of Subjects Randomized**	**Inspection Date**	**Preliminary Classification**
Roberto Salvatori Site #516	C2305 3 subjects	2/25/- 3/7/2014	VAI
Marcello Bronstein Site #152 Site #901	C2402 23 subjects C2305 9 subjects	5/12/- 5/16/2014	VAI
Monica Gadelha Site #151 Site #904	C2402 27 subjects C2305 12 subjects	5/19/- 5/23/2014	NAI
Feng Gu Site # 771	C2305 33 subjects	5/12/- 5/16/2014	NAI
Chiung-Chyi Shen Site #681	C2305 14 subjects	3/31- 4/4/2014	NAI
Syne qua non Ltd	C2305 All above sites	5/19/- 5/28/2-14	NAI

Key to Classifications

NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. Roberto Salvatori, M.D.
550 North Broadway
Room 107
Baltimore, MD 21205*

*Address where subjects were seen. All correspondence should be addressed to:
Roberto Salvatori, M.D.
1830 E. Monument Street, Suite 333
Baltimore, MD 21287

a. What was inspected: The inspection included review of the regulatory binder, IRB correspondence, sponsor correspondence, curriculum vitaes, licenses, 1572s, financial disclosures, monitoring logs, all subject records, training records, case report forms, test article accountability and all consent forms. The study records were located in the Clinical Trials Unit of Johns Hopkins University, 1830 E. Monument Street, Baltimore, MD 21287

b. General observations/commentary: There were four subjects screened and three subjects enrolled. First subject signed informed consent on 5/8/2009. Two subjects completed. One subject (004) is ongoing. Records were organized and legible. Comparisons of dates and times of study drug injection from the source records to the paper CRFs found no discrepancies. The primary endpoint was verifiable for all three enrolled subjects. Randomly selected secondary endpoint data from source records were compared to line listings and were verifiable. There was no under-reporting of adverse events.

For Subject 004, during the study it was discovered that the subject received an incorrect dose of blinded study drug administered monthly during visits V8E, V9E and V10E. She received the dose increase “30 mg of Octreotide LAR or 60 mg of pasireotide” instead of the starting dose “20 mg Octreotide LAR or 40 mg pasireotide”. The dose of medication the subject received was based on the mean GH level and /or IGF-1 value, done by the central lab. Subject was informed of the error. Possible side effects are increased blood glucose and risk of gallstones. Fasting plasma glucose (FPG) levels for all visits were assessed and reported to the sponsor. After the incorrect dose was administered, the FPG raised from 110 mg/dL to 132 mg/dL. It returned to 108 mg/dL. This error was reported to the IRB. It is not clear how the error occurred as the IGF-1 level was normal; therefore, the labs did not support a dose increase. The order is checked off for a dose increase. The PI did sign off on the order. To prevent the

error in the future, the PI and the study coordinator will independently review the participant's past labs and compare their conclusions, so that the correct protocol-directed dose will be provided to the participant.

(b) (4)

[redacted]

OSI Reviewer Comment: Dr Salvatori responded to the 483 item in a letter dated March 14, 2014. He acknowledged the omissions and put corrective actions into place to prevent recurrence. His response is acceptable.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Although there were some protocol deviations noted, data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Marcello Bronstein, M.D., Ph.D.
Avenida Doutor Eneas de
Carvalho Aguiar, 255
São Paulo, SP 05403-000
Brazil

*Correspondences to be sent to:
Marcello Bronstein, M.D., Ph.D.
Principal Investigator, Endocrinologist
Hospital das Clínicas da Universidade de São Paulo
Avenida Doutor Eneas de Carvalho Aguiar, 255
Sao Paulo, 05403-000
Brazil

a. **What was inspected:** (b) (4), a consulting company for the pharmaceutical industry in Brazil, provided translation between the hospital staff and FDA investigators, as well as translation of documents. The inspection included review of IRB approvals and communications, curriculum vitaes, training, recruitment, informed consents, blinding procedures, financial disclosure, inclusion/exclusion, adverse events, drug accountability and line listing verification. Six of the nine subject records for Study C2305 and 12 of the 23 subject records for Study C2402 were reviewed, including the laboratory results, MRIs, ultrasounds, ECGs, hospital charts and progress notes for each subject.

b. General observations/commentary: For protocol C2402, there were 23 subjects enrolled, 23 subjects randomized, and 21 subjects completed the study. There were no screen failures according to the Investigator. For protocol C2305, there were nine subjects enrolled, nine subjects randomized, and eight subjects completed study. One subject was lost to follow-up.

The IRB/Ethics Committee was identified as (b) (4) The subjects were screened on the same day as they signed consent forms. In general, the site adhered to the study protocol with respect to inclusion/exclusion, drug accountability, dose, follow-up visits, and adverse event assessments. The investigators conducted the trial visits with the subjects and recorded their findings from the visits on paper hospital records and later would enter the data into the computer data base for the hospital, print them out and sign them. According to staff, the hospital records were generated the same day of the visits. Later the sub-investigators would fill out hard copy CRFs that would be sent to the sponsor.

The clinical study report, amendment 3, for Study C2305, submitted with the original NDA, referenced both blinded and unblinded activities being conducted by the same individual at a different site (Site 904) in Brazil. A letter dated May 7, 2014 was submitted to the review division stating that a similar situation

recently came to the Sponsor's attention while preparing for the inspection at Site 901 (Bronstein) in Brazil for the same study. The study was initiated with an unblinded pharmacist responsible for study drug dispensation who later became the study coordinator. She was performing both unblinded and blinded study tasks at the same time as documented in the drug accountability forms and site personnel delegation log, e.g. dispensing study medication, filling out the unblinded drug accountability patient form and the drug accountability blinded treatment form as well as other CRF pages. Additionally, she scheduled patient visits and performed regulatory activities. Further investigation revealed that the site had a second study coordinator who also performed both blinded and unblinded tasks as noted above during a different time period.

The FDA investigators were asked to assess the procedures at the site. For Study C2305, they observed the site had study specific procedures to ensure only the "Unblinded Pharmacist" had access to the assignment, distribution and documentation of the unblinded study drug. The FDA investigators audited study data for several subjects during this time period for these two "unblinded" pharmacists. Their review did not reveal any direct reporting of study data by these two individuals. Additionally, the CRF completion and various reports were not signed by the preparer. Only clinical assessments were signed by the Investigators. The Lead Study Coordinator served as the Unblinded Pharmacist early in the trial when the Unblinded Pharmacist was out on leave. The FDA investigators did not discover any evidence that the Investigators or patients at the site had been unblinded during the study, or any evidence that the unblinded coordinator biased the data in any manner.

The information from the application has that the site was under IND. However, Form FDA 1572s were not signed for either study. A Novartis Sr. GCP Auditor was at the site inspection and stated that it was the sponsor's policy that the Form FDA 1572 was not signed for any of the studies conducted in Brazil, nor in most foreign countries.

(b) (4)

(b) (4)

OSI Reviewer Comment: Dr. Bronstein responded to all observations in a letter dated July 2, 2014. He states that the local regulations and the IRB do not have established deadlines for reporting serious adverse events. Their site reported adverse events and protocol deviations approximately annually to the ethics committee. The site did not have any requirements/SOPs from the IRB. However, according to the contract/study agreement signed by Dr. Bronstein, he will conduct the study in accordance with good clinical practice. In the future, in spite of no IRB deadlines, he will report all SAEs within 30 days. He also contacted the coordinator of the IRB and explained the importance of setting deadlines for SAE reporting to the IRB.

(b) (4)

(b) (4)

<u>OSI Reviewer Comment</u>: Dr. Bronstein responded to all observations in a letter dated July 2, 2014. He states that since 2011 he has been using a checklist to ensure all subjects meet inclusion/exclusion criteria. Going forward, if it is not a quantifiable criterion, he will clearly describe in the medical records/case histories that the inclusion/exclusion criteria have been verified and documented.

(b) (4)

(b) (4)

[redacted]

OSI Reviewer Comment: Dr. Bronstein responded to all observations in a letter dated July 2, 2014. He states that since 2011 he has been following an SOP to obtain informed consent. The SOP documented a practice already adopted by the study team. In addition, he will document in the case histories that the subject signed the informed consent prior to performing any study related procedure. He will review the medical records and ensure that all adverse events will be investigated and reported regardless if it is captured by the site staff or by other physicians from other departments in the institution.

c. Assessment of data integrity: A draft Establishment Inspection Report (EIR) was available for review. Although there were some protocol deviations noted as discussed above, there were no serious deviations/findings. The unblinding issues reported by the Sponsor were confirmed. The Sponsor has stated that it considers that the information collected at this site by the unblinded study coordinators was not biased since they only entered objective information and did not provide any subjective clinical assessments. This has been confirmed by the site inspection and it does not appear that any bias was present. We recommend that the review division take these findings into consideration, as well as the objective endpoints, when determining the impact of the site unblinding procedures regarding the validity or reliability of the submitted data.

3. Monica Gadelha, M.D., Ph.D.
Avenida Brigadeiro
Trompwski, s/n Cidade
Universitária
Rio de Janeiro, RJ 21941-913
Brazil

a. What was inspected: The inspection included review of IRB approvals and communications, curriculum vitaes, training, recruitment, informed consents, blinding procedures, financial disclosure, inclusion/exclusion, adverse events, drug accountability and line listing verification. Eight subject records for study C2305 were reviewed and 10 subject records for study C2402 were reviewed.

b. General observations/commentary: For protocol C2402, 48 subjects were screened, 27 subjects were enrolled, 26 subjects were treated, and 24 subjects completed the study. For protocol C2305, 17 subjects were screened, 12 subjects were enrolled and treated, and nine subjects completed the study. The subjects were screened on the same day as they signed consent forms and the site did not document that the consent process was completed before any study related procedures were done. In general, the site adhered to the study protocol with respect to inclusion/exclusion, drug accountability, dose, follow-up visits, and adverse event assessments. The primary efficacy endpoint was verifiable. There was no under-reporting of adverse events.

The clinical study report, amendment 3, for Study C2305 submitted with the original NDA, referenced both blinded and unblinded activities being conducted by the same individual at Dr. Gadelha's Site 904 in Brazil. It was reported that the only study coordinator at Site 904 in Brazil was responsible for the study drug handling and administration. She was also responsible for blood samples collections and handling (including shipments for local and central analysis), and collection of the ECG examinations. She had access to both the blinded and unblinded databases, and transcribed medical information (collected by the sub-investigator only) from the hospital chart to the paper CRF during the entire unblinded phase of the study.

During the inspection it was noted that each CRF page is not signed and it was impossible to determine who actually wrote each entry. Dr. Gadelha was questioned regarding the blinding issues at the site and she confirmed that the study coordinator entered the data into the CRFs. In addition, only the PI and sub-investigators were permitted to make any clinical assessments, medication changes, etc. Dr. Gadelha stated that the coordinator's interaction with the subjects was strictly non-clinical. The FDA investigators did not discover any evidence that the Investigators or patients at the site had been unblinded during the study, or any evidence that the unblinded coordinator biased the data in any manner.

The information from the application has that the site was under IND. However, Form FDA 1572s were not signed for either study. A Novartis Sr. GCP Auditor was at the site inspection and stated that it was the sponsor's policy that the Form FDA 1572 was not signed for any of the studies conducted in Brazil, nor in most foreign countries.

At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. The unblinding issues reported by the Sponsor were confirmed. The Sponsor has stated that it considers that the information collected at this site by the unblinded study coordinator was not biased since she only entered objective information and did not provide any subjective clinical assessments. This has been confirmed by the site inspection and it does not appear that any bias was present. We recommend that the review division take these findings into consideration, as well as the objective endpoints, when determining the impact of the site unblinding procedures regarding the validity or reliability of the submitted data.

4. Feng Gu, M.D.
Department of Endocrinology
Peking Union Medical College Hospital

No.1 Shuai Fu Yuan
Dongcheng District
Beijing 100730
China

a. **What was inspected:** Records reviewed during the inspection included credentials, financial disclosures, drug accountability logs, study enrollment logs, screening records, consent forms, paper case report forms, monitoring visit documentation, sponsor correspondence, IRB correspondence and training records. During the inspection, the files of 17 subjects were reviewed, as follows: 07710000-1, 3, 7, 10, 13, 20, 21, 22, 23, 28, 29, 30, 37, 39, 40, 44, and 46.

b. **General observations/commentary:** Subjects were first enrolled in the study on 3/9/2009. Amendment 3 was a local amendment for China only that changed the exclusion criterion for serum creatinine as requested by the Chinese Health Authorities. Patients to be enrolled into the study in China needed to have a normal serum creatinine level for inclusion. There were 46 subjects screened, 33 subjects enrolled, and 26 subjects completed the core study. Of the 26 subjects who completed the core study, 12 subjects completed the extension study. The [redacted] (b) (4) IRB was the IRB of record. Dr. Gu's staff was responsible for entering information onto the Novartis CRFs and the completed CRFs were forwarded to the designated CRO Syne Qua Non for data entry and processing. There was no under-reporting of adverse events and the primary efficacy endpoint was verifiable.

Inspection confirmed that the protocol specifies [redacted] (b) (4) as the central lab but testing was done by [redacted] (b) (4) labs. There was documentation that Novartis notified FDA of the use of these labs in China.

Inspection revealed no deviations and no Form FDA-483, Inspectional Observations, was issued.

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

5. Chiung-Chyi Shen, M.D., Ph.D.
Taichung Veterans General Hospital
Department of Neurosurgery
1650 Taiwan Blvd.
Section 4, ROC
Taichung
Taiwan 40705*

*Address is different from the original consult. The FDA investigator reported that the address was renamed but it is still the same site location.

a. **What was inspected:** The inspection reviewed protocol compliance, informed consent, credentials, training, financial disclosure forms, IRB review and approval, inclusion/exclusion criteria, test article accountability/disposition, blinding/randomization, case report forms (CRF) documentation, efficacy endpoints, and adverse events and reporting. A 100% review was conducted of subjects' informed consent forms. A total of seven subject binders were reviewed.

b. **General observations/commentary:** A total of 16 patients were screened and 14 subjects were randomized into the study. The first administration of the test article was on 6/11/08. The last follow-up visit was on 3/26/14. The IRB overseeing the study is (b) (4)

The documents were organized, in good condition, and legible. Many records, however, were found to be cut and pasted into the patient's record from computer printouts so that they could fit on the templates attached in the binder. It was discussed with the investigator that this was a bad practice because the documents could eventually lose the adhesion and fall out of the binder.

Per protocol, hemoglobin levels could not be less than the lower limit value number. Subject 004's recorded value was 12.0 g/dl, with a value range of 12.3-18.3 g/dl. The deviation was noted and submitted to the IRB, but the deviation was not forwarded to the sponsor. The IRB allowed the patient to be included in the study because they did not feel there were any safety issues. Protocol amendment 4 added that the hemoglobin value was changed to be 90% of the lower limit number, thereby allowing a slightly larger range for inclusion to the study.

A monitoring visit found the deviation on the 11/12-13/08 visit, but Dr. Shen did not submit the deviation until 2012. The IRB required him to complete a four hour good clinical practice course. He completed the course as indicated by his course completion certificate.

An unblinding event occurred with Subject 006 less than one week prior to Visit 16. Unblinding was due to occur at Visit 16. It could not be determined exactly why the subject was unblinded at that time, but it may have been due to confusion of visit dates and when the unblinding was actually due to occur. During a CRA monitoring visit, this deviation was reported to the sponsor, but the sponsor determined it had no effect on the outcome of the study and there were no safety issues. No other patient unblinding events were noted.

Prior to travel, the FDA inspector was not provided the necessary and appropriate hardware by the FDA IT security office. Therefore, the FDA inspector was unable to open and use the background information stored on the computer hard drive. In an attempt to verify some data, an international phone call was made and FDA Headquarters provided limited data points during the extended call to verify for several subjects. From the limited data provided, it appeared that there were no discrepancies noted in the subjects' binder CRFs/source documents regarding efficacy endpoints, AE/SAE, protocol deviations, subject randomization, subject discontinuations, and concomitant medications.

At the conclusion of the inspection, no FDA 483, Inspectional Observations, was issued.

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

6. Syne qua non Ltd
c/o Mr. Tony Rees
Gostling House
Diss Business Park
Hopper Way, Sandy Lane
Diss Norfolk IP22 4GT
United Kingdom

a. What was inspected: The FDA investigator met with several staff of the sponsor and the contract research organization to clarify duties. Syne qua non (SQN) was involved with study C2305. The inspection included review of documentation to assess contractual obligations and their performance that were transferred to SQN by the sponsor. Also reviewed were standard operating procedures (SOPs), data management documents, data transfer specifications, SAE reporting, audit trails, process mapping, policies, adherence to the Master Trial Agreement, data locking/unlocking, laboratory certifications, and training and credentials of staff members. A full file review was taken from randomly chosen subjects from the above five clinical sites (516/001, 516/003, 681/001, 681/005, 681/009, 681/013, 771/002, 771/012, 771/021, 771/028, 771/035, 771/039, 771/044, 901/003, 901/010, 904/003, 904/007, 904/015).

b. **General observations/commentary:** Records were found to be well organized and complete. The company has a "clean desk" policy and all records are put away each day in the appropriate secured area. The archival area is controlled with limited access by the archivist and QA. SQN was hired by Novartis to perform data collection, compilation and interaction with the study sites, and data queries. All data collection responsibilities were transferred to SQN. SQN used a combination of their internal

SOPs as well as some of Novartis' SOPs. SQN's role was to collect the data from the clinical sites, compile it and then send it to Novartis for interpretation and statistical analysis. The data handling duties also included generating queries to the clinical sites, reviewing reported SAEs, maintaining audit trials, assigning proper coding, resolving any data issues, creating lab transfer specifications and adherence to the Validation Analysis Plan. All listings were verified to be factually recorded.

Monitoring was performed by the sponsor. SQN had access to the monitoring correspondences. Paper CRFs were sent to SQN as well as electronic data sent by the labs. The China ECGs were sent to ERT, read and inputted into the database and sent electronically to SQN for compilation. Novartis selected the clinical investigator sites. Novartis trained the sites in data entry. Novartis audited SQN. Novartis verified other vendors. Novartis statisticians developed the statistical plan. The studies were registered with ClinicalTrials.gov.

The database locking and unlocking was discussed. The sponsor has a data base lock committee. The database was initially unlocked and locked as data came in and then it was decided to review all the data in bulk. Staff stated that there were soft locks and hard locks on scheduled dates. Paper CRFs or other reporting such as the Unblinded Dosage Administration Record, is received at SQN and is then sorted for routing to blinded or unblinded data input staff in geographically separated areas. Review is performed by those not associated with data entry or editing of the data. The data may then generate a query for clarification or confirmation of a protocol deviation. Accidental unblinding of the data management team did not occur at SQN. SOPs and VAP documents regarding database lock and unlocking were reviewed and were properly followed. Changes to the database are tracked and comments are made to clarify those changes.

SQN has developed its own electronic data capture (EDC) software and tailors it to meet the needs of its customers. This EDC system was not used for study C2305. SQN performs audits using both independent contractors and in-house auditors for vendors and in-office audit assessments. Vendors are assessed every two years.

Novartis would initially receive information regarding any SAE and SQN would submit any queries as needed. Serious deviations would be queried by SQN, reviewed by SQN QA, and final opinion would be directed to the Novartis QA and Medical Consultant. The SQN database was reviewed and compared against that reported to the FDA by the Sponsor for SAEs. There was no evidence of under-reporting of SAEs.

Validation of the data system was reviewed which included design, process mapping, peer review assessment of instituting amendment 4 changes and tracking of subjects, error trapping, and dummy data testing. No issues were found. Data is backed up daily, weekly and monthly and stored in a secured area off-site.

At the conclusion of the inspection no Form FDA 483, Inspectional Observations, was issued. During the close-out meeting, it was discussed that the firm needed to identify

original documents versus copies and to encourage sufficient notation or notes to file to adequately identify the responsible individual so as to trace handling of hardcopy records and correspondence.

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

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of one domestic and four foreign clinical sites as well as the contract research organization (CRO).

Observations noted above for Drs. Salvatori, Gu and Shen, and the CRO Syne qua non are based on the preliminary review of the Establishment Inspection Reports (EIRs). Observations noted above for Dr. Bronstein are based on communications from the field investigator, the Form FDA 483 and preliminary review of a draft EIR. Observations noted above for Dr. Gadelha are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

For Study C2305, the Sponsor has reported both blinded and unblinded activities being conducted by the same individual at Dr. Gadelha's Site 904 and Dr. Bronstein's Site 901. These activities were confirmed during the inspections of these two sites. There was no indication of any accidental unblinding of the patients, investigators, sub-investigators, or Sponsor staff. We recommend that the review division take these findings into consideration, as well as the objective endpoints, when determining the impact of the site unblinding procedures regarding the validity or reliability of the submitted data from these two sites.

Two clinical sites inspected, Drs. Salvatori and Bronstein, were each issued a Form FDA 483 citing inspectional observations and classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for the two sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information; however, OSI defers assessment of the significance of the unblinding issues on data integrity to the review division.

Three clinical sites, Drs. Gadelha, Gu and Shen, and the CRO Syne qua non were not issued a Form FDA 483; classifications for each of these inspections are NAI (No Action Indicated). Data from these sites and the CRO are considered reliable based on the available information; however, OSI defers assessment of the significance of the unblinding issues identified at the Brazil sites on data integrity to the review division.

In general, based on the inspections of the five clinical study sites (representing seven protocol sites) and the CRO, the inspectional findings support validity of the data as reported by the

sponsor under this NDA. However, OSI defers assessment of the significance of the unblinding issues identified at the Brazil sites on data integrity to DMEP.

{See appended electronic signature page}

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

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Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	203255
Brand Name	SIGNIFOR® LAR
Generic Name	Pasireotide
Sponsor	Novartis Pharmaceutical Corp.
Indication	Treatment of patients with acromegaly (b) (4)
Dosage Form	Long-acting depot injection: 20, 40, and 60 mg, powder for suspension to be suspended in diluent immediately prior to (b) (4) intramuscular injection
Drug Class	Somatotropin release inhibiting Factor (SRIF) analog
Therapeutic Dosing Regimen	Recommended initial dose is 40 mg by (b) (4) intramuscular injection once every 4 weeks; Dose adjustment based on biochemical response and tolerability
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1950 µg s.c. b.i.d
Submission Number and Date	SDN 001, January 21, 2014
Review Division	DMEP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Pasireotide as a solution for s.c. injection is currently approved at a dose range of 0.3 to 0.9 mg b.i.d. for treatment of patients with Cushing's disease. Two TQT studies (B2113, B2125) have been performed on the s.c. formulation and have been reviewed by QT-IRT. Significant QTc prolongation effect of pasireotide was detected with a maximum mean (2-sided 90% CI upper bounds) ΔΔQTcI of 12.7 (14.7) ms and 16.6 (18.6) ms for s.c. doses of 0.6 mg and 1.95 mg b.i.d., respectively. Although the QT prolongation is dose related, there is a time lag (~ 2 hours) between the peak in pasireotide concentration and peak in the QT effect.

The Sponsor is currently developing a new, long acting release formulation (LAR) of pasireotide for treatment of patients with acromegaly at a dose range of 20 mg to 60 mg, supported by two phase 3 trials (C2305 and C2402). The C_{max} following the supratherapeutic dose (1.95 mg b.i.d.) in the TQT study is expected to be 3-fold that of the LAR formulation. And the C_{max} following the highest therapeutic LAR dose is similar

to that of the 0.6-mg bid therapeutic dose in the TQT study. It is expected that the QT effect of the LAR formulation is likely to be covered by those observed with the s.c solution. Within this submission, the sponsor performed concentration-QT analysis with data from the two registration trials (C2305, C2402) using the LAR formulation in patients with acromegaly. No significant QT effect was observed.

The predicted worst case scenario for exposure is patients with modest and severe hepatic impairment, in which case AUCinf is increased by 60% and 79%, C_{max} increased by 67% and 69%, respectively, relative to the control group. The pasireotide LAR is to be avoided in severe hepatic impaired patients according to the proposed label. The sponsor proposes a maximum dose of 40 mg in patients with moderate hepatic impairment. The C_{max} for supra-therapeutic dose of 1.95 mg sc bid is approximately 2-fold that for this worst case scenario.

2 PROPOSED LABEL

The sponsor has included information on bradycardia and QT prolongation in the Warnings and Precautions, Adverse Reactions, Drug Interactions and Clinical Pharmacology sections of the package insert. We agree with the sponsor that no new cardiac safety concerns have emerged in these studies conducted in the acromegaly population. We defer final labeling decisions to the Division. The followings are the major proposed QT-related labeling language:

5.2 Bradycardia and QT Prolongation

Bradycardia

Bradycardia has been reported with the use of SIGNIFOR LAR [see Adverse Reactions (6)]. Patients with cardiac disease and/or risk factor for bradycardia, such as history of clinically significant bradycardia, high-grade heart block, or concomitant use of drugs associated with bradycardia, should be (b) (4) monitored. (b) (4)

QT Prolongation

(b) (4)

SIGNIFOR LAR should be used with caution in patients who are at significant risk of developing prolongation of QTc, such as those (b) (4)

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

A baseline ECG is recommended prior to initiating therapy with SIGNIFOR LAR. Monitoring for an effect on the QTc interval [redacted] (b) (4) . Hypokalemia or hypomagnesemia must be corrected prior to SIGNIFOR LAR administration and should be monitored periodically during therapy.

7.1 Effect of Other Drugs on SIGNIFOR LAR

[redacted] (b) (4)

Co-administration of drugs that prolong the QT interval with SIGNIFOR LAR may have additive effects on the prolongation of the QT interval. [redacted] (b) (4) [see Warnings and Precautions (5.2)].

12.2 Pharmacodynamics

Cardiac Electrophysiology

QTcI interval was evaluated in a randomized, blinded, crossover study in healthy subjects investigating pasireotide subcutaneous doses of 0.6 mg b.i.d. and 1.95 mg 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) beats per minute (bpm) observed at 1.5 hours for pasireotide 0.6 mg b.i.d., and -15.2 (-16.5) bpm at 0.5 hours for pasireotide 1.95 mg b.i.d.

The predicted peak concentrations for the [redacted] (b) (4) SIGNIFOR LAR dose of 60 mg in acromegaly patients [redacted] (b) (4) are similar to the observed peak concentration (24.3 mg/mL) of the subcutaneous Signifor 0.6 mg b.i.d dose and [redacted] (b) (4) below the observed peak concentration (80.6 ng/mL) of the subcutaneous Signifor 1.95 mg b.i.d dose.

[redacted] (b) (4)

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

SIGNIFOR® LAR (pasireotide, SOM230), a second generation somatostatin analog, is a peptide hormone commonly known as somatotropin release-inhibiting factor. 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. Because of its broad binding profile to somatostatin receptors, pasireotide has the potential to stimulate both SSTR2 and SSTR5 subtype receptors relevant for inhibition of GH and IGF-1 secretion and therefore to be more effective for the treatment of acromegalic patients compared to other somatostatin analogues.

3.2 MARKET APPROVAL STATUS

SIGNIFOR® (pasireotide s.c.) was approved by the FDA (NDA 200677) on 14 December 2012 for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. EMA on 24 April 2012 (EMEA/H/C/002052//0000) and a marketing authorization application for pasireotide in Cushing's disease were also approved in Switzerland on 2 November 2012. Signifor® is currently approved in more than 40 countries worldwide.

3.3 PRECLINICAL INFORMATION

The cardiovascular safety of pasireotide was examined in appropriate preclinical models in vitro and in vivo. In vitro electrophysiology data from the hERG channel assay revealed no inhibition of the hERG tail currents up to 10 μM (10472 ng/mL) and pasireotide did not exert any electrophysiological effects on rabbit Purkinje fibers up to the concentration of 30 μM (31416 ng/mL). The concentration of 10 μM (9549 ng/mL) used in hERG assay was well above the maximum systemic exposure observed so far in clinical trials, i.e. C_{max}, ss: 40.6 ± 17.8 ng/mL at 900 μg sc bid (N=12) in carcinoid syndrome from Study B2202. In addition to the standard cardiovascular assays, the potential effects of SOM230 on major ion cardiac channels (potassium (KCNQ1 and Kv3.4/Kir3.1), sodium (Nav1.5) and calcium (Cav1.2) channels) were also assessed. No interference with any of the examined channels was seen at concentrations up to 30 μM (31.42 μg/ml). No ECG changes were seen in the up to 39-week toxicity study in monkeys at 3.2 mg/kg dose level (N=4). A single dose telemetry study in male monkeys, after subcutaneous administration, was performed with doses of up to 2 mg/kg, with no effect on cardiovascular function.

3.4 PREVIOUS CLINICAL EXPERIENCE

Effect of pasireotide on cardiac conduction intervals in healthy volunteers

Two TQT studies were conducted using s.c. formulation to characterize the effect of pasireotide on cardiac conduction intervals in healthy volunteers. [Study B2113] was

conducted to determine whether pasireotide sc, at the maximum tolerated dose (MTD), has an effect on cardiac repolarization. The study showed a maximum placebo-subtracted QTcF change from baseline of 17.5 ms at the supratherapeutic dose of 1950 µg bid. Pasireotide treatment was associated with heart rate (HR) decreases up to 4 hours post-dose (maximum change from baseline of 10.7 bpm). There were no notable QTcF or QTcB outlier values exceeding 480 ms, and no QTcF, QTcI or QTcB prolongation exceeding 60 ms compared to baseline in this study. A second TQT study [Study B2125] was conducted to further characterize the impact of pasireotide on QTc. Given the observed bradycardia effect with pasireotide in Study B2113, an individual QT correction for HR (QTcI) was used. Study B2125 encompassed 2 pasireotide dose levels (a therapeutic dose of 600 µg bid and a supra-therapeutic dose of 1950 µg bid), intense capturing of ECG and HR data (via 24-hour Holter ECGs) to, characterize individual QT-RR relationships over a wide range of HRs needed to determine QTcI, and to enable timematched ECG analysis and strict standardization procedures with regards to posture and meals to minimize intrinsic variability.

The results from Study B2125 were consistent with those from Study B2113, and confirmed that pasireotide is associated with QT interval prolongation and bradycardia in healthy volunteers at therapeutic and supra-therapeutic doses. The maximal placebo-subtracted change from baseline in QTcI was 13.19 ms (600 µg bid) and 16.12 ms (1950 µg bid) at 2 hours post dose, ~1.5 hours later than the peak in pasireotide concentration which was observed at ~0.5 hour. This delay between maximal drug concentration and QT effect suggests that pasireotide does not interact directly with cardiac ion channels, which is consistent with the absence of a signal for QT prolongation in preclinical studies. The dose-response effect for QTc prolongation was relatively flat between pasireotide doses 600 µg bid and 1950 µg bid. The small difference between the 2 doses in terms QTcI prolongation (i.e. 13 vs. 16 ms) suggests that the pasireotide QTcI effect is reaching a plateau in this dose range (corresponding to a concentration range of 25 to 90 ng/mL).

In order to further characterize the pasireotide QT effect, the 24h Holter ECGs were analyzed to assess the effect of pasireotide on cardiac electrical activity and repolarization and arrhythmogenic potential. It is known that pro-arrhythmic liability is not only related to the level of QT prolongation as some drugs that cause QT prolongation have not convincingly been demonstrated to be arrhythmogenic, e.g. amiodarone, ranolazine and ziprasidone. This seems to indicate that arrhythmogenicity potential is also determined by genetic predisposition, the compound effect on other cardiac ion channels, autonomic effects, and the presence of spatial or temporal electrical inhomogeneity.

No morphology changes (ST or T wave changes) have been observed to date with pasireotide that may indicate minimal spatial change, therefore an assessment of temporal arrhythmia liability was undertaken by quantifying ECG dynamicity from ECG beat-to-beat restitution. In contrast to moxifloxacin, pasireotide was found to significantly improve restitution parameters during rest on profile days in the presence of QT prolongation. This suggests that pasireotide-associated QT prolongation may not be associated with increased arrhythmogenic potential.

QT prolongation and bradycardia in supportive studies with LAR formulation

Notable abnormalities in heart rate corrected QT intervals for Study C2110 are presented in **Table 1.**

Table 1. Patients with notable QT/QTc intervals – Study C2110 (SAS)

		Pasireotide LAR							
		20 mg N=10		40 mg N=12		60 mg N=13		Any dose N=35	
		Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
QTcF (ms)	New >450	10	0	12	2 (16.7)	13	0	35	2 (5.7)
	New >480	10	0	12	0	13	0	35	0
	New >500	10	0	12	0	13	0	35	0
	Increase from baseline >30	10	1 (10.0)	12	2 (16.7)	13	1 (7.7)	35	4 (11.4)
	Increase from baseline >60	10	0	12	0	13	1 (7.7)	35	1 (2.9)
QTcB (ms)	New >450	10	0	10	1 (10.0)	12	1 (8.3)	32	2 (6.3)
	New >480	10	0	12	0	13	0	35	0
	New >500	10	0	12	0	13	0	35	0
	Increase from baseline >30	10	2 (20.0)	12	2 (16.7)	13	2 (15.4)	35	6 (17.1)
	Increase from baseline >60	10	0	12	1 (8.3)	13	1 (7.7)	35	2 (5.7)
QT (ms)	New >450	10	0	12	0	13	1 (7.7)	35	1 (2.9)
	New >480	10	0	12	0	13	0	35	0
	New >500	10	0	12	0	13	0	35	0
	Increase from baseline >30	10	2 (20.0)	12	4 (33.3)	13	6 (46.2)	35	12 (34.3)
	Increase from baseline >60	10	0	12	1 (8.3)	13	1 (7.7)	35	2 (5.7)

Total is the number of subjects at risk for a specific category. For new abnormality post-baseline values, this is the number of subjects with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of subjects with both baseline and post baseline evaluations.
n is the number of subjects meeting the criteria at least once.
Baseline is defined as the last available value prior to start of first treatment.
If more than one measurement was available during any time point, the average is used.
Source: [SCS-Appendix 1-Table 4.1-15]

The majority of patients entering the extension phase did not have clinically notable increases n QTcF. Increases from baseline in QTcF >30 ms were observed in 24.1% of patients treated with pasireotide LAR at any dose. Increases from baseline in QTcF >60 ms were observed for patients (13.8%) (**Table 2**), a higher proportion than was observed in Study C2305. Patient C2110E-0202-10010 had a QTcF value >500 ms. The patient developed bronchitis (Day 1342) and was treated with moxifloxacin hydrochloride. No action was taken with the study medication. On Day 1345 ECG showed prolonged QTc interval (grade 3) with QTcF at 570 ms, which the investigator reported was due to the moxifloxacin hydrochloride. No action was taken with the study medication and no treatment was reported. Bronchitis resolved and treatment with moxifloxacin hydrochloride was stopped. On Day 1354, the event (electrocardiogram QT prolonged) resolved with QTcF normal at 385 ms, 387 ms, and 390 ms at 3 consecutive ECG

readings. The investigator did not suspect a relationship between the event (ECG QT prolonged) and the study medication.

Additionally, a patient in the pasireotide LAR 60 mg treatment group (Patient C2110-0652- 10003) was reported with intermittent Wolff-Parkinson-White Syndrome of grade 1 severity that did not require any treatment for resolution. This event was not suspected by the Investigator to be related to study drug (Study C2110).

Table 2. Patients with notable QT/QTc intervals – Study C2110E (SAS)

		Pasireotide LAR	
			Any dose N=29
		Total	n (%)
QTcF (ms)	New >450	29	2 (6.9)
	New >480	29	0 (0.0)
	New >500	29	1 (3.4)
	Increase from baseline >30	29	7 (24.1)
	Increase from baseline >60	29	4 (13.8)
QTcB (ms)	New >450	29	3 (10.3)
	New >480	29	1 (3.4)
	New >500	29	1 (3.4)
	Increase from baseline >30	29	9 (31.0)
	Increase from baseline >60	29	4 (13.8)
QT (ms)	New >450	29	2 (6.9)
	New >480	29	1 (3.4)
	New >500	29	1 (3.4)
	Increase from baseline >30	29	17 (58.6)
	Increase from baseline >60	29	4 (13.8)

Total is the number of subjects at risk for a specific category. For new abnormality post-baseline values, this is the number of subjects with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of subjects with both baseline and post baseline evaluations.
n is the number of subjects meeting the criteria at least once.
Baseline is defined as the last available value prior to start of first treatment.
If more than 1 measurement was available during any time point, the average is used.
Source: [Study C2110E-Table 14.3-4.2]

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of the clinical pharmacology for pasireotide s.c. formulation. The following is the highlight of clinical pharmacology for the LAR formulation:

- Except for absorption, which is purposely controlled by the extended release of the LAR formulation, the distribution, metabolism and excretion properties of pasireotide between the sc and LAR formulations are similar because the same active entity (pasireotide) is present in both formulations.

- PK profiles in healthy volunteers show an initial burst release on the injection day, followed by a dip from Day 2 to Day 7, a slow increase to peak around Day 20, and a slow declining phase over the next 7 weeks. The PK exposures are approximately dose proportional in the 10 to 60 mg range. The extended release of pasireotide LAR is uitable for q28d dosing. Pasireotide LAR has low apparent clearance (4.5-8.5 L/h), large volume of distribution (>100 L), and long apparent half-life (~16 days). The relative bioavailability of the LAR formulation to the sc formulation is complete. Pasireotide is excreted mainly in feces as unchanged form.
- In patients with acromegaly, PK exposures of pasireotide are approximately dose proportional within the evaluated dose range (20 to 60 mg LAR). Trough concentrations reach steady state after 3 injections with low accumulation. PK is comparable between patients with acromegaly and healthy volunteers, and between Western and Asian healthy volunteers.
- High inter-subject variability and moderate intra-subject variability were observed in PK exposure. The inter-subject variability in healthy volunteers was 20.6-53.4% for Cmax, and 8.2-47.2% for AUCinf. For trough concentrations in patients with acromegaly, the inter-patient and intra-patient variability was 3.5-78.4% and 26.4-35.5%, respectively.
- Dose adjustment is recommended for patients with moderate hepatic impairment (starting dose 20 mg, maximum dose 40 mg), whereas patients with severe hepatic impairment should not be treated with pasireotide LAR. No dose adjustment is required for race, age, gender, body weight, mild hepatic impairment, or renal impairment.
- At therapeutic dose levels, the potential of DDI between pasireotide LAR and comedications is low.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed two TQT studies of the s.c. formulation and study consult for NDA 200677LAR formulation under IND 74642. The sponsor submitted the study report CSOM230C2305 and CSOM230C2402 for pasireotide LAR, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Study C2305: A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly

Study C2402: A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus openlabel octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly

4.2.2 Protocol Number

Study C2305: Protocol no CSOM230C2305, EudraCT no. 2007-001972-36

Study C2402: CSOM230C2402, EudraCT no.2009-016722-13

4.2.3 Study Dates

Study C2305: 11-Feb-2008 to 29-Dec-2011

Study C2402: 19-Jul-2010 to 22-Jan-2013

4.2.4 Objectives

Study C2305: To compare the proportion of patients with a reduction of mean GH level to <2.5 μg/L and the normalization of IGF-1 to within normal limits (age and sex related) between the two treatment groups at 12 months.

Study C2402: .To compare the proportion of patients achieving biochemical control (defined as mean growth hormone (GH) levels <2.5 μg/L and normalization of sex- and age-adjusted insulin-like growth factor (IGF-1)) at 24 weeks with pasireotide long acting release (LAR) 40 mg and pasireotide LAR 60 mg separately versus continued treatment with octreotide LAR 30 mg or lanreotide autogel (ATG) 120 mg.

4.2.5 Study Description

4.2.5.1 Design

Study C2305: Multicenter, randomized, blinded study comparing pasireotide LAR (40 mg every 28 days) vs. octreotide LAR (20 mg every 28 days) in patients with active acromegaly, consisting of 2 blinded phases: a 12-month core phase and an optional extension in which patients who responded could continue their randomized treatment, and non-responders could cross over to the other treatment. 151 patients were planned per treatment group; the study enrolled 358 patients, of which 176 and 182 were randomized to receive pasireotide and octreotide, respectively.

Study C2402: Multicenter, randomized, parallel-group, three-arm study of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR 30 mg or lanreotide ATG 120 mg in patients with inadequately controlled acromegaly. The study consisted of a core and extension phase. This report presents data of the core phase. A total of 186 patients were planned to be enrolled in the study; 198 patients were randomized (65 patients in each of the pasireotide arms and 68 patients in the active control arm).

4.2.5.2 Controls

Neither placebo nor positive (moxifloxacin) controls were used in the study. The active-control arms were used for comparison of efficacy.

4.2.5.3 Blinding

Study C2305: Treatment remained blinded until Month 26; thereafter patients on pasireotide could receive open-label pasireotide, whereas those on octreotide were no longer followed.

Study C2402: Pasireotide LAR 40 mg and pasireotide LAR 60 mg arms were double-blinded; the active control arm was not.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Study C2305: Double-blind pasireotide LAR (40 mg every 28 days) and octreotide LAR (20 mg every 28 days)

Study C2402: Double-blind pasireotide LAR 40 mg, 60 mg, and open-label octreotide LAR 30 mg or lanreotide ATG 120 mg

4.2.6.2 Sponsor's Justification for Doses

For Efficacy: Results from a phase 2 study B2201 with pasireotide sc indicated that the effective concentration (Ceffective) required for GH normalization was 5.09±4.19 ng/mL in patients with acromegaly, and that doses of 0.6 mg bid and higher should be tested in further clinical development. In Study C2110, trough concentrations achieved at steady-state with 40 mg (5.92±2.85 ng/mL) and 60 mg pasireotide LAR (8.87±4.53 ng/mL) but not 20 mg LAR (2.74±1.33 ng/mL) were above Ceffective for GH normalization. As the 40 mg dose (q28d) with the LAR formulation is the closest to the dose strength of the pasireotide sc 0.6 mg bid dose in terms of monthly dose loading (i.e. 1.2 mg/day × 28 days = 33.6 mg q28d), pasireotide LAR 40 mg q28d was chosen as the starting dose in Study C2305, and as one of two pasireotide doses that were explored in Study C2402. Because some patients may require doses higher or lower than 40 mg of pasireotide LAR, a dose increase to 60 mg was permitted in Study C2305 for patients who did not achieve biochemical control after 3 months (i.e. at steady-state) of treatment, and the 60 mg dose was included as a randomized treatment in Study C2402.

For QT assessment: Two thorough clinical QT/QTc (TQT) studies were conducted in healthy volunteers to evaluate the effect of pasireotide sc on cardiac repolarization, as detected by QT/QTc prolongation (Study B2113 and Study B2125). For the pasireotide sc formulation, the observed Cmax,ss (mean±SD) at the supra-therapeutic dose of 1950 µg bid (as MTD; maximum tolerated dose) was comparable between Study B2113 and Study B2125: 80.3±15.8 ng/mL (Study B2113; Part I, n=6) and 67.1±27.3 ng/mL (Study B2113; Part II, n=84), versus 80.6±25.3 ng/mL (Study B2125; n=103). The Cmax,ss for the therapeutic dose of 600 µg bid was 24.3±7.20 ng/mL (Study B2125; n=105). For the pasireotide LAR formulation, the mean values of predicted Cmax,ss for the highest therapeutic doses in acromegaly patients would be 25.8 ng/mL (60 mg for patients with normal liver function) and 28.7 ng/mL (40 mg for patients with moderate hepatic impairment) which were similar to the observed mean Cmax,ss 24.3 ng/mL from the sc 600 µg bid in healthy volunteers with normal liver function. As such, Cmax,ss 80.6 ng/mL from sc MTD 1950 µg bid in healthy volunteers with normal liver function is approximately three-fold coverage for Cmax,ss over the highest therapeutic doses of LAR formulation in acromegaly patients.

Based on the Cmax,ss comparison mentioned above, ΔΔQTcI (i.e., QTcI change from baseline compared to placebo) and ΔΔQTcF (i.e., QTcF change from baseline compared to placebo) at the highest therapeutic doses of LAR in acromegaly patients are expected

to be similar to those from the 600 µg bid sc (maximum mean ΔΔQTcI 13.2 ms; maximum mean ΔΔQTcF 11.8 ms) and fully covered by those observed at the 1950 µg bid sc dose (maximum mean ΔΔQTcI 16.1 ms; maximum mean ΔΔQTcF 14.0 ms). As such, the results from the two TQT studies conducted with the sc formulation (Study B2113, Study B2125), are adequate and sufficient to characterize the potential effect of the LAR formulation on QT intervals.

Data from the pivotal Ph III study C2305, following pasireotide LAR 40 mg im depot injection once every 28 days in acromegaly patients up to crossover, with possible dose modification (20 or 60 mg LAR) are in line with above assumption, no patient experienced a newly occurring QTcF over 500 ms. Three patients (1.7%) in the pasireotide LAR arm experienced a newly occurring QTcF of over 480 ms. Notable increases in QTcF of >30 ms and >60 ms were observed in 14.6% (26 patients) and 1.1% (two patients) of the patients in the pasireotide LAR arm, respectively. After crossover from octreotide to pasireotide, no QTcF values >500 ms were reported. One patient who crossed over to pasireotide had a QTcF value that was >480 ms and which had increased by >60 ms from baseline, which was reported as an AE.

Reviewer's Comment: Acceptable. IRT has reviewed sponsor's justification and agreed that the TQT studies performed with pasireotide s.c. formulation would cover the potential effect of pasireotide LAR formulation on QT interval.

4.2.6.3 Instructions with Regard to Meals

Meals and food were allowed during treatment.

Reviewer's Comment: This is a product of intramuscular administration; thus food effects are not anticipated.

4.2.6.4 ECG and PK Assessments

Study C2305

ECG: One 12-lead electrocardiogram (ECG) and rhythm strip will be performed at Visits 1 (to assess eligibility) and at all visits throughout the study, except at visits 3 and 6. Every 3 months (at Visit 2, 7, 10 and 13 and EOS visit) an ECG and rhythm strip will be performed prior to and 30 minutes after the LAR injection.

PK: Starting at visit 2 and through study completion (EOS visit), except visits 3, one blood sample for PK assessment will be taken at pre-dose (t0) with respect to the LAR i.m. injection. As a requirement introduced with Amendment 5 - for all patients in the core study or extension - one additional visit is required. Patients were asked to return once - on Day 21 after the last or next scheduled injection for an ECG recording and PK sampling as soon as the amendment was approved at the site.

Study C2402

ECG: ECGs were performed at all visits for patients randomized to the double-blind pasireotide LAR treatment arms. ECGs will be performed at all visits except for visit 3 and visit 7 for patients randomized to the open-label, active control arm (octreotide LAR, lanreotide ATG).

PK: Visit schedules for pasireotide LAR PK blood sampling are shown in Table 3. As a requirement introduced with Amendment 5 - patients were asked to return once - on Day 21 after the last or next scheduled injection for an ECG recording and PK sampling as soon as the amendment was approved at the site.

Table 3. Pasireotide LAR pharmacokinetic blood collection plan –Study 2402

Sample	Volume (mL)	Visit #	Week #	Day #	PK Collection #	Sample #	Scheduled time (hr)
Blood	2.5	2	0	0	1	1	0 (pre-dose)
Blood	2.5	3	3	20	1	2	0
Blood	2.5	4	4	28	2	3	0 (pre-dose)
Blood	2.5	5	8	56	3	4	0 (pre-dose)
Blood	2.5	6	12	84	4	5	0 (pre-dose)
Blood	2.5	7	15	104	4	6	0
Blood	2.5	8	16	112	5	7	0 (pre-dose)
Blood	2.5	9	20	140	6	8	0 (pre-dose)
Blood	2.5	10	24	168	6	9	0[1]
Blood[2]	2.5	Unscheduled	Unscheduled	Unscheduled	NA	1001, 1002…..	NA

[1] Please note: this sampling is considered post-dose in the core study (in reference to Visit 9 administration). However, for patients participating in the extension study, Visit 10 will also be considered as the first visit of the extension study. Therefore, PK sampling should be taken prior to the first administration of pasireotide LAR in the extension study.
[2] In case of abnormal liver function criteria (refer to Section 7.5.2.3) a PK sample needs to be collected.

Source: Clinical Study Report No. CSOM230C2402, Table 7-2, Page 4602

Reviewer's Comment: Study C2305 and C2402 are not dedicated TQT studies. The timing of ECGs and PK assessment for exploring the exposure-QTc purposes is acceptable.

4.2.6.5 Baseline

Baseline is defined as the last available value prior to study drug start.

4.2.7 ECG Collection

Study C2305

ECG: One 12-lead electrocardiogram (ECG) and rhythm strip will be performed at Visits 1 (to assess eligibility) and at all visits throughout the study, except at visits 3 and 6. Every 3 months (at Visit 2, 7, 10 and 13 and EOS visit) an ECG and rhythm strip will be performed prior to and 30 minutes after the LAR injection.

Study C2402

ECG: ECGs were performed at all visits for patients randomized to the double-blind pasireotide LAR treatment arms. ECGs will be performed at all visits except for visit 3 and visit 7 for patients randomized to the open-label, active control arm (octreotide LAR, lanreotide ATG).

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Study C2402

A total of 198 patients were randomized, of whom six patients did not receive study treatment. Two of these six patients had incorrect data entered in the Dosing CRF and are therefore listed as treated in **Table 4**. Of the 192 patients treated, the majority completed the 24-week core phase and entered the optional extension. Discontinuations prior to Week 24 were as follows: six patients (9.2%) from pasireotide LAR 40 mg, eight patients (12.3%) from pasireotide LAR 60 mg, and three patients (4.4%) from active control. Baseline demographic characteristics are presented in

Table 5**.**

Table 4. Patient disposition by treatment –Study 2402

Disposition Reason	SOM LAR 40 mg N=65 n (%)	SOM LAR 60 mg N=65 n (%)	Active control N=68 n (%)
Patients randomized			
Not treated	2 (3.1)	1 (1.5)	1 (1.5)
Treated	63 (96.9)	64 (98.5)*	67 (98.5)*
Completed 24-week core phase	59 (90.8)	57 (87.7)	65 (95.6)
Not continuing into extension	3 (4.6)	4 (6.2)	3 (4.4)
Continuing into extension	56 (86.2)	53 (81.5)	62 (91.2)
Discontinued core phase	6 (9.3)	8 (12.3)	3 (4.4)
AEs	2 (3.1)	4 (6.2)	0
Patient withdrew consent	2 (3.1)	2 (3.1)	2 (2.9)
Administrative problems	2 (3.1)	1 (1.5)	0
Protocol deviation	0	1 (1.5)	1 (1.5)

FAS: Full analysis set

*Patient C2402-0340-00002 (Active control) and patient C2402-0340-00004 (pasireotide LAR 60 mg) did not receive any study medication but had incorrect data entered in the Dosing CRF. These patients are incorrectly counted in the Treated row, instead of the Not treated row.

Source: Table 14.1-1.1

Table 5. Demographic summary by treatment group (FAS) –Study 2402

	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
Age (years)			
n	65	65	68
Mean (SD)	42.9 (14.05)	45.8 (14.07)	46.2 (13.11)
Median	46.0	45.0	46.5
Min - max	18 - 80	20 - 83	18 - 74
Age category (years), n (%)			
<65	62 (95.4)	57 (87.7)	63 (92.6)
≥ 65	3 (4.6)	8 (12.3)	5 (7.4)
Gender, n (%)			
Female	38 (58.5)	35 (53.8)	38 (55.9)
Male	27 (41.5)	30 (46.2)	30 (44.1)
Race, n (%)			
Caucasian	53 (81.5)	52 (80.0)	56 (82.4)
Black	3 (4.6)	8 (12.3)	4 (5.9)
Asian	3 (4.6)	1 (1.5)	0
Other	4 (6.2)	3 (4.6)	7 (10.3)
Native American	2 (3.1)	1 (1.5)	1 (1.5)
Ethnicity, n (%)			
Hispanic/Latino	28 (43.1)	36 (55.4)	31 (45.6)
Indian (Indian subcontinent)	1 (1.5)	0	0
Japanese	1 (1.5)	0	0
Mixed ethnicity	0	1 (1.5)	1 (1.5)
Other	35 (53.8)	27 (41.5)	35 (51.5)
Missing	0	1 (1.5)	1 (1.5)
Weight (kg)			
n	64	65	68
Mean (SD)	84.2 (19.12)	86.2 (19.81)	85.9 (18.10)
Median	79.6	85.0	82.0
Min - max	54.0 - 142.5	55.0 - 139.2	48.0 - 131.6
Height (cm)			
n	62	64	67
Mean (SD)	169.5 (11.00)	170.2 (10.65)	170.1 (11.48)
Median	167.0	169.0	171.0
Min - max	149.0 - 200.0	152.0 - 196.0	146.0 - 195.0
Body mass index (kg/m^2)			
n	62	64	67
Mean (SD)	29.1 (4.97)	29.8 (6.20)	29.5 (5.69)
Median	28.4	27.5	28.2
Min -max	20.0 - 42.1	21.8 - 49.9	19.2 - 48.0
Mean GH (µg/L)			
n	65	65	68
Mean (SD)	17.6 (35.75)	12.1 (21.76)	9.5 (12.02)
Median	7.1	5.3	6.1
Min- max	0.98 – 200.00	1.44 – 113.80	0.96 – 92.38
Standardized IGF-1			
n	65	65	68
Mean (SD)	2.6 (1.05)	2.8 (1.13)	2.9 (1.10)
Median	2.3	2.6	2.9
Min - max	0.93 – 6.21	1.10 – 6.71	1.10 – 5.96

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Study 2402:

ECG changes from baseline over time were similar between the two pasireotide LAR doses and active control (Table 14.3-4.9). There was no trend towards prolongation of mean QTcFor QTcB values over time (mean QTcF values ranged between 410 and 422 ms at all visits up to Week 24 in the three treatment groups).

ECG interval: QT Interval fridericia (corr.) (ms)

Visit / Treatment	Actual n	Actual mean	Actual SD	Actual median	Change from baseline n	Change from baseline mean	Change from baseline SD	Change from baseline median	Change from baseline 90% CI
Baseline									
SOM LAR 40 mg (N=63)	61	419.9	20.87	425.0					
SOM LAR 60 mg (N=62)	61	414.2	21.43	416.0					
Active control (N=66)	65	413.9	21.93	417.0					
Week 3									
SOM LAR 40 mg (N=63)	59	420.4	22.59	427.0	59	0.25	17.490	2.00	(-3.55, 4.06)
SOM LAR 60 mg (N=62)	54	415.8	20.74	418.0	54	0.85	16.520	-1.00	(-2.91, 4.62)
Active control (N=66)	0	0	0	0	0	0	0	0	
Week 4									
SOM LAR 40 mg (N=63)	59	419.7	18.71	417.0	59	-0.10	15.826	0.00	(-3.55, 3.34)
SOM LAR 60 mg (N=62)	57	415.5	20.43	417.0	57	0.74	14.753	-1.00	(-2.53, 4.01)
Active control (N=66)	61	415.9	21.14	414.0	61	2.25	20.200	-1.00	(-2.08, 6.57)
Week 8									
SOM LAR 40 mg (N=63)	60	419.2	20.94	418.5	60	-0.73	16.470	3.00	(-4.29, 2.82)
SOM LAR 60 mg (N=62)	57	417.2	20.36	419.0	57	3.05	18.654	2.00	(-1.08, 7.19)
Active control (N=66)	63	415.0	20.15	419.0	63	2.03	17.542	2.00	(-1.66, 5.72)
Week 12									
SOM LAR 40 mg (N=63)	59	421.5	20.78	422.0	59	1.90	19.935	3.00	(-2.44, 6.24)
SOM LAR 60 mg (N=62)	58	416.7	23.26	420.0	58	1.76	19.686	-5.00	(-2.56, 6.08)
Active control (N=66)	59	416.8	19.49	418.0	59	3.78	15.511	2.00	(0.40, 7.16)

- Baseline is defined as the last available value prior to study drug start.
- If more than one measurement was available during any time point, the average is used.
- For each ECG interval, only patients with a value at both baseline and at least one one post baseline within the defined time period are included.
- Includes scheduled visits only.

Reviewer's Comments: please see reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

There is no assay sensitivity analysis for both studies.

4.2.8.2.3 Categorical Analysis

Study 2305:

Up to crossover

The proportion of patients with newly occurring notable QT/QTc intervals was comparable between pasireotide and octreotide groups up to crossover, with few notable outlying values (Table 12-32). No patient had a QTcF value >500 ms. QTcF >480 ms was reported for 3 vs. 2 patients in the pasireotide and octreotide groups, respectively, and QTcF >60 ms prolonged from baseline was reported for 2 vs. 1 patients in the respective groups.

One patient (C2305-0904-00015) in the octreotide group discontinued treatment due to QTc prolongation. The patient had a QTcB value >500 ms (QTcF 485 ms) predose of her second LAR injection. At the next scheduled visit the patient's QTcF and QTcB were normal (451 ms and 434 ms, respectively). The patient's screening QTcF and QTcB were

unremarkable at 453 ms and 460 ms, respectively, however baseline (i.e. Day 1 predose) QTcF and QTcB were prolonged at 488 ms and 485 ms, respectively.

After crossover:

The proportion of patients with newly occurring notable QT/QTc abnormalities were comparable after crossover (Table 12-33). No QTcF values >500 ms were reported. One patient who crossed over to pasireotide had a QTcF value that was >480 ms and >60 ms increased from baseline (C2305-0771-00003; the abnormality was reported as an AE (see narrative in Section 14.3.3 for details).

Study 2402:

QTcF intervals >450 ms were observed in 18.6% and 15.3% of patients in the pasireotide LAR 40 mg and 60 mg groups, and in 10.9% of patients in the active control group (Table 12-17). One patient (pasireotide LAR 40 mg) had a QTcF interval >480 ms. No patient had a QTcF >500 ms, or a QTcF interval >60 ms increase from baseline. No AEs related to QT prolongation were reported during the study (Table 14.3.1-5.1).

One patient (C2402-0156-00003 in the active control group) had a QTcF equal to 462 ms at baseline and a QTcF equal to 480 ms on Day 30 (Listing 16.2.9-1.3). This patient discontinued with a reason reported as protocol deviation. The event was not reported as an AE.

4.2.8.3 Safety Analysis

Study 2305 up to crossover:

The most common grades 3-4 AEs for pasireotide LAR group were diabetes mellitus (5.1%) and hyperglycemia and blood creatine phosphokinase increased (3.4% each). In the octreotide LAR group most common grade 3-4 AEs were diarrhea (2.8%) and headache (2.8%).

AEs that were more frequent (at least 5% difference) in the pasireotide LAR group were mostly related to glucose metabolism: hyperglycemia, diabetes mellitus, blood glucose increased, and type 2 diabetes mellitus (Table 2-2). AEs that were less frequent in the pasireotide LAR than octreotide LAR were mostly related to GI disorders: diarrhea (39.9% vs. 45.0%), cholelithiasis (32.6% vs. 39.4%), abdominal pain (18.5% vs. 24.4%), nausea (15.2% vs. 22.8%) and constipation (5.6% vs. 10.6%).

Study 2402:

In Study C2402 most patients in all 3 treatment groups experienced at least one AE during the study. Metabolism and nutrition disorders was the most frequent SOC in all 3 treatment groups. Most frequent AEs are presented in Table 2-3. The three common AEs in the pasireotide LAR 40 mg and 60 mg groups were hyperglycemia (33.3% and 30.6%) and diabetes mellitus (20.6% and 25.8%), followed by diarrhea (15.9% and 19.4%). In the active control group they were hyperglycemia and cholelithiasis (13.6% each) and diabetes mellitus (7.6%). The type of AEs is similar to what was reported for medically naïve patients in Study C2305. The patients treated with pasireotide LAR (40 mg and 60

mg) had a higher incidence of grades 3-4 AEs than the patients treated with the active control (17.5% and 19.4% vs. 7.6%).

In the Study C2305 after crossover results were similar to Study C2402 and pooled inadequately controlled analysis (patient from Studies C2402 and C2305 after crossover). The most frequent AEs were hyperglycemia (30.9%) and diarrhea (24.7%) in the pasireotide LAR group and diarrhea (18.4%) and nasopharyngitis (18.4%) in the octreotide LAR group. The patients treated with pasireotide LAR had more high grades AEs (28.4% vs. 21.1% in octreotide LAR). The difference was mainly due to a higher frequency of grade 3-4 hyperglycemia (4.9% vs. none) and diabetes mellitus (2.5% vs. none).

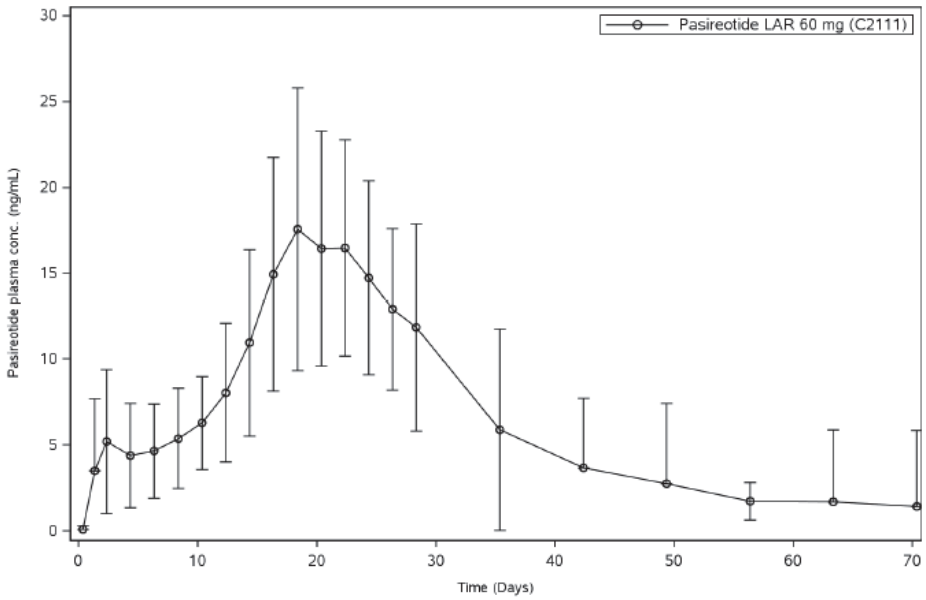
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Median plasma concentration-time profiles for pasireotide LAR in healthy volunteers and acromegaly patients are presented in **Figure 1** and

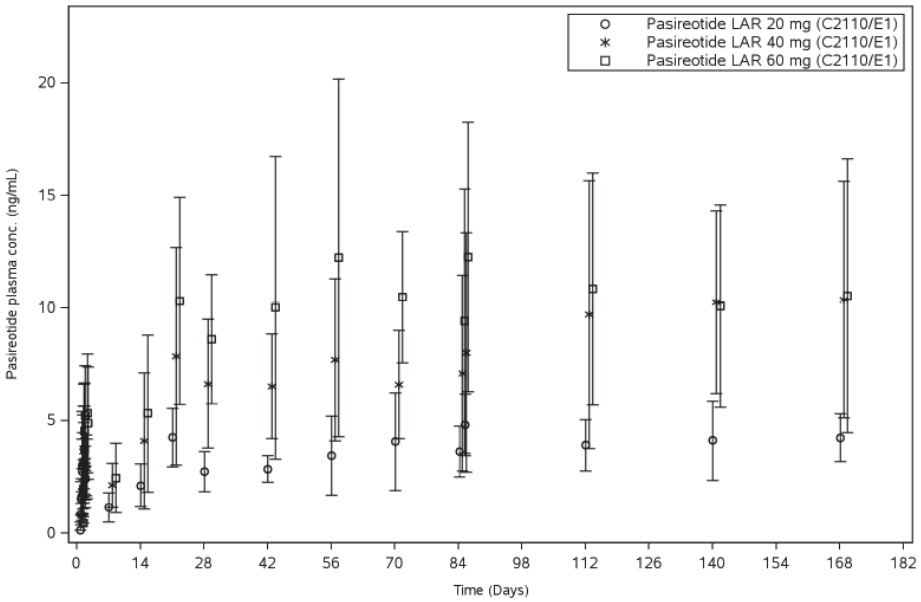
Figure 2. Median plasma pasireotide concentration-time profiles in study C2305 and C2402 are presented in **Figure 3** and **Figure 4**. Following administration of 1950 µg s.c. b.i.d, C_{max} and AUC values in the thorough QT study were approximately 3-fold what was seen with 60 mg and 40 mg pasireotide LAR, the intended clinical dose.

Figure 1: Mean (SD) plasma concentration versus time profile for pasireotide LAR 60 mg in healthy volunteers (Study C2111)



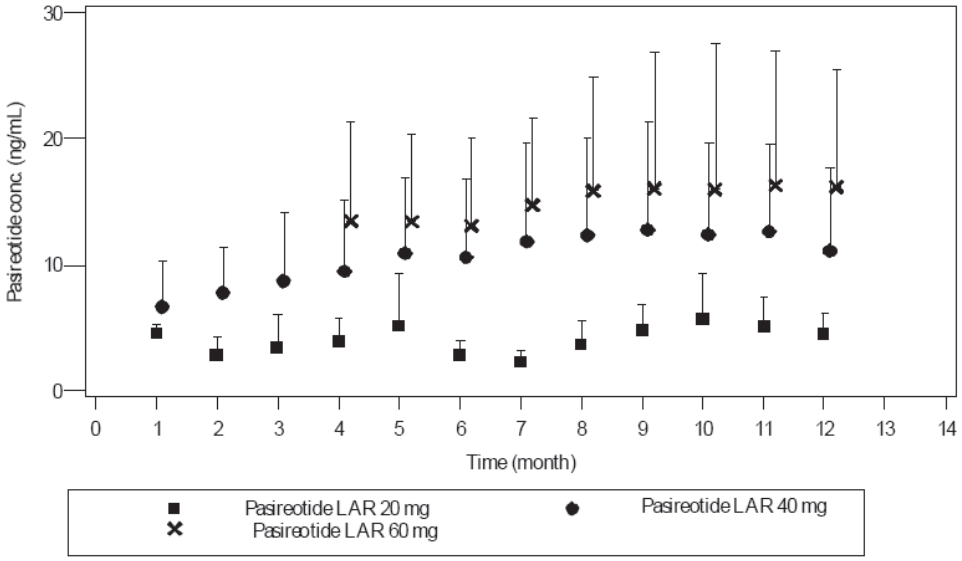
Source: Summary of Clinical Pharmacology, Figure 3-1, Page 42

Figure 2: Time profiles of pasireotide following six monthly im injections of 20, 40 and 60 mg pasireotide LAR in acromegaly patients (Phase2 Study C2110)



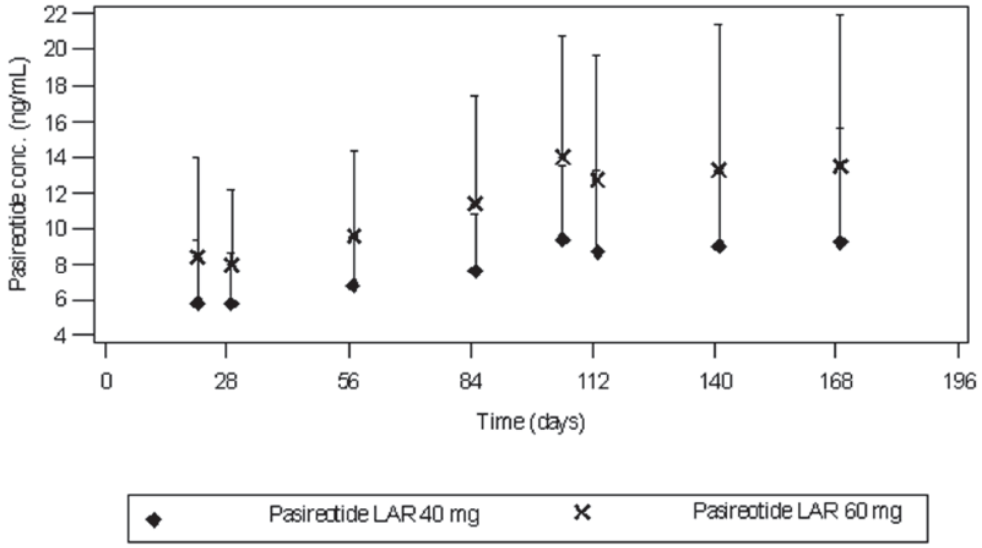
Source: Summary of Clinical Pharmacology, Figure 3-2, Page 43

Figure 3: Mean (SD) plasma concentration versus time profiles by incident dose following pasireotide LAR 20, 40 and 60 mg in medically naïve acromegaly patients (Study C2305)



Source: Summary of Clinical Pharmacology, Figure 3-3, Page 44

Figure 4: Mean (SD) plasma concentration versus time profiles by incident dose following pasireotide LAR 40 and 60 mg in inadequately controlled acromegaly patients (Study C2402)

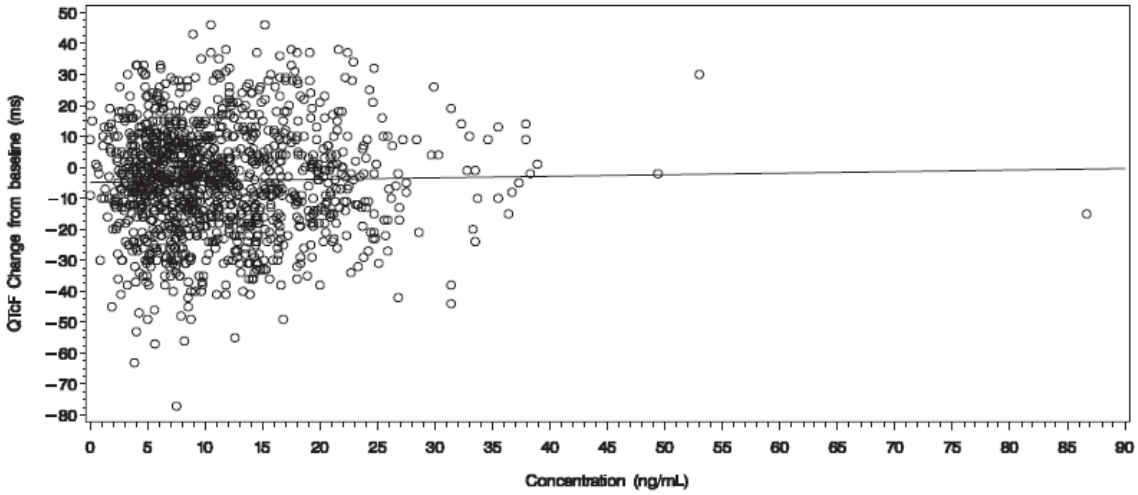


Source: Summary of Clinical Pharmacology, Figure 3-4, Page 46

4.2.8.4.2 Exposure-Response Analysis

Linear mixed models were used to explore the relationships of QTcF and QTcB with pasireotide LAR concentration for both studies. Overall, a relatively flat relationship was shown for pasireotide concentration with both QTcB and QTcF (**Figure 5** and **Figure 6**). The relationship between pasireotide LAR concentration and QTcF was not statistically significant. The relationship between pasireotide LAR concentration and QTcB was found to be statistically significant, with increasing concentration causing a larger reduction from baseline QTcB (**Table 6** and **Table 7**). However, it was claimed that there was one extreme outlier which may have driven this relationship and without which the relationship was relatively flat.

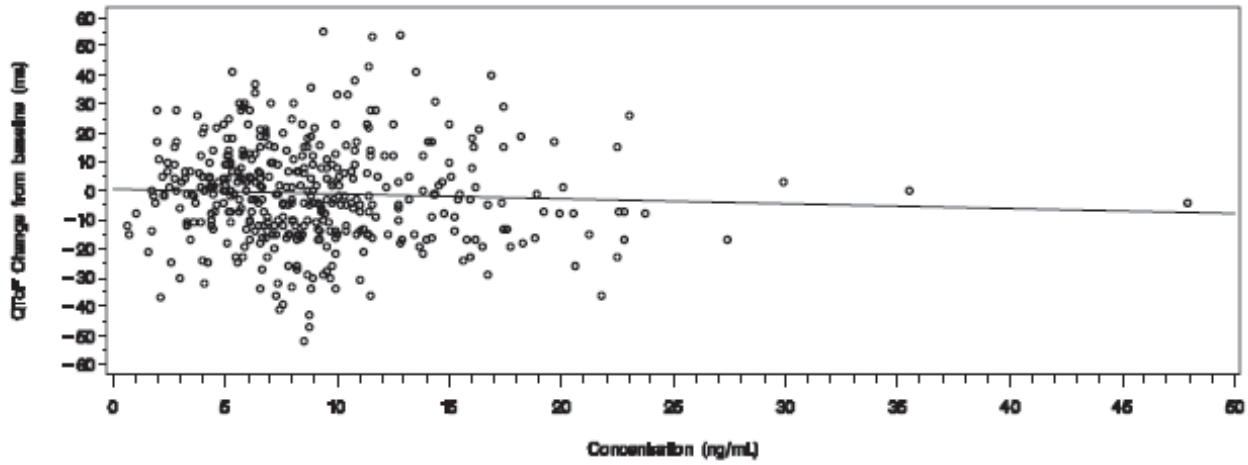
Figure 5: ΔQTcF vs. pasireotide plasma concentration (Study C2305)



Regression Equation:
CHGECG = -4.903474 + 0.050223*CONC1N

Source: Clinical Study Report No. CSOM230C2305, Figure 14.2-24.1, Page 1099

Figure 6: ΔQTcF vs. pasireotide plasma concentration (Study C2402)



Regression Equation:
CHGECG = 0.677235 - 0.166737* CONC1N

Source: Clinical Study Report No. CSOM230C2402, Figure 14.2-6.9, Page 474

Table 6. Estimated ΔQTcF and ΔQTcB from linear mixed model on pasireotide concentration vs. ΔQTcF and ΔQTcB, separately (Study C2305)

Dose	Label	Concentration (ng/mL)	QTcF change from baseline Estimate * (90% CI)	QTcB change from baseline Estimate ** (90% CI)
40 mg	At 25th percentile trough concentration	6.25	-4.48 (-6.00, -2.95)	-12.53 (-14.37,-10.68)
	At Median trough concentration	9.70	-4.33 (-5.78, -2.87)	-12.98 (-14.74,-11.22)
	At mean trough concentration	11.22	-4.26 (-5.71, -2.81)	-13.18 (-14.94,-11.43)
	At 75th percentile trough concentration	14.40	-4.12 (-5.61, -2.64)	-13.60 (-15.40,-11.81)
	At 25th percentile Cmax concentration	8.19	-4.39 (-5.87, -2.91)	-12.78 (-14.57,-11.00)
	At Median Cmax concentration	12.30	-4.21 (-5.67, -2.76)	-13.33 (-15.08,-11.57)
	At mean Cmax concentration	13.34	-4.17 (-5.63, -2.70)	-13.46 (-15.23,-11.69)
	At 75th percentile Cmax concentration	16.40	-4.03 (-5.57, -2.50)	-13.87 (-15.72,-12.01)
60 mg	At 25th percentile trough concentration	9.65	-4.33 (-5.79, -2.87)	-12.98 (-14.74,-11.21)
	At Median trough concentration	14.40	-4.12 (-5.61, -2.64)	-13.60 (-15.40,-11.81)
	At mean trough concentration	15.43	-4.08 (-5.59, -2.57)	-13.74 (-15.56,-11.92)
	At 75th percentile trough concentration	19.40	-3.90 (-5.56, -2.25)	-14.26 (-16.26,-12.26)

Source: Clinical Study Report No. CSOM230C2305, Figure 14.2-3.20, Page 918

Table 7. Estimated ΔQTcF and ΔQTcB from linear mixed model on pasireotide concentration vs. ΔQTcF and ΔQTcB, separately (Study C2402)

Dose	Percentile	Concentration (ng/mL)	QTcF change from baseline Estimate *(90% CI)	QTcB change from baseline Estimate **(90% CI)
SOM LAR 40 mg	At 25th percentile trough concentration	5.90	-0.17 (-2.43, 2.09)	0.54 (-2.25, 3.34)
	At median trough concentration	8.05	-0.43 (-2.57, 1.71)	-0.13 (-2.78, 2.51)
	At mean trough concentration	8.81	-0.52 (-2.64, 1.60)	-0.37 (-3.00, 2.26)
	At 75th percentile trough concentration	10.60	-0.73 (-2.87, 1.41)	-0.93 (-3.58, 1.72)
	At 25th percentile Cmax concentration	5.03	-0.07 (-2.41, 2.27)	0.82 (-2.06, 3.70)
	At median Cmax concentration	7.02	-0.31 (-2.49, 1.88)	0.19 (-2.51, 2.89)
	At mean Cmax concentration	7.88	-0.41 (-2.55, 1.74)	-0.08 (-2.73, 2.57)
	At 75th percentile Cmax concentration	9.74	-0.63 (-2.75, 1.49)	-0.66 (-3.29, 1.96)
SOM LAR 60 mg	At 25th percentile trough concentration	8.17	-0.44 (-2.58, 1.69)	-0.17 (-2.81, 2.47)
	At median trough concentration	10.85	-0.76 (-2.91, 1.39)	-1.01 (-3.67, 1.65)
	At mean trough concentration	12.66	-0.98 (-3.24, 1.29)	-1.58 (-4.37, 1.21)
	At 75th percentile trough concentration	15.05	-1.26 (-3.77, 1.25)	-2.33 (-5.42, 0.76)
	At 25th percentile Cmax concentration	6.33	-0.22 (-2.45, 2.00)	0.41 (-2.34, 3.16)
	At median Cmax concentration	10.15	-0.68 (-2.81, 1.45)	-0.79 (-3.43, 1.84)
	At mean Cmax concentration	11.21	-0.80 (-2.97, 1.36)	-1.12 (-3.80, 1.55)
	At 75th percentile Cmax concentration	15.00	-1.25 (-3.76, 1.25)	-2.32 (-5.40, 0.76)

Source: Clinical Study Report No. CSOM230C2402, Figure 14.2-3.12, Page 275

Reviewer's Comments: A relatively shallow relationship was shown between pasireotide LAR concentration and change from baseline for both QTcF and QTcB. Specifically, the coefficient parameter for concentration in the linear mixed model was negative but close to zero, with estimated ΔQTcF and ΔQTcB all close to zero at the expected Cmax pasireotide LAR concentration at 40 mg or 60 mg.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB) for both studies. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis.

Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment											
	Active Control		Octreotide LAR		Pasireotide LAR		SOM LAR 40 mg		SOM LAR 60 mg		All	
method	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**
QTcB	66	0.0181	180	0.0091	178	0.0117	63	0.2986	61	0.0111	543	0.0448
QTcF	66	0.0071	180	0.0025	178	0.0041	63	0.2590	61	0.0039	543	0.0335

The relationship between different correction methods and RR for study C2305 and C2402 are presented in **Figure 7** and Figure 8: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line) - Study C2402, respectively.

Figure 7: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line) – Study C2305

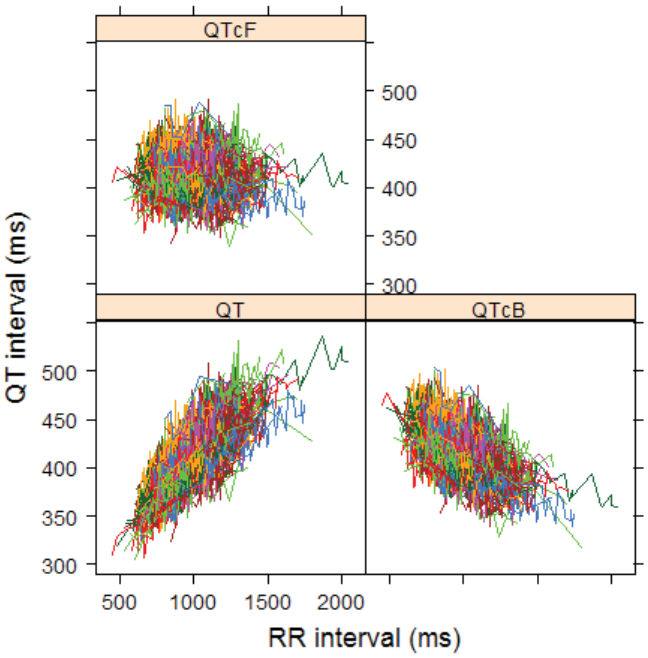
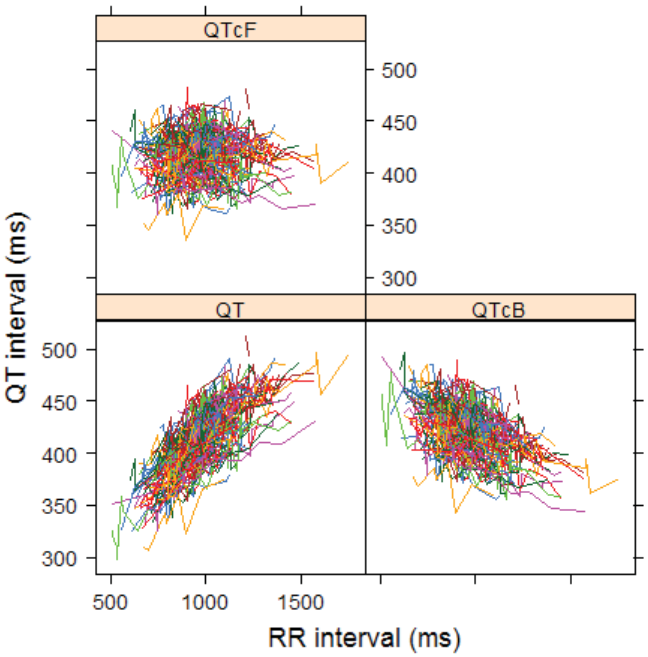


Figure 8: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line) - Study C2402



5.2 Statistical Assessments

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

Both studies are not TQT studies. The statistical reviewer used descriptive analysis of the ΔQTcF effect. The analysis results are listed in the following tables.

Table 9: Analysis Results of ΔQTcF for Study 2305

	Treatment Group					
	Octreotide LAR			Pasireotide LAR		
	dQTcF			dQTcF		
Visit	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)
2	-2.4	-4.3	-0.6	-1.1	-3.3	1.0
4	-1.2	-3.9	1.4	-1.3	-3.7	1.1
5	-1.7	-4.3	0.8	-4.7	-7.1	-2.2
7	-2.8	-4.7	-1.0	-3.8	-5.5	-2.0
8	-3.8	-6.4	-1.2	-4.0	-6.7	-1.2
9	-2.5	-5.2	0.1	-5.3	-7.8	-2.8
10	-2.5	-4.5	-0.5	-4.0	-6.1	-1.8
11	-2.1	-4.9	0.6	-4.3	-7.1	-1.4
12	-1.6	-4.1	0.9	-3.9	-6.7	-1.1
13	-2.9	-5.0	-0.8	-3.6	-5.7	-1.5
14	-0.9	-3.8	2.1	-5.7	-8.6	-2.8
15	-4.2	-7.1	-1.3	-5.5	-8.3	-2.6
17	-5.0	-8.5	-1.4	-3.5	-7.3	0.2
19	-1.2	-4.2	1.9	-4.9	-8.1	-1.8
20	0.1	-2.9	3.2	-1.6	-5.0	1.8
22	0.3	-2.5	3.0	-3.2	-6.4	0.1
23	1.9	-1.5	5.4	-0.6	-4.1	2.9
24	2.2	-1.5	5.9	-2.3	-5.4	0.9
25	1.0	-2.0	3.9	-2.8	-6.5	0.9
26	0.7	-2.6	3.9	-0.7	-4.5	3.1

Table 10: Analysis Results of ΔQTcF for Study 2402

	Treatment Group								
	Active Control			SOM LAR 40 mg			SOM LAR 60 mg		
	dQTcF			dQTcF			dQTcF		
Visit	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)
End of Study	2.4	-2.0	6.8	-2.6	-7.3	2.1	2.4	-2.7	7.6
Unscheduled visit	-0.9	-5.1	3.3	-11.3	-21.0	-1.5	-2.2	-7.7	3.3
Visit 3	.	.	.	0.3	-4.3	4.8	0.9	-3.7	5.4
Visit 4	2.2	-2.9	7.4	-0.1	-4.2	4.0	0.7	-3.2	4.7
Visit 5	2.0	-2.4	6.4	-0.7	-5.0	3.5	3.1	-1.9	8.0
Visit 6	3.8	-0.3	7.8	1.9	-3.3	7.1	1.8	-3.4	6.9
Visit 7	.	.	.	-1.4	-7.0	4.2	-0.4	-5.9	5.1
Visit 8	1.3	-3.7	6.2	-6.1	-10.6	-1.6	-1.0	-5.9	4.0
Visit 9	3.7	-0.5	7.9	-6.0	-10.9	-1.1	1.3	-4.5	7.2

None of the treatment group has upper bound > 10 ms at any visit.

5.2.1.2 Assay Sensitivity Analysis

Not applicable since there is no moxifloxacin arm.

5.2.1.3 Graph of ΔQTcF over Time

The following figure displays the time profile of ΔQTcF for different treatment groups.

Figure 9: Mean and 90% CI ΔQTcF by Visit for Study 2305

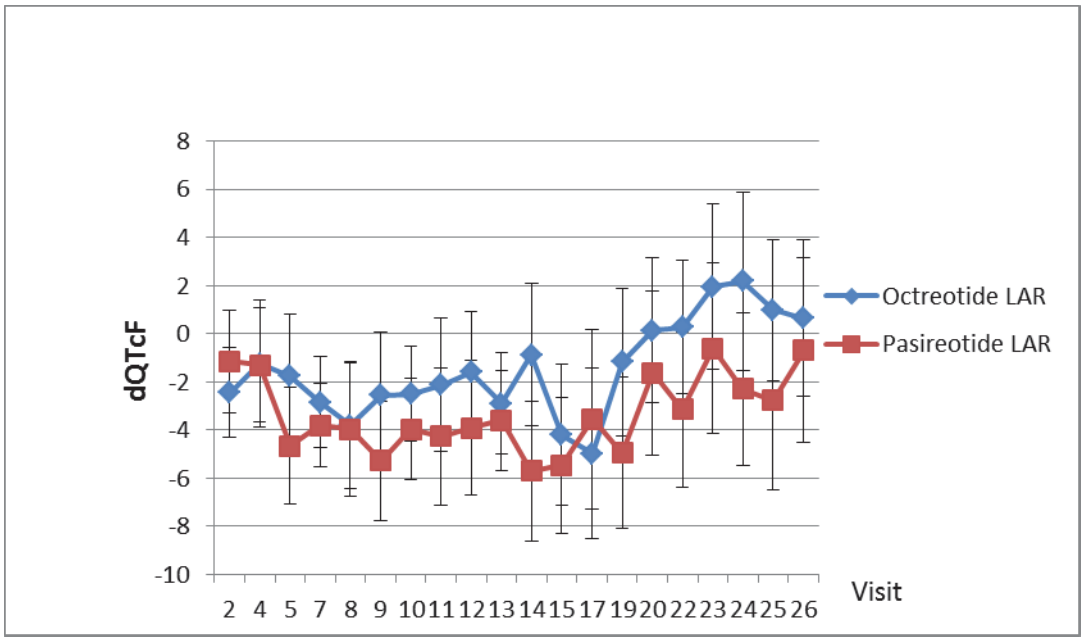
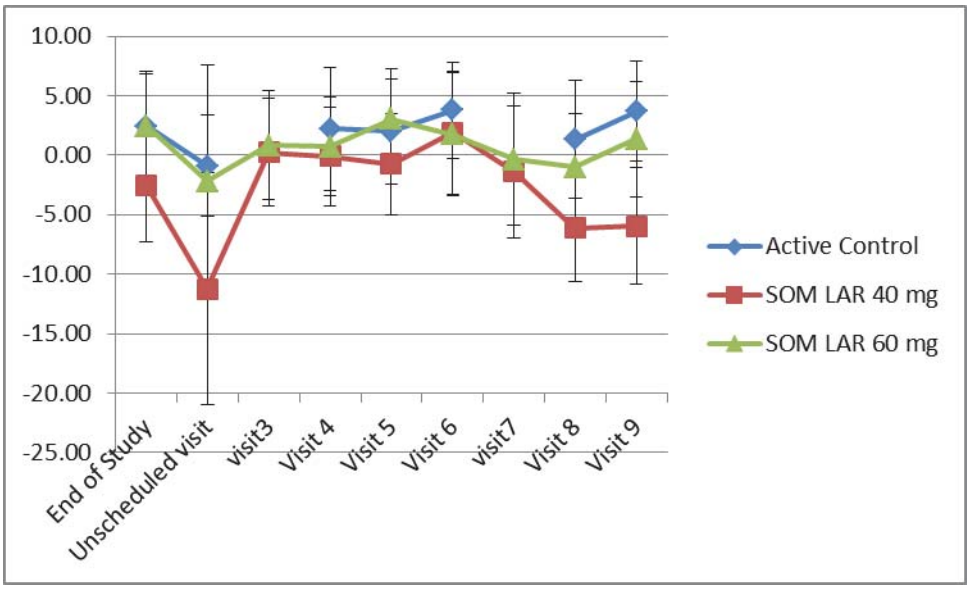


Figure 10: Mean and 90% CI ΔQTcF by Visit for Study 2402



5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms for both studies.

Table 11: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Active Control	66	408	57 (86.4%)	394 (96.6%)	9 (13.6%)	14 (3.4%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)
Octreotide LAR	180	4421	136 (75.6%)	4272 (96.6%)	40 (22.2%)	143 (3.2%)	4 (2.2%)	6 (0.1%)	0 (.%)	0 (0.0%)
Pasireotide LAR	178	4048	148 (83.1%)	3946 (97.5%)	27 (15.2%)	99 (2.4%)	3 (1.7%)	3 (0.1%)	0 (.%)	0 (0.0%)
SOM LAR 40 mg	63	480	50 (79.4%)	453 (94.4%)	12 (19.0%)	26 (5.4%)	1 (1.6%)	1 (0.2%)	0 (.%)	0 (0.0%)
SOM LAR 60 mg	61	474	50 (82.0%)	448 (94.5%)	11 (18.0%)	26 (5.5%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)

Table 12 lists the categorical analysis results for ΔQTcF for both studies.

Table 12: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Active Control	65	403	51 (78.5%)	375 (93.1%)	14 (21.5%)	28 (6.9%)	0 (0.0%)	0 (0.0%)
Octreotide LAR	180	4421	128 (71.1%)	4268 (96.5%)	50 (27.8%)	151 (3.4%)	2 (1.1%)	2 (0.0%)
Pasireotide LAR	178	4034	144 (80.9%)	3903 (96.8%)	32 (18.0%)	129 (3.2%)	2 (1.1%)	2 (0.0%)
SOM LAR 40 mg	61	474	50 (82.0%)	458 (96.6%)	11 (18.0%)	16 (3.4%)	0 (0.0%)	0 (0.0%)
SOM LAR 60 mg	60	467	48 (80.0%)	438 (93.8%)	12 (20.0%)	29 (6.2%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The descriptive analysis and the 90% confidence intervals are presented in Table 13 and Table 14.

Table 13: Analysis Results of ΔHR for Study 2305

	Treatment Group					
	Octreotide LAR			Pasireotide LAR		
	dHR			dHR		
Visit	Mean (bpm)	Lower 95% (bpm)	Upper 95% (bpm)	Mean (bpm)	Lower 95% (bpm)	Upper 95% (bpm)
2	-3.8	-4.7	-2.8	-1.0	-2.0	0.1
4	-7.7	-9.0	-6.3	-7.7	-9.3	-6.0
5	-7.4	-8.8	-6.0	-8.0	-9.5	-6.5
7	-8.6	-9.7	-7.5	-9.4	-10.6	-8.2
8	-5.9	-7.7	-4.1	-9.0	-10.6	-7.4
9	-7.9	-9.2	-6.5	-8.4	-10.1	-6.7
10	-8.3	-9.3	-7.3	-8.8	-10.1	-7.5
11	-6.8	-8.3	-5.3	-7.8	-9.4	-6.1
12	-6.8	-8.3	-5.3	-8.0	-10.0	-6.1
13	-7.3	-8.3	-6.2	-8.6	-10.0	-7.3
14	-6.8	-8.3	-5.3	-7.2	-9.2	-5.1
15	-6.4	-7.9	-4.9	-8.3	-10.1	-6.5
17	-6.3	-8.0	-4.6	-8.4	-10.5	-6.3
19	-6.6	-8.4	-4.8	-9.0	-11.1	-7.0
20	-3.8	-5.5	-2.0	-5.7	-7.8	-3.5
22	-2.9	-4.4	-1.3	-4.9	-6.8	-3.0
23	-3.9	-5.7	-2.0	-6.4	-8.4	-4.5
24	-3.7	-5.5	-1.9	-4.3	-6.7	-1.9
25	-2.5	-4.4	-0.5	-4.6	-7.0	-2.3
26	-4.9	-7.0	-2.8	-7.3	-9.9	-4.7

Table 14: Analysis Results of ΔHR for Study 2402

	Treatment Group								
	Active Control			SOM LAR 40 mg			SOM LAR 60 mg		
	dHR			dHR			dHR		
Visit	Mean (bpm)	Lower 95% (bpm)	Upper 95% (bpm)	Mean (bpm)	Lower 95% (bpm)	Upper 95% (bpm)	Mean (bpm)	Lower 95% (bpm)	Upper 95% (bpm)
End of Study	-0.8	-3.5	2.0	-0.7	-3.0	1.6	-1.9	-4.6	0.9
Unscheduled visit	-1.5	-4.2	1.2	5.8	-0.4	12.1	-3.9	-9.7	2.0
Visit 3	.	.	.	-0.6	-3.6	2.4	-2.8	-5.3	-0.2
Visit 4	0.0	-2.2	2.2	0.3	-2.6	3.3	-3.2	-5.3	-1.0
Visit 5	-1.4	-3.7	1.0	1.7	-1.2	4.6	-0.4	-3.0	2.2
Visit 6	-1.5	-4.1	1.2	-1.7	-3.9	0.6	-3.0	-5.4	-0.6
Visit 7	.	.	.	2.6	-0.4	5.6	-1.1	-3.8	1.6
Visit 8	-0.3	-2.7	2.1	-0.1	-3.2	2.9	-1.2	-4.2	1.8
Visit 9	-0.0	-2.5	2.4	0.5	-2.3	3.3	-1.1	-3.9	1.6

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The descriptive analysis and the 90% confidence intervals are presented in Table 15 and Table 16.

The outlier analysis results for PR are presented in Table 17.

Table 15: Analysis Results of ΔPR for Study 2305

	Treatment Group					
	Octreotide LAR			Pasireotide LAR		
	dPR			dPR		
Visit	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)
2	0.5	-1.1	2.1	0.1	-1.5	1.7
4	4.8	2.7	6.9	3.1	1.1	5.1
5	3.1	0.8	5.3	3.3	1.1	5.4
7	4.2	2.8	5.7	4.2	2.7	5.7
8	4.3	2.2	6.3	1.9	-0.3	4.1
9	4.4	2.1	6.6	2.5	0.0	4.9
10	4.9	3.4	6.3	2.9	1.3	4.5
11	2.8	0.7	5.0	1.7	-0.8	4.2
12	3.3	1.2	5.4	2.4	0.3	4.5
13	4.5	2.8	6.1	2.0	0.4	3.7
14	4.1	1.8	6.3	3.2	1.0	5.4
15	2.8	0.4	5.2	2.6	0.1	5.1
17	5.7	3.2	8.2	4.2	1.4	7.1
19	3.4	0.7	6.1	4.0	1.2	6.8
20	3.2	0.8	5.5	2.5	-0.1	5.1
22	2.2	-0.1	4.6	1.2	-1.3	3.6
23	1.8	-0.7	4.3	1.5	-1.1	4.2
24	2.8	0.3	5.3	1.1	-2.0	4.2
25	1.6	-0.8	3.9	2.6	-0.0	5.3
26	3.6	0.9	6.4	4.9	1.6	8.2

Table 16: Analysis Results of ΔPR for Study 2402

	Treatment Group								
	Active Control			SOM LAR 40 mg			SOM LAR 60 mg		
	dPR			dPR			dPR		
Visit	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)
End of Study	0.3	-4.0	4.6	4.6	-0.3	9.5	4.0	-2.0	9.9
Unscheduled visit	-1.7	-6.4	3.1	6.3	-8.1	20.8	9.5	1.3	17.6
Visit 3	.	.	.	4.4	-0.1	9.0	1.5	-2.4	5.4
Visit 4	-1.3	-4.7	2.0	3.9	-0.9	8.6	2.8	-1.2	6.9
Visit 5	1.5	-1.2	4.2	3.8	-0.8	8.5	0.8	-3.1	4.6
Visit 6	1.1	-2.4	4.5	4.9	-0.2	10.1	2.1	-1.8	5.9
Visit 7	.	.	.	5.2	-0.0	10.4	-1.4	-5.9	3.1
Visit 8	-1.0	-4.6	2.6	7.0	2.0	12.0	2.4	-2.0	6.8
Visit 9	-0.7	-4.3	2.9	3.3	-2.1	8.7	2.0	-3.0	7.1

Table 17: Categorical Analysis for PR for both Studies

	T		Value<=200 ms		Value>200 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Active Control	66	407	63 (95.5%)	398 (97.8%)	3 (4.5%)	9 (2.2%)
Octreotide LAR	180	4418	155 (86.1%)	4243 (96.0%)	25 (13.9%)	175 (4.0%)
Pasireotide LAR	178	4050	149 (83.7%)	3806 (94.0%)	29 (16.3%)	244 (6.0%)
SOM LAR 40 mg	63	480	55 (87.3%)	438 (91.3%)	8 (12.7%)	42 (8.8%)
SOM LAR 60 mg	61	468	51 (83.6%)	418 (89.3%)	10 (16.4%)	50 (10.7%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The descriptive analysis and the 90% confidence intervals are presented in Table 18 and

	Treatment Group					
	Octreotide LAR			Pasireotide LAR		
	dQRS			dQRS		
Visit	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)
2	0.9	-0.0	1.9	0.4	-0.5	1.4
4	1.7	0.5	2.9	1.6	0.5	2.7
5	1.5	0.3	2.6	1.6	0.5	2.7
7	1.4	0.5	2.3	2.0	1.2	2.8
8	0.9	-0.4	2.2	0.6	-0.7	1.8
9	0.9	-0.4	2.2	1.8	0.6	3.0
10	1.5	0.6	2.4	1.6	0.7	2.4
11	1.6	0.3	2.9	1.7	0.5	2.9
12	1.2	-0.1	2.5	1.6	0.4	2.7
13	1.2	0.3	2.2	1.6	0.8	2.5
14	0.9	-0.3	2.2	1.3	-0.1	2.7
15	0.7	-0.6	2.1	2.3	0.8	3.7
17	1.2	-0.3	2.8	2.4	0.6	4.1
19	1.1	-0.5	2.7	1.0	-0.4	2.5
20	0.6	-0.8	2.0	2.0	0.6	3.5
22	1.2	-0.2	2.6	2.2	0.9	3.6
23	0.5	-1.0	2.1	1.0	-0.4	2.4
24	0.6	-1.0	2.1	0.9	-0.7	2.5
25	0.6	-0.7	1.9	0.9	-0.5	2.4
26	0.7	-0.7	2.2	1.0	-0.6	2.7

Table 19.

The outlier analysis results for QRS are presented in Table 20

Table 18: Analysis Results of ΔQRS for Study 2305

	Treatment Group					
	Octreotide LAR			Pasireotide LAR		
	dQRS			dQRS		
Visit	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)
2	0.9	-0.0	1.9	0.4	-0.5	1.4
4	1.7	0.5	2.9	1.6	0.5	2.7
5	1.5	0.3	2.6	1.6	0.5	2.7
7	1.4	0.5	2.3	2.0	1.2	2.8
8	0.9	-0.4	2.2	0.6	-0.7	1.8
9	0.9	-0.4	2.2	1.8	0.6	3.0
10	1.5	0.6	2.4	1.6	0.7	2.4
11	1.6	0.3	2.9	1.7	0.5	2.9
12	1.2	-0.1	2.5	1.6	0.4	2.7
13	1.2	0.3	2.2	1.6	0.8	2.5
14	0.9	-0.3	2.2	1.3	-0.1	2.7
15	0.7	-0.6	2.1	2.3	0.8	3.7
17	1.2	-0.3	2.8	2.4	0.6	4.1
19	1.1	-0.5	2.7	1.0	-0.4	2.5
20	0.6	-0.8	2.0	2.0	0.6	3.5
22	1.2	-0.2	2.6	2.2	0.9	3.6
23	0.5	-1.0	2.1	1.0	-0.4	2.4
24	0.6	-1.0	2.1	0.9	-0.7	2.5
25	0.6	-0.7	1.9	0.9	-0.5	2.4
26	0.7	-0.7	2.2	1.0	-0.6	2.7

Table 19: Analysis Results of ΔQRS for Study 2402

	Treatment Group								
	Active Control			SOM LAR 40 mg			SOM LAR 60 mg		
	dQRS			dQRS			dQRS		
Visit	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)	Mean (ms)	Lower 95% (ms)	Upper 95% (ms)
End of Study	4.5	2.0	6.9	1.3	-0.6	3.2	3.5	1.1	5.9
Unscheduled visit	1.7	-1.1	4.5	-0.3	-4.8	4.3	5.4	1.6	9.1
Visit 3	.	.	.	1.7	0.1	3.3	0.6	-1.2	2.5
Visit 4	0.9	-1.1	3.0	1.6	-0.3	3.5	0.5	-1.4	2.5
Visit 5	1.8	-0.7	4.3	1.1	-0.5	2.6	0.3	-1.5	2.0
Visit 6	2.1	-0.1	4.3	2.0	0.2	3.8	2.1	0.0	4.2
Visit 7	.	.	.	1.1	-0.9	3.1	2.2	-0.1	4.5
Visit 8	2.5	0.4	4.6	0.8	-0.9	2.6	1.7	-0.2	3.6
Visit 9	2.3	0.4	4.3	0.7	-1.0	2.4	2.6	0.0	5.1

Table 20: Categorical Analysis for QRS for both Studies

	T		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Active Control	66	408	22 (33.3%)	276 (67.6%)	34 (51.5%)	114 (27.9%)	10 (15.2%)	18 (4.4%)
Octreotide LAR	180	4424	62 (34.4%)	3535 (79.9%)	101 (56.1%)	787 (17.8%)	17 (9.4%)	102 (2.3%)
Pasireotide LAR	178	4052	55 (30.9%)	3197 (78.9%)	101 (56.7%)	704 (17.4%)	22 (12.4%)	151 (3.7%)
SOM LAR 40 mg	63	480	26 (41.3%)	356 (74.2%)	33 (52.4%)	115 (24.0%)	4 (6.3%)	9 (1.9%)
SOM LAR 60 mg	61	474	19 (31.1%)	329 (69.4%)	34 (55.7%)	133 (28.1%)	8 (13.1%)	12 (2.5%)

5.3 Clinical Pharmacology Assessments

Based on the information provided, it appears that the TQT studies performed with pasireotide s.c. formulation would cover the potential effect of pasireotide LAR formulation on QT interval.

A time delay between the plasma concentration Tmax and the peak QTc prolongation was observed in the TQT studies in healthy volunteers. The reason for the delay between maximum concentration and maximum QT effect is unclear. Upon requested by QT-IRT, an effect-compartment PK/ΔΔQTcI model was developed based on data from Study

B2125, where the s.c. formulation of pasireotide was used. The models were then used to predict ΔΔQTcI at 900μg s.c. b.i.d. in healthy volunteers and Cushing's patients.

These effect-compartment models were not applied for the LAR formulation. The steady-state PK profile for pasireotide sc exhibited a sharp peak at 0.52-0.60 h after dose administration. In contrast, the PK behavior of the LAR formulation is relatively flat. The sponsor stated that it was not appropriate to extrapolate the effect-compartment model from sc formulation to make predictions about QTc effect with the flat PK profile of the LAR formulation. Instead, they proposed to base the exposure-QTc modeling for the LAR formulation on exposure levels and QTc measurements in Study C2305 and C2402. This approach was reviewed and accepted by QT-IRT.

Based on observed data and modeling results from study C2305 and C2402, there does not appear to be clinically significant relationship between pasireotide LAR concentration and change from baseline for both QTcF and QTcB, at the proposed therapeutic dose levels.

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines--i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death--occurred in either study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects of pasireotide on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Cushing's disease patients: B2305 (PhIII), B2208 (PhII), B2208E1 (PhII) 300, 600, 900 µg s.c. b.i.d.	
Maximum tolerated dose	Cushing's disease patients: NA (not applicable) Healthy volunteers: studies B2113 (PhI), B2125 (PhI) 1,950 µg s.c. b.i.d.	
Principal adverse events	Hyperglycemia, GI (nausea, diarrhea), QT prolongation, liver function test elevation, and cholelithiasis	
Maximum dose tested	Single Dose	Cushing's disease patients: NA Healthy volunteers: study B2106 (PhI) 1500 µg s,c, single dose
	Multiple Dose	Cushing's disease patients: study B2305 (PhIII) 1200 µg s.c. b.i.d. Healthy volunteers: study B2113 (PhI) 2100 µg s.c. b.i.d.
Exposures Achieved at Maximum Tested Dose	Single Dose	Cushing's disease patients: NA Healthy volunteers: study B2106 (PhI) Cmax (ng/mL): 36.9 ± 5.7 (15.5%) (n=8) AUCinf (hr*ng/mL): 188 ± 51.8 (27.6%) (n=8)
	Multiple Dose	Cushing's disease patients: NA Healthy volunteers: study B2113 (PhI) $C_{max,ss}$ (ng/mL): 82.8 ± 15.6 (18.8%) (n=5) $AUC_{0-12hr,ss}$ (hr*ng/mL): 330 ± 108 (32.6%) (n=5)
Range of linear PK	Cushing's disease patients: study B2305 (PhIII) 300-1200 µg s.c. b.i.d. Healthy volunteers (PhI): studies B2101, B2106, C2101: 1-1500 µg s.c. single dose study B2106: 450-750 µg s.c. b.i.d.	

	Terminal t½	Pasireotide: Healthy volunteers (PhI): studies B2101, B2106 Terminal T1/2: 28-32 hr for 900-1500 µg s.c. single dose Terminal T1/2: 44-66 hr for 600-1200 µg s.c. single dose Healthy volunteers (PhI): study B2102 Effective T1/2: ~12 hr Metabolites: NA
	CL/F or CL	Cushing's disease patients: studies B2305 (PhIII), B2208 (PhII) with Pop PK CL/F: ~3.8 L/hr as typical value Healthy volunteers (PhI): studies B2101, B2102, B2106, B2108, C2101 with Pop PK CL/F: ~6.7 L/hr as typical value
Intrinsic Factors	Age	Cushing's disease patients: studies B2305 (PhIII), B2208 (PhII) with Pop PK Age impact is not clinically relevant: In patients age range 18-73 years old, simulated AUC0-12hr,ss is predicted to be 86-111% of that of a patient with typical (median) age of 41 years old.
	Sex	Cushing's disease patients: studies B2305 (PhIII), B2208 (PhII) with Pop PK and Pop PK/PD No gender effect
	Race	Cushing's disease patients: studies B2305 (PhIII), B2208 (PhII) with Pop PK and Pop PK/PD No race effect
	Hepatic & Renal Impairment	Hepatic impairment: study B2114 (PhI) After adjustment with age, BMI and albumin as covariates, in comparison with normal (control) group, subjects with mild, moderate and severe hepatic impairment based on Child-Pugh classification had 8%, 60% and 79% increase in AUCinf; 7%, 67% and 69% in Cmax. Results based on NCI-

		CTEP classification were similar to those based on Child-Pugh classification. Renal impairment: Pasireotide is highly metabolic stable and predominantly eliminated as unchanged form via hepatic clearance (biliary excretion), and renal clearance makes a small contribution to the elimination of pasireotide (study B2112). Therefore, effect of renal impairment on PK of pasireotide is not expected.
Extrinsic Factors	Drug interactions	DDI potential for pasireotide s.c. is expected to be low because pasireotide: - has moderate protein binding - is not a substrate, inhibitor or inducer of CYP450 enzymes - is not a substrate of BCRP, OCT1, OATP1B1, 1B3 or 2B1 - is not an inhibitor of OATP 1B1 or 1B3 - appears to be a substrate of P-gp - not conclusive whether pasireotide is an inhibitor of P-gp
	Food Effects	Pasireotide s.c. is administered via parenteral route and thus food effect is unlikely to occur.
Expected High Clinical Exposure Scenario	Cmax and AUC at the highest therapeutic dose of 900 µg s.c. b.i.d. in Cushing's disease patients with normal and mild hepatic impairment, and at the highest therapeutic dose of 600 µg s.c. b.i.d. in patients with moderate and severe hepatic impairment, are expected to be close to Cmax and AUC of MTD 1950 µg s.c. b.i.d. in healthy volunteers.	

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/s/

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LABEL AND LABELING REVIEW

HUMAN FACTORS AND USABILITY REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 28, 2014
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 203255
Product Name and Strength:	Signifor LAR (Pasireotide) for Injectable Suspension, 20 mg/vial, 40 mg/vial, 60 mg/vial
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis
Submission Date:	November 15, 2013
OSE RCM #:	2013-2664 2014-113
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review is written to evaluate the results of the Applicant's Human Factor Validation Study, as well as the proposed Prescribing Information, container label, carton labeling, and Instructions for Use (IFU) to ensure the intended population is able to use the proposed product, Signifor LAR (Pasireotide), NDA 203255, safely and effectively.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Human Factors Usability Study demonstrated that there are no approvability issues based on the results of the study. There were no failures in essential tasks required for proper reconstitution and administration of the product. However, the study identified 11 failures in non-essential steps that do not constitute a safety risk if omitted or completed incorrectly. The non-essential steps included steps that are part of good clinical practice and are not directly related to the design or use of the specific product being investigated. These 11 failures in non-essential steps included the following:

1. Eighteen participants failed to state intent to wait 30 minutes before reconstitution. We attribute this error to the fact that the scheduled interview length is only 30 minutes long and the delivery system packaging used in the study was removed from the refrigerator immediately prior to each interview and placed in a cooler in the interview

room. Therefore, the package was out of the refrigerator for 5 to 10 minutes for the inductor part of the interview and may not have felt cold by the time the participant takes the delivery system out of the cooler. Failure to allow the drug product to acclimatize for 30 minutes may cause patient discomfort but have no effect on the deliverable dose. Therefore, this error is associated with clinical practice and not directly related to the product packaging and design. Nevertheless, we recommend increasing the prominence of the instructions regarding to allowing the product to acclimatize for 30 minutes to mitigate this type of error.

2. Nine participants failed to state intent to wash hands or wear gloves. This error is associated with clinical practice and not directly related to the product packaging and design.

3. Two participants failed to peel lid film from blister tray containing delivery system far back enough to find the drug vial. Both participants were aware that there should have been a vial in the delivery system. While the IFU and the carton labeling clearly states that there's a drug vial, the tray lid has been modified to only cover the main body of the tray. As a result, the tray that holds the vial is uncovered and can be easily detected. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.

4. One participant failed to detach the flip-off cap from the vial. The participant was a physician who was unfamiliar with the product and did not notice the cap on the vial. This error is not unique to the design of this product as most health care practitioners are accustomed to removing the flip-cap for single-use vials prior to drug reconstitution. Additionally, the IFU clearly states to "remove the plastic cap from the vial" with a graphic demonstrating the step in Step 2. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.

5. Seven participants failed to clean the rubber stopper with an alcohol swab. Five participants stated that they would not normally clean the stopper because they assume it is sterile if it has not been touched. One participant said she normally would clean the stopper, but forgot to act as she normally would. One participant thought she cleaned the stopper, but did not remember that she did not complete this step. This error is not unique to the design of this product. Additionally, the IFU clearly states to "clean the rubber stopper of the vial with an alcohol wipe" in Step 2. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.

6. One participant failed to lift the blister tray off the vial adaptor and attempted to peel apart the plastic of the vial adaptor. Failure to do this step will result in the participant asking for help and will not result in patient harm. Additionally, the IFU clearly states to "lift the packaging of the vial adaptor with a vertical movement" with a graphic demonstrating the step in Step 2. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.
7. One participant used the injection needle to inject the diluent into the vial through the vial adaptor. She realized her mistake when she later experienced difficulties withdrawing the vial contents, and detached the needle, and connected the syringe to the vial adaptor to continue withdrawing. We attribute this error to the fact that some health care practitioners may be more comfortable using a needle than a vial adaptor during drug reconstitution. Additionally, the IFU clearly illustrates the need to use the vial adaptor to withdraw the vial content with a graphic demonstrating the step in Step 5. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.
8. Seven participants failed to tape the syringe to remove any visible bubbles. We attribute this error to the fact that in practice, health care practitioners do not frequently check for bubbles prior to intramuscular injections and the bubbles may not always be visible. Additionally, the IFU clearly states to "gently tap the syringe to remove any visible bubbles and expel them from the syringe" with a graphic demonstrating the step in Step 6. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.
9. Four participants failed to state the intent to clean the injection site with an alcohol swab. This error is associated with clinical practice and not directly related to the product packaging and design. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.
10. One participant failed to activate the safety guard over the needle after injection. The participant stated that she had not used that type of safety guard before and would just put the syringe directly in the sharps bin. This error is associated with clinical practice and not directly related to the product packaging and design. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.
11. One participant disposed the syringe in the biohazard waste bin rather than the sharps container. She thought she was disposing the syringe in the sharps container but got confused during the study. As a result, this error is a study artifact and does not affect the results of the study in terms of safe use of the product.

Based on the results of this Human Factors Usability Study, we concluded that the failures that occurred with non-essential tasks are not unique to this product. There are multiple products that require reconstitution that demonstrate the same type of issues (e.g., Sandostatin LAR Depot, Invega Sustenna, Risperdal Consta, etc.). As a result, we find the product's design acceptable.

4 CONCLUSION & RECOMMENDATIONS

The HF Study demonstrated that the delivery system can be used safely and effectively by health care practitioners without training. We conclude that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Section 11, Description, Full Prescribing Information

    1. We note the use of trailing zeros in the section on "Each diluent pre-filled syringe contains:" such as Mannitol 90.0 mg, Carboxymethylcellulose sodium 14.0 mg, Poloxamer 188 4.0 mg, and Water for injections, 2.0 mL. Remove the trailing zeros for all ingredients (e.g. 90 mg, 14 mg, 4 mg, and 2 mL) to avoid a ten-fold misinterpretation.

B. Section 16, How Supplied, Full Prescribing Information

    1. Remove the trailing zero in the statement "a pre-filled syringe containing 2.0 mL of diluent" to avoid a ten-fold misinterpretation.

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

A. Container Labels – Vial

1. There is insufficient differentiation between the different strengths. The only difference between the three strengths is the font color of the strength placement, which may be inadequate in preventing selection of the wrong strength error. Thus, provide sufficient differentiation between the three strengths through the use of colors, boxing, or other means for the background to highlight the different strengths.

2. As currently presented, there are two barcodes on the vial container labels. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes on products is confusing to the frontline staff. The practitioner may scan the wrong

barcode, realizing it won't scan properly, and may override the barcode medication administration (BCMA) system to administer the medication, leading to potential wrong drug errors.[1] Therefore, we recommend you remove the barcode that does not contain the NDC number.

B. Container Labels – Syringe

1. As currently presented, the proprietary name "Signifor LAR" in the statement "Diluent for suspension of Signifor LAR" appears more prominent than the word "Diluent". Revise the statement to increase the prominence and readability of the word "Diluent" to reduce the risk of wrong drug error where the diluent is administered instead of the actual drug. For example:

Diluent
for suspension of
Signifor LAR

2. As currently presented, the label for the pre-filled syringe appears more prominent than the drug vial label. Since the diluent amount in the pre-filled syringes is the same for all drug vials regardless of the strength, remove the background color for the syringe label and change the font color to black for the diluent part of the syringe label to make the syringe label less prominent than the drug vial label. The only exception to this recommendation for font color change is to make the statement "(b) (4) PEEL OFF OUTER LAYER AFTER PRODUCT SUSPENSION" more prominent through the use of colors, boxing, or other means to indicate that the drug has been reconstituted. We recommend this to minimize the risk of wrong drug error where the diluent is administered instead of the actual drug based on our post-marketing experiences.

3. Increase the prominence of the important information on the clear syringe label (bottom half) for Signifor LAR by enhancing the contrast of the font color in comparison with the clear label to improve readability.

4. We note the use of trailing zeros on the pre-filled syringe labels for the list of ingredients (e.g. sodium CMC 14.0 mg, water for injection, 2.0 mL, etc). Remove the trailing zeros for all ingredients (e.g. 14 mg, 2 mL) to avoid a ten-fold misinterpretation.

[1] Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-3.

C. Tray Labeling

1. Add the statement “For single use only” on the principal display panel to minimize the risk of the product components being used multiple times.
2. The tray labeling does not have any differentiation features to facilitate strength selection due to black font on a white background. Add differentiating features to the tray labeling by using colors, boxing, or other means to facilitate strength differentiation and prevent product confusion since our post-marketing experiences indicate that box labeling and tray labeling are frequently separated prior to drug administration.
3. Increase the prominence of the instructions regarding to store the injection kit at room temperature for a minimum of 30 minutes by using a different font color or by boxing the information to highlight the important instructions since 18 participants failed to state intent to wait a minimum of 30 minutes in the human factors study.

D. Carton Labeling – Box Labeling

1. See Section B.4.
2. See Section C.3.
3. Add the statement “Should only be administered by a trained health care professional” on the principal display panel if space permits.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Signifor LAR that Novartis submitted on November 15, 2013.

Table 2. Relevant Product Information for Signifor LAR	
Active Ingredient	Pasireotide
Indication	treatment of patients with acromegaly
Route of Administration	Intramuscular
Dosage Form	Powder for injection
Strength	20 mg/vial, 40 mg/vial, 60 mg/vial
Dose and Frequency	Initial: 40 mg IM every 4 weeks May titrate to: 20 mg or 60 mg IM every 4 weeks
How Supplied	Single-use kit containing: • 6 mL vial (20 mg, 40 mg, or 60 mg) • Pre-filled syringe with 2 mL diluent solution • 1 sterile 20 G x 1.5" safety needle • 1 vial adapter for drug product reconstitution
Storage	2°C – 8°C (36°F – 46°F). Do not freeze.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on December 23, 2013 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[2]

Table 3: FAERS Search Strategy	
Date Range	December 23, 2013
Drug Names	Pasireotide (active ingredient) Signifor (trade name)
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search identified no cases of medication errors.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on December 23, 2013 using the terms, Signifor to identify reviews previously performed by DMEPA.

C.2 Results

DMEPA had previously reviewed Signifor Labels and Labeling under OSE Review #2012-473 dated December 14, 2012 and we looked at the review to ensure all our recommendation were implemented.

APPENDIX D. HUMAN FACTORS STUDY

D.1 Objective

The Human Factors validation testing was intended to assess the safe and effective handling of the SOM230C delivery system through observed use of the system in a simulated preparation and injection activity by participants representative of intended users.

D.2 Study Population

The study included 44 participants who were health care professionals (HCPs):

- 21 secondary care doctors who specialize in the field of endocrinology (b) (4)
- 23 secondary care nurses who specialize in the fields of endocrinology

Table 6 – Validation Study Participant Background Summary

Type	Average intragluteal injections per month:	
	Prepared	Administered
Group 1(n=21): Secondary care medical doctors (MDs)	11 (0 - 120)	14 (0 - 120)
Group 2 (n=23): Secondary care registered nurses (RNs)	23 (2 - 120)	28 (2 - 120)

All participants reported either preparing or administering at least one intragluteal injection per month, though some participants reported only preparing or only administering the injections.

D.3 Study Design

All HCPs who prepare and administer intragluteal injections are trained and certified to do so as part of their vocational training. While some form of in-service training is expected to be made available as part of the introduction of the SOM230C delivery system, it is foreseeable that some users would receive this training, while others would not receive any system-specific training prior to their first use of the system. No training of participants enrolled in any of the studies was conducted prior to the use assessment, which represents the worst-case condition with respect to user training.

The investigation was conducted as a single performance trial followed by an individual interview in market research interview facilities, which provided a representative simulation of an end-use environment. The environment emulated the expected use environment as a generally low-traffic, low-distraction, low-noise settings with normal office environment lighting conditions.

Participants were given the IFU and asked to prepare an injection using the delivery system and administer it into an injection pad. Participants were permitted to refer to the IFU at any time, but were not required to use it.

D.4 Results

Each user task was assigned a criterion type per the task analysis:

- **Essential:** Essential steps are those that are required for the safe and effective use of the product.
- **Non-essential:** Non-essential steps are those that do not constitute a safety risk if omitted or completed incorrectly. This includes those steps that are part of good clinical practice but are not directly related to the design or use of the specific product being investigated.
-

Table 7 - Summary of primary objective results

ID	Objective description	Performance results	
		Failures	Difficulties
P1	Successful use: Measure the number and percentage of participants that can successfully, without training or assistance, use the SOM230C delivery system to deliver a single dose into a simulated injection site (injection pad) having been provided with the IFU, on first use. Each participant will complete one trial only. The applicable primary variables define whether a dose is safely and effectively administered and do not address every use step from the IFU. Requirement 3.7.1 "The devices must be easy to use and compatible with a manual use" per current URS document.	**44** out of 44 participants (**100%**) were able to successfully use the delivery system without failure on 'Essential' steps.	**36** out of 44 participants (**82%**) were able to successfully use the delivery system without difficulty on 'Essential' steps.
P2	Measure the number and percentage of participants that can successfully, without training or assistance, perform all of the steps detailed in the IFU for the SOM230C delivery system. (Every use step is successfully performed) Requirement 3.8.3 "The instructions for use must be very explicit in order to avoid misunderstanding during the reconstitution and the delivery of the drug" per current URS document.	**15** out of 44 participants (**34%**) successfully performed every use step detailed in the IFU without failure on 'Non-essential' steps.	**38** out of 44 participants (**86%**) successfully performed every use step detailed in the IFU without difficulty on 'Non-essential' steps.

6.6.1 *Performance assessment of 'essential' steps*

No participants were observed to have any failures on the 7 essential tasks. A total of 8 difficulties were experienced, by 8 different participants, on 4 of the 7 essential tasks. None of the observed difficulties prevented the participants from completing the simulated injection.

Observed difficulties on essential steps			
IFU Step	**Essential User Task**	**Observed Failures**	**Observed Difficulties**
2.4	Position vial adapter on vial and push down to snap in place	0	4 (9%)
5.1	Push plunger all the way down to transfer solution to vial	0	0
6.1	Keep plunger pressed, shake vial moderately for minimum of 15s *Note: Shaking times were measured as <15s or ≥15s, but were not measured beyond 15s.*	0	2 (5%)
6.2	Check visually that powder is completely suspended, shake again if needed	0	1 (2%)
7.2	Pull plunger out and withdraw entire content into syringe	0	1 (2%)
11.2	Insert needle fully into injection pad	0	0
11.3	Slowly depress plunger rod to inject entire dose	0	0

The essential user tasks are detailed below.

1. **Difficulty with position the vial adaptor on vial and push down to snap in place (n=4 difficulties)**
    - Participant 1 (a doctor) was uncertain whether the vial adapter was on, having not heard the click, and kept trying to push it down.
    - Participant 12 (a doctor) put the vial adapter on the uncapped end of the syringe at first, then later realized his mistake and moved it to the vial.
    - Participant 15 (a nurse) was confused about which "tray" the IFU referred to. She initially left the vial, still in its blister tray, in the delivery system tray and tried to press the vial down onto it. She later removed the lid film and attached it correctly.
    - Participant 30 (a doctor) initially stuck the vial adapter into the flipoff cap, which was still attached to the vial. She then removed the vial adapter, and the flip-off cap stuck to it. Then she attached the vial adapter to the vial, pushing hard

enough to pierce through the flip-off cap. She did not experience any other failures or difficulties aside from failing to remove the flip-off cap and ensuing difficulty inserting the vial adapter.

2. **Keep plunger pressed, shake vial moderately for minimum of 15s Note: Shaking times were measured as <15s or ≥15s, but were not measured beyond 15s. (n=1 difficulty)**

    - Participant 25 (a nurse) experienced minor leakage between the vial adapter and the vial while shaking. She held the syringe plunger in one hand and the vial in the other hand, which appeared to cause the vial adapter to separate slightly from the vial while shaking. Accurate measurement of leakage was not possible during the study. However, the volume of fluid that leaked is estimated to be vehicle only and less than 15% of the total volume. Participant 34 (a doctor) used an extremely gentle movement to shake the vial that led to some powder remaining stuck to the bottom of the vial. The participant did appear to visually check the solution and did continue shaking (step 6.2), but a small quantity of powder was still left stuck to the vial.

3. **Check visually that powder is completely suspended, shake again if needed (n=1 difficulty)**

    - Participant 29 (a doctor) appeared to leave a small amount of powder left in the vial stuck to the bottom. The participant did shake the vial moderately for at least 15 seconds (step 6.1), though the exact time was not recorded. She had been checking the suspension throughout shaking and later reported it was easy to see when the product was suspended.

4. **Pull plunger out and withdraw entire content into syringe (n=1 difficulty)**

    - Participant 19 (a nurse) used the injection needle to inject the diluent into the vial (through the vial adapter). When she later experienced difficulties withdrawing the vial contents, she realized her mistake, detached the needle, and connected the syringe to the vial adapter to continue withdrawing.

6.6.2 *Performance assessment of 'non-essential' steps*

On non-essential tasks, 29 participants experienced a total of 52 failures. Additionally, 6 participants were observed to have difficulties on 9 occasions. These failures and difficulties are discussed in detail in Table 9.

Observed failures and difficulties on non- essential steps			
IFU Step	**Non-Essential User Task**	**Observed Failures**	**Observed Difficulties**
1.1	Remove delivery system from refrigerated storage	0	0
1.2	State intent to wait a minimum of 30 minutes	18 (41%)	0
1.3	State intent to wash hands or wear gloves	9 (20%)	0
1.4	Peel lid film from blister tray containing delivery system	2 (5%)	1 (2%)
1.5	Detach the flip-off cap from the vial	1 (2%)	0
2.1	Clean the rubber stopper with an alcohol swab	7 (16%)	0
2.2	Do not touch the rubber stopper after cleaning	0	0
2.3	Peel lid film from blister tray containing vial adapter	0	0
3.1	Lift blister tray off the vial adapter	1 (2%)	2 (5%)
4.1	Pull cap from the pre-filled syringe and screw syringe onto vial adapter	1 (2%)	1 (2%)
7.1	Turn syringe and vial upside-down	0	1 (2%)
8.1	Unscrew syringe from vial adapter	0	0
	Remove safety injection needle from blister	0	0
9.1	Screw safety injection needle onto syringe	0	0
10.1	Pull protective cover straight off needle	0	2 (5%)
10.2	Gently invert syringe to maintain suspension	0	0
10.3	Gently tap syringe to remove any visible bubbles and expel from the syringe	7 (16%)	0
11.1	State intent to clean site with alcohol swab	4 (9%)	0
12.1	Withdraw needle from injection site and activate safety guard over needle	1 (2%)	2 (5%)
12.2	Dispose of syringe immediately in a sharps container	1 (2%)	0

The non-essential user tasks are detailed below.

1. **State intent to wait a minimum of 30 minutes (n=18 failures)**
    - 13 participants (5 doctors, Participants 16, 18, 21, 29, and 39; and 8 nurses, Participants 11, 15, 23, 24, 28, 32, 33, and 35) reported they assumed they should not wait 30 minutes because of the length of the interview (30 minutes) but that they would do that step normally.
    - Participants 2 and 42 (both nurses) did not see the note in the IFU about leaving it out for 30 minutes, though Participant 42 noted that in her practice they generally left refrigerated medications out for 30-60 minutes anyway.
    - Participant 20 (a doctor) said she did not really read the beginning of the IFU because she assumed they weren't doing that in the interview, but later said that if she were really going into a cold fridge she thinks she would have read that part better.
    - Participant 12 (a doctor) called attention to the 30-60 minutes during the trial, but did not indicate he would do that step, and later said the delivery system packaging felt warm enough to the touch that it did not need to wait out for 30 minutes.
    - Participant 31 (a nurse) said she did not mention waiting 30 minutes because of "nerves," but also said she would either wait the 30 minutes or hold the vial in her hands to warm it.
2. **State intent to wash hands or wear gloves (n = 9 failures)**
    - 7 doctors (Participants 1, 4, 5, 7, 16, 20, and 39) and 2 nurses (Participants 24 and 32) did not state they would wash their hands or wear gloves.
3. **Peel lid film from blister tray containing delivery system (n = 2 failures, 1 difficulties)**
    - Participant 28 (a nurse) did not peel the lid film back far enough to find the vial. She stated that she knew there should be a vial, but because she did not find it, she injected just the diluent. When she was throwing away the components, she saw the vial from the underside of the delivery system tray. She was given a new delivery system and was able to fully peel back the lid film, locate the vial, and complete all subsequent use steps without failure or difficulty.
    - Participant 43 (a nurse) did not peel the lid film back far enough to find the vial and thought that the vial was missing from that delivery system. She said in that situation she would call the pharmacy technician and get a new delivery system. She was then shown where the vial was and continued with the injection.
    - Participant 39 (a doctor) did not peel the lid film back far enough to find the vial at first and had significantly difficulty locating it.

4. **Detach the flip-off cap from the vial (n = 1 failure)**

    - Participant 30 (a doctor) was not familiar with and did not notice the cap on the vial. She attached the vial adapter to the vial by piercing through the flip-off cap. She recognized her mistake as she was filling out the questionnaire after the performance trial. She did not experience any other failures or difficulties aside from failing to remove the flip-off cap and ensuing difficulty inserting the vial adapter.

5. **Clean the rubber stopper with an alcohol swab (n = 7 failures)**

    - 5 participants (2 doctors, Participants 7 and 12; and 3 nurses, Participants 23, 27, and 31) said they would not normally clean the stopper because they assume it is sterile if it has not been touched. One of these participants (Participant 23) said she assumed it was sterile but after reading in the IFU to clean it, she was worried it was not sterile.
    - 1 participant (Participant 30, a doctor) said she normally would clean the stopper but forgot to act as she normally would.
    - 1 participant (Participant 11, a nurse) said she thought she had cleaned the stopper – she did not remember she had not done this step.

6. **Lift blister tray off the vial adapter (n = 1 failure, 2 difficulties)**

    - Participant 4 (a doctor) was trying to peel apart the plastic of the vial adapter and did not figure out to lift the whole piece off until after the moderator directed him to Step 3 of the IFU.
    - Participant 11 (a nurse) twisted the blister tray to try to remove it instead of lifting.
    - Participant 39 (a doctor) tried to attach the syringe to the blister tray before realizing to remove the blister tray.

7. **Pull cap from the pre-filled syringe and screw syringe onto vial adapter (n = 1 failure, 1 difficulties)**

    - Participant 19 (a nurse) used the injection needle to inject the diluent into the vial (through the vial adapter). When she later experienced difficulties withdrawing the vial contents, she realized her mistake, detached the needle, and connected the syringe to the vial adapter to continue withdrawing.

- Participant 34 (a doctor) took the cap off the syringe and reattached it several times, thinking that she should see a needle. She eventually realized to connect the syringe directly to the vial adapter.

8. Turn syringe and vial upside-down (n = 1 difficulty)

- Participant 22 (a nurse) pulled the vial adapter off the vial and started to open the injection needle as though to use this to withdraw the content, then read in the IFU to leave the vial adapter on and reattached it to continue.

9. Pull protective cover straight off needle (n = 2 difficulties)

- Participant 4 (a doctor) pulled on the safety guard to remove the cap and nearly activated the safety guard in the process.
- Participant 39 (a doctor) unscrewed the needle the first time he tried to remove the cap, then reattached it. He may have slightly twisted when removing the cap the second time, but the needle remained attached throughout the rest of the process. No leakage was observed.

10. Gently tap syringe to remove any visible bubbles and expel from the syringe (n = 7 failures)

- 4 participants (1 doctor, Participant 12; 3 nurses, Participants 24, 27, and 43) said that it was not important to remove visible bubbles with IM injections.
- 1 participant (a doctor, Participant 7) said she would remove the bubbles if there were any, but didn't see any.
- 2 participants (both nurses, Participants 15 and 23) said they would normally remove the bubbles but forgot to do it during the interview.

11. State intent to clean site with alcohol swab (n = 4 failures)

- 4 doctors (Participants 5, 6, 14, and 34) did not state intent to clean the site with an alcohol swab.

12. Withdraw needle from injection site and activate safety guard over needle (n = 1 failure, 2 difficulties)

- Participant 34 (a doctor) had not used that type of safety guard before and did not know how to activate it. She said either the nurse would show her how or, as she did in this case, she would just put the syringe directly in the sharps bin. In the study, she briefly tried activating the safety guard but then just disposed of it in the sharps container.
- 2 nurses (Participants 22 and 43) only partially activated the safety guard. Both of these participants immediately disposed of the syringe in the sharps container.

13. Dispose of syringe immediately in a sharps container (n = 1 failure)

- Participant 19 (a nurse) disposed of the syringe in the biohazard waste bin rather than the sharps bin because they looked different than what she normally sees. She thought she was disposing of the syringe in the sharps container and the safety guard was on.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on February 11, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Newsletters Searched	Acute Care, Community
ISMP Newsletter Search Strategy	Select one of the following: Boolean query
Search Terms	Signifor OR pasireotide

E.2 Results

Our search identified no cases of medication errors.

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

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

/s/

TINGTING N GAO
03/28/2014

YELENA L MASLOV
03/28/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 203255

Application Type: New NDA

Name of Drug/Dosage Form: Signifor LAR (pasireotide) intramuscular injection; 20 mg, 40 mg, 60 mg

Applicant: Novartis Pharmaceuticals Corporation

Receipt Date: November 15, 2013

Goal Date: September 15, 2014

1. Regulatory History and Applicant's Main Proposals

Signifor (pasireotide) LAR intramuscular injection, a somatostatin analog, is being developed to treat patients with acromegaly (b) (4) Currently approved drug treatments for acromegaly include Sandostatin Injection (octreotide acetate), Sandostatin LAR Depot (octreotide acetate) and Somatuline Depot (lanreotide) Injection, all of which are also somatostatin analogs. Proposed advantages to the pasireotide formulation include a higher binding affinity to all five somatostatin receptors, as well as a more pronounced IGF-1 suppression.

A pre-submission guidance meeting was held with the sponsor on September 9, 2013, as a follow-up to the Pre-NDA meeting held with the sponsor on November 29, 2011. The purpose of this follow-up pre-submission meeting was to discuss additional new data from pivotal clinical study C2402, entitled, "A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly." The sponsor has included this data in its NDA submission, along with data from pivotal clinical study C2305 (discussed during the Pre-NDA meeting), entitled "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly."

This application is supported mainly by these two pivotal clinical studies, along with data cross-referenced from NDA 200677, Signifor (pasireotide) subcutaneous injection (short-acting formulation), approved on December 14, 2012, for the treatment of patients with Cushing's disease. The planned dosages for pasireotide LAR are 20 mg, 40 mg and 60 mg, administered every 28 days.

This drug is also being developed for the treatment of patients with Cushing's disease under this IND (and under IND 068635, the IND corresponding to approved NDA 200677), (b) (4)

Pasireotide received orphan designation on August 25, 2009, for the treatment of acromegaly.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 11, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space is present between the HL Heading and HL Limitation Statement.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *The preferred presentation was used for most cross-references in the FPI, except for two mentioned in subsection 5.2, referring to subsection 12.2 in the Clinical Pharmacology section.*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JENNIFER L JOHNSON
01/27/2014
PLR Format Review #1

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 # 203255 BLA# N/A	NDA Supplement #:S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Signifor LAR Established/Proper Name: pasireotide Dosage Form: intramuscular injection Strengths: 20 mg, 40 mg, 60 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A		
Date of Application: November 15, 2013 Date of Receipt: November 15, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: September 15, 2014	Action Goal Date (if different):	
Filing Date: January 14, 2014	Date of Filing Meeting: January 6, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Treatment of patients with acromegaly (b) (4)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.*** .	**X** 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	**X** Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? **X** ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	**X** Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review **X** Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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 074642

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	**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)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	**X**	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	**X**		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	N/A	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**	☐		

User Fee Status ***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.***	Payment for this application: ☐ Paid **X** Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: **X** Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	**X**	☐	
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)].**	☐	**X**	☐	
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)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	**X**	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	☐	**X**	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	**X**		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	X	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	X	☐	
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	X	

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

Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	**X**	☐		
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	**X**	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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*	X	☐		Application waived from requirement of pediatric studies because the moiety and indication were granted orphan designation on August 25, 2009.

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	X	
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? ***If no, request in 74-day letter***	☐	☐	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)? ***If no, request in 74-day letter***	☐	☐	X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	X	☐	The applicant did not submit a REMS but did submit a risk management plan, which was consulted to OSE/DRISK.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) X Patient Package Insert (PPI) X Instructions for Use (IFU) ☐ Medication Guide (MedGuide) X Carton labels X Immediate container labels X Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X	☐		
Is the PI submitted in PLR format?[4]	X	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	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.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
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	X	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent: IRT-QT consult to be sent 1/15/14***				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 15, 2007 ***If yes, distribute minutes before filing meeting***	**X**	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 29, 2011 (Pre-NDA follow-up meeting on September 9, 2013) ***If yes, distribute minutes before filing meeting***	**X**	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** Carcinogenicity SPA submitted on November 12, 2004; Stability SPA submitted on November 7, 2007 ***If yes, distribute letter and/or relevant minutes before filing meeting***	**X**	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 6, 2014

NDA #: 203255

PROPRIETARY NAME: Signifor LAR

ESTABLISHED/PROPER NAME: pasireotide

DOSAGE FORM/STRENGTH: intramuscular injection; 20 mg, 40 mg, 60 mg

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with acromegaly (b) (4)

BACKGROUND:

Signifor (pasireotide) LAR intramuscular injection, a somatostatin analog, is being developed to treat patients with acromegaly (b) (4) Currently approved drug treatments for acromegaly include Sandostatin Injection (octreotide acetate), Sandostatin LAR Depot (octreotide acetate) and Somatuline Depot (lanreotide) Injection, all of which are also somatostatin analogs. Proposed advantages to the pasireotide formulation include a higher binding affinity to all five somatostatin receptors, as well as a more pronounced IGF-1 suppression.

A pre-submission guidance meeting was held with the sponsor on September 9, 2013, as a follow-up to the Pre-NDA meeting held with the sponsor on November 29, 2011 (meeting minutes issued on December 20, 2011). Meeting minutes issued on October 10, 2013.

The purpose of this follow-up pre-submission meeting was to discuss additional new data from pivotal clinical study C2402, entitled, "A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly." The sponsor has included this data in its NDA submission, along with data from pivotal clinical study C2305, entitled "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly." (Study C2305 was discussed during the Pre-NDA meeting held on November 29, 2011.)

This application is supported mainly by these two pivotal clinical studies, along with data cross-referenced from NDA 200677, Signifor (pasireotide) subcutaneous injection (short-acting formulation), approved on December 14, 2012, for the treatment of patients with

Cushing's disease. The planned dosages for pasireotide LAR are 20 mg, 40 mg and 60 mg, administered every 28 days.

This drug is also being developed for the treatment of patients with Cushing's disease under this IND (and under IND 068635, the IND corresponding to approved NDA 200677), (b) (4)

Pasireotide received orphan designation on August 25, 2009, for the treatment of acromegaly.

On January 20, 2011, the sponsor submitted a request for review of its proposed proprietary name for this product, Signifor LAR. On July 19, 2011, a conditionally acceptable letter issued. As previously advised, the sponsor included a request for review of the proprietary name again in this NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Johnson	Y
	CPMS/TL:	Pam Lucarelli	N
Cross-Discipline Team Leader (CDTL)	Dragos Roman		Y
Clinical	Reviewer:	Smita Abraham	Y
	TL:	Dragos Roman	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Sang Chung	Y
	TL:	Immo Zadezensky	N
Biostatistics	Reviewer:	Jennifer Clark	Y
	TL:	Mark Rothmann	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Karen Davis Bruno	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Ravindra Kasliwal	N
	TL:	Su Tran Danae Christodoulou	Y Y
Quality Microbiology *(for sterile products)*	Reviewer:	Vinayak (Vinnie) Pawar	N
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:	Ravindra Kasliwal	N
	TL:	Su Tran Danae Christodoulou	Y Y
Facility Review/Inspection	Reviewer:	Ravindra Kasliwal	N
	TL:	Su Tran Danae Christodoulou	Y Y
OSE/DMEPA (proprietary name)	Reviewer:	Tingting Gao	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Robert Pratt	Y
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Selena Ready, OSE/DPV Terrolyn Thomas, OSE RPM John Duan, ONDQA Biopharmaceutics Tapash Ghosh, ONDQA Biopharmaceutics		Y Y N N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	**X** Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	**X** YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable **X** FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	**X** YES

If no, explain:	☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: **X** NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	**X** Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	**X** Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	**X** Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable **X** FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES **X** NO
BIOSTATISTICS	☐ Not Applicable **X** FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable **X** FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	**X** Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable **X** FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	**X** YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable **X** YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable **X** YES ☐ NO **X** YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	**X** Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: None	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	**X** N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Jean-Marc Guettier, DMEP Acting Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): TBD

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: TBD

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. **X** Review issues have been identified for the 74-day letter. List (optional): Review Classification: **X** Standard Review ☐ Priority Review

ACTIONS ITEMS

X	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • 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
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

/s/

JENNIFER L JOHNSON
01/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: December 30, 2013
From: Keith Marin, Combination Product Team Lead, GHDB, WO66, RM 2567
General Hospital Devices Branch, DAGRID, ODE, CDRH

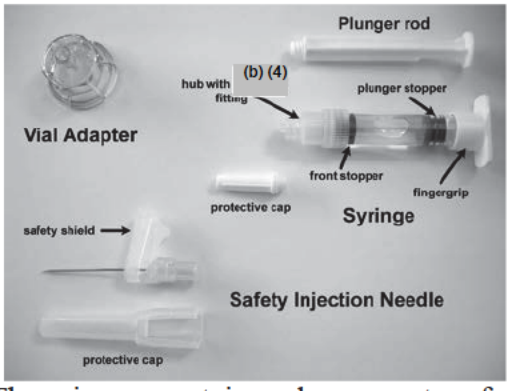
To: Jennifer Johnson, Regulatory Health Program Manager,
CDER/OMPT/CDER/OND/ODEII/DMEP

Subject: CDRH Consult NDA 203255/ICC1300623/S001 , Filing Review, Syringe and syringe-vial adapter for Signifor LAR (pasireotide) intramuscular injection

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 203255. The device constituent of this combination product consists of a syringe and syringe-vial adapter for use with Signifor LAR (pasireotide) intramuscular injection.

2. Device Description



The primary container closure system for the vehicle for powder for suspension for injection, 2ml solution (Figure 1-1) is a pre-filled syringe which consists of the following components:

- a 3ml colorless glass syringe which is closed at both ends with grey rubber stoppers (a front and a plunger stopper)

Additionally the syringe contains administration features/accessories, i.e.:

- a hub with a (b) (4) fitting
- a cap to protect the (b) (4) end of the hub
- a finger-grip, and
- a plunger rod

In addition, along with the pre-filled syringe and drug product a vial adapter and a safety injection needle will be provided.

The (b) (4) syringe barrel used is compliant with (b) (4) It does not correspond to the ISO 11040-4 design by concept as the tip and the flange are plastic components assembled onto the barrel and consequently the syringe cannot comply with the dimensional requirements of this standard. The hydrolytic resistance grain corresponds to type I according to USP 660 and Ph.Eur. 3.2.1, as alternatively required of the ISO 11040-4. The 3ml glass is not annealed, consequently the annealing requirement of ISO 11040-4 is not applicable.

3. Documents Reviewed

K963583
K012736
DMF (b) (4)
DMF
DMF
NDA 203255, 3.2.P.7

4. CDRH Review and Comments

The sponsor has stated in their submission that they are proposing to use the Medimop vial adapter (K963583). The proposed vial adaptor is a needle free device (b) (4) transfer liquid drug product (DP) from the primary container (vial) to a delivery syringe. Based on a past review of this 510(k) on November 14, 2013, it appears that complete performance, biocompatibility and sterility testing have been done on this device component. There are no additional concerns related to the vial adapter at this time.

The sponsor has stated in their submission that they are proposing to use the Monoject® safety needle with the syringe and vial adapter. This device has been cleared under K012736. The needle is a manually operated safety hypodermic needle that is designed to reduce the potential for inadvertent needle sticks.

Drug Master File (b) (4) contains information regarding the (b) (4) syringe system. The (b) (4) syringe system is composed of the syringe barrel with or without the needle, elastomeric closures (front and plunger stoppers), and plunger rod. The syringe barrel consists of the glass barrel, needle, needle hub, needle guard, and finger grips.

Drug Master File (b) (4) contains information about the front stopper and plunger stopper. As these are in contact with the drug, CDRH will defer to CDER on evaluation of this component.

Drug Master File (b) (4) contains information about the front stopper and plunger stopper. As these are in contact with the drug, CDRH will defer to CDER on evaluation of this component.

Human Factors Usability studies will be reviewed under a separate consult by CDRH Human Factors Team, LCDR Quynh Nguyen.

5. CDRH Comments for Review Team

The syringe appears to be the same as the (b) (4) syringe that is described in DMF (b) (4). However, breakloose and glide force testing for the final finished combination product (with needle) and the actual drug product could not be located. This will need to be provided.

Please indicate if you would like CDRH to review sterilization of the syringe.

Biocompatibility testing was not assessed as the will be evaluated for the syringe component of the device in terms of contact with the drug as this compatibility will be deferred to CDER. However, CDRH was unable to locate biocompatibility testing for the plunger rod, finger grips, and cap on the syringe. The sponsor mentioned that the 3ml glass syringe is not annealed and thus does not follow ISO 11040-4. However, it is not clear what process they have used to ensure the syringe does not shatter. This information should be provided.

Human Factors Usability studies will be reviewed under a separate consult by CDRH Human Factors Team

Please ensure that a separate consult has been sent to CDRH Office of Compliance to assist with any necessary regulation requirements for design, purchasing controls, manufacturing validations, acceptance tests for products, or device facilities inspections that may be required for approval of this NDA.

6. CDRH Recommendations for Master File Holder

Based on our review, the following deficiencies should be conveyed to the NDA Holder:

1. In NDA 203255, you have stated that the you intend to use the Medimop Medical Projects Mixject Dispensing pin/with detachable vial holder/with preattached needle (K963583) with the (b) (4) syringe sytem. However, not all of the testing has been provided to demonstrate the safety of this device with your drug. Provide a complete test report (protocol, acceptance criteria, results, and conclusion) for the following testing:

a. Demonstrate that the vial adaptor/syringe doesn't result in air or liquid leakage
b. Provide torque testing force necessary to disconnect syringe's (b) (4) connection from vial adapter
c. Provide force necessary to draw up Signifor LAR (pasireotide) in syringe
d. Provide break loose and glide force of syringe for injection

Based on our review, the following deficiencies should be conveyed to the MAF Holder:

(b) (4)

2. No biocompatibility data were found in the master file or in the NDA for the plunger rod, finger grip, and cap. You should submit applicable biocompatibility data for the autoinjector using a risk analysis framework according to ISO 10993-1: 2003, Biological evaluation of medical devices—Part 1: Evaluation and testing. If you will submit materials data safety sheets for the materials of construction in lieu of testing recommended by the standard for a device with limited contact duration with intact skin, you should provide a rationale as to why testing was not conducted. Additionally, it is not clear based on the information that you have provided on whether the kit components for your device have been sterilized once or twice. If the kit components are supplied sterile and are re-sterilized, you will need to provide biocompatibility according to ISO 10993, not just the material safety data sheets.

3. You have indicated that the 3ml glass is not annealed and consequently the annealing requirement of ISO 11040-4 is not applicable. It is not clear how you have addressed the risk of your device shattering inadvertently. Please provide rationale on why you have deviated from the ISO requirement and how you have addressed the risk of breakage of the syringe.

If you have any questions, please contact LCDR Keith Marin at 301-796-2462.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Keith G. Marin -S Digitally signed by Keith G. Marin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -S, 0.9.2342.19200300.100.1.1=0011250397 Date: 2013.12.30 13:53:10 -05'00'
Branch Chief Sign-Off	Digitally signed by Richard C. Chapman Date: 2014.01.02 09:23:44 -05'00'

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

/s/

JENNIFER L JOHNSON
01/03/2014
CDRH (device) filing review completed by Keith Marin and Richard Chapman on 1/2/14