

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203255Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## ONDQA BIOPHARMACEUTICS REVIEW

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**NDA#:** 203-255/S-000 Amendment  
**Submission Date:** 9/3/2014  
**Drug Name:** Signifor LAR (pasireotide pamoate) Injection  
**Formulation:** Powder for Injection  
**Strength:** 20, 40, and 60 mg  
**Applicant:** Novartis  
**Reviewer:** John Duan, Ph.D.  
**Submission Type:** Amendment for dissolution specification

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### BACKGROUND

Biopharmaceutics recommendation for NDA 203-255 has been pending on the Applicant's response for updating the specification table and other relevant documents in the NDA. The current review evaluates the Applicant's responses and makes final recommendations.

### COMMENTS

1. The Applicant's response is acceptable for updating the product specification table and other relevant documentations of the NDA.
2. The proposed IVIVC is not acceptable [REDACTED] (b) (4)

### RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed the pending issue of NDA 203-255 and found it acceptable from the Biopharmaceutics perspective. An approval is recommended. Please include the following comment in the action letter.

Your proposed in vitro-in vivo correlation (IVIVC) model is not acceptable due to the fact that the IVIVC model [REDACTED] (b) (4)

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John Duan, Ph.D.  
Reviewer  
ONDQA Biopharmaceutics

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Date

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Tapash Ghosh, Ph.D.  
Team Leader  
ONDQA Biopharmaceutics

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Date

cc: NDA 203-255 DARRTS

# BIOPHARMACEUTICS EVALUATION

## 1. Introduction

Pasireotide (SOM230) is a second generation somatostatin analogue proposed for the treatment of patients with acromegaly (b) (4). In the previous review, the Biopharmaceutics recommendation is pending upon the update of the specification table and other relevant documents. Below is a brief history about this issue.

In the 74-day letter, the following comments were sent to the Applicant.

*Your proposed dissolution acceptance criteria are not adequate. The (b) (4) (b) (4). The range of the acceptance criteria at any dissolution time point should be  $\pm 10\%$  deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Modify the proposed dissolution acceptance criteria according to this principle. Provide the dissolution data of the available batches, including the dissolution values for individual unit, the mean, the standard deviation (or CV%) and the plot.*

Further, on 5/29/2014, another information request was sent as follows.

*As stated in the 74-day letter, (b) (4) (b) (4) setting the acceptance criteria of in vitro drug release. Based on the data provided, the following in vitro drug release acceptance criteria are recommended. Provide concurrence and update your NDA specification table.*

(b) (4)

On 6/12/2014, the Applicant provided a response, which acknowledges FDA's view on (b) (4) (b) (4) setting acceptance criteria on in vitro drug release. Based on the data available, the Applicant made a new proposal as shown in the following table.

Time point	Originally proposed	FDA recommendation	Newly proposed
1 h	(b) (4)	(b) (4)	(b) (4)
24 h	(b) (4)	(b) (4)	(b) (4)
48 h	(b) (4)	(b) (4)	(b) (4)
96 h	(b) (4)	(b) (4)	(b) (4)
144 h	(b) (4)	(b) (4)	(b) (4)

In response to the Applicant's proposal, the Agency sent the following information request on 8/29/2014.

*The dissolution acceptance criteria you proposed in your response dated 6/12/2014 are acceptable. Update and resubmit the specification table and other relevant documents in your NDA.*

In the information request dated 8/29/2014, another issue was also raised about IVIVC as follows.

*In the same response (dated 6/12/14),*

(b) (4)

(b) (4)

The current submission provided responses to these two issues.

## **2. The Applicant's responses**

### 1) Update of the specification table

Updated Testing Monographs, considering the newly proposed dissolution criteria in the test 'Drug release', have been included in Module 3.2.P.5 Control of Drug Product (see PP 7006571 013 RUS 01 (20mg), PP 7004687 021 RUS 01 (40mg), PP 7006874 012 RUS 01 (60mg)). All relevant documents have been updated including Drug product 3.2.P.5.1 'Specifications', 3.2.P.5.4 'Batch Analyses', 3.2.P.5.6 'Justification of Specifications' and 3.2.P.8.3 'Stability data'.

***Reviewer's comments:*** *The reviewer confirmed the update of the specification table and relevant documents in the NDA. The response is acceptable and the pending issue has been resolved.*

### 2) The justification of IVIVC method

The applicant stated that the calculated in vitro dose normalization for the IVIVC was based on the following theoretical considerations:

(b) (4)

(b) (4)

**Reviewer's comments:** *The truth is that as shown in the following figure, the dissolution profiles*

(b) (4)

**Reviewer's comments:**

(b) (4)

(b) (4)

(b) (4)

*Reviewer's comments:*

(b) (4)

(b) (4)

*In conclusion, the proposed IVIVC is not acceptable*

(b) (4)

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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.**  
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/s/  
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JOHN Z DUAN  
09/05/2014

TAPASH K GHOSH  
09/05/2014

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	203255
<b>Submission Date(s)</b>	November 15, 2013
<b>Brand Name</b>	SIGNIFOR <sup>®</sup> LAR injection
<b>Generic Name</b>	Pasireotide
<b>Pharmacometrics Reviewer</b>	Lian Ma, Ph.D.
<b>Pharmacometrics Team Leader</b>	Nitin Mehrotra, Ph.D.
<b>Reviewer</b>	Sang M. Chung, Ph.D.
<b>Team Leader</b>	Immo Zadezensky, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology 2
<b>OND Division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	Novartis
<b>Submission Type</b>	Standard
<b>Formulation; Strength(s)</b>	Powder and solvent for suspension for injection
<b>Indication</b>	Treatment of patients with acromegaly [REDACTED] (b) (4)
<b>Dosage &amp; Administration</b>	<ul style="list-style-type: none"><li>• Recommended initial dose is 40 mg by [REDACTED] (b) (4) intramuscular injection once every 4 weeks (Q4W).</li><li>• The dose may be increased to a maximum of 60 mg for patients whose GH and/or IGF-1 levels are not fully controlled after 3 months.</li><li>• The dose may be decreased for management of suspected adverse reactions, either temporarily or permanently by 20 mg decrement.</li><li>• The recommended initial dose for patients with moderately impaired hepatic function (Child-Pugh B) is 20 mg every 4 weeks and the maximum recommended dose is 40 mg every 4 weeks.</li></ul>

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## **1 Executive Summary**

### **1.1 Recommendation**

The Office of Clinical Pharmacology / Division of Pharmacometrics (OCP/DPM) and Division of Clinical Pharmacology 2 (OCP/DCP-2) have reviewed NDA 203255 for SIGNIFOR<sup>®</sup> LAR (Pasireotide) injection and recommend approval. Specific recommendations are listed below:

- Proposed starting dosing regimen of 40 mg Q4W with up titration to 60 mg Q4W based on Growth Hormone (GH) and Insulin-like growth factor-1 (IGF-1) levels and down titration to 20 mg Q4W to manage adverse reactions is acceptable.
- Proposed initial dose of 20 mg Q4W for patients with moderately impaired hepatic function (Child-Pugh B) with a maximum recommended dose 40 mg Q4W is acceptable.

### **1.2 Phase IV Commitments**

None

### **1.3 Summary of Important Clinical Pharmacology Findings**

Two formulations of pasireotide have been developed: an immediate release formulation for subcutaneous (s.c.) injection and a long-acting release (LAR) formulation for intramuscular injection. Both formulations have been characterized by Phase 1 studies in healthy volunteers, and Phase 1-3 studies in patients with acromegaly and Cushing's disease, for the IR and LAR formulation respectively. The pasireotide s.c. formulation (Signifor<sup>®</sup>) was approved in the EU on 24-Apr-2012, in Switzerland on 02-Nov-2012, and by the US FDA on 14-Dec-2012 for the treatment of Cushing's disease. For both treatment of acromegaly and Cushing's disease, pasireotide was granted orphan designation.

#### **Clinical Pharmacology Data**

Since the s.c. and LAR formulations has the same active entity pasireotide, sponsor proposed to bridge results from human absorption, distribution, metabolism and excretion (ADME), thorough QT (TQT), renal impairment, hepatic impairment, and drug-drug interactions (DDI) studies conducted with the s.c. formulation to the LAR formulation. This approach was agreed upon with the FDA during at pre-submission meetings. Studies where relevant information was available with the s.c. formulation were not repeated with the LAR formulation. Please refer to the Clinical Pharmacology review under NDA200677 (dated October 25, 2012) for more relevant information of the s.c.

formulation. Please refer to Section 2.2.1 of the review for lists of clinical pharmacology studies in the pasireotide LAR formulation.

### **Adequacy of the proposed dosing regimen and titration scheme**

The proposed initial dose of 40 mg Q4W appears reasonable given the modest trend of higher response rate (GH and IGF-1 normalization), and potential risk of elevated plasma glucose levels at higher dose. Following dose increase from 40 mg to 60 mg, 12.4% (11/89) and 18% (16/89) of the patients who did not respond by the initial 3 months achieved full response and partial response, respectively at month 12 with pasireotide LAR (Study C2305).

### **Exposure-response analysis for Efficacy and Safety**

The proposed initial dose of 40 mg is supported by exposure-response relationship for efficacy and safety. There was a modest trend showing higher probability of response (GH < 2.5 µg/L and IGF-1 normalization) with increasing exposure (i.e., average trough concentration), suggesting additional benefit of 60 mg over 40 mg Q4W. In addition, exposure-response analysis was also conducted using GH and IGF-1 levels as continuous variables for efficacy and conclusions regarding the exposure-response relationship for efficacy remain the same. There is a clear trend toward increasing probability of experiencing >36 mg/dL post-baseline glucose with increasing exposure, suggesting that 60 mg will result in a higher risk of post-baseline hyperglycemia than 40 mg. Furthermore, patients with higher baseline GH and IGF-1 levels tend to have lower probability of response, and higher likelihood of requiring higher dose. Patients with higher baseline HbA1c levels tend to have higher risk of developing post-baseline hyperglycemia.

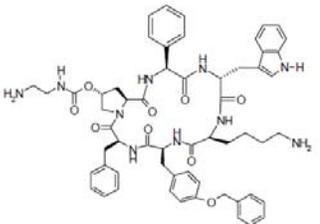
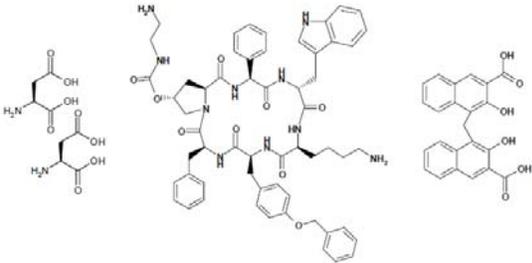
## **2 Question Based Review**

### **2.1 General attributes**

2.1.1 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

Pasireotide is presented as the diaspartate salt form in the s.c. formulation, and as the pamoate salt form in the LAR formulation. A comparative summary of these two formulations is presented in **Table 1**.

**Table 1. Comparative summary of pasireotide s.c. and pasireotide LAR formulations**

	Pasireotide sc	Pasireotide LAR
Drug substance name	Pasireotide (SOM230) diaspartate	Pasireotide (SOM230) pamoate
Drug substance structural formula		
Solubility in water (25°C):	>100 mg/mL	<1 mg/mL
Drug product dosage form	Solution for injection	Powder and solvent for suspension for injection
Dosage strengths	0.2 mg/mL, 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL	Powder: 10 mg, 20 mg, 40 mg, 60 mg Solvent (vehicle solution): 2 mL

Source: Sponsor's Summary of Biopharmaceutics, Table 1-1, Page 4

Except for absorption, which is controlled by the extended release of the LAR formulation, the distribution, metabolism and excretion properties of pasireotide between the s.c. and LAR formulations are expected to be similar because of the same active entity (pasireotide) in both formulations.

Pasireotide LAR formulation consists of:

- Microparticles (powder for suspension for injection) in vials containing the drug substance pasireotide pamoate, and
- Solvent (vehicle solution composed of commonly used excipients, i.e. (b) (4) mannitol, poloxamer 188 and water for injection) in ampoules (clinical presentation) or prefilled syringes (commercial presentation) in which the microparticles are suspended prior to i.m. injection.

### 2.1.2 What is the mechanism of action and therapeutic indication?

The proposed indication is for the treatment of patients with acromegaly (b) (4). Acromegaly is a severely debilitating condition characterized by chronic hypersecretion of growth hormone (GH). The prevalence is estimated to be 40-70 cases per million, with an annual new cases of 3-4 per million globally. In over 90% of patients, acromegaly is caused by a GH-secreting pituitary adenoma. Insulin like growth factor-1 (IGF-1), which mediates most of the growth-promoting actions of GH, is elevated in parallel with the of GH concentration.

Pasireotide exerts its pharmacological activity by binding to four of the five known somatostatin receptors (SSTR) (i.e. sst1, sst2, sst3, and sst5), as shown in **Table 2**. Activation of somatostatin receptors results in inhibition of hormone release such ACTH and growth hormone.

**Table 2. Binding Affinities of Somatostatin (SRIF-14), Pasireotide, Octreotide, and Lanreotide to the Five Human SSTR Subtypes (SSTR 1-5)**

Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin (SRIF-14)	0.93±0.12	0.15±0.02	0.56±0.17	1.5±0.4	0.29±0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	> 100	0.16±0.01
Octreotide	280±80	0.38±0.08	7.1±1.4	> 1000	6.3±1.0
Lanreotide	180±20	0.54±0.08	14±9	230±40	17±5

Results are the mean±SEM of IC<sub>50</sub> values expressed as nmol/l (nM).

### 2.1.3 *What are the proposed dosage and route of administration?*

Long-acting release (LAR) depot injection is available in 20, 40, and 60 mg powder for suspension to be suspended in a diluent immediately prior to intramuscular injection.

The sponsor's proposed labeling for the dosage and administration is as follows:

- The recommended initial dose is 40 mg administered by (b) (4) intramuscular injection once every 4 weeks (Q4W).
- The dose may be increased to a maximum of 60 mg for patients whose GH and/or IGF-1 levels are not fully controlled after 3 months of treatment at 40 mg.
- Management of (b) (4) adverse reactions may require dose. The dose may be decreased, either temporarily or permanently, by 20 mg decrements.
- The recommended initial dose for patients with moderately impaired hepatic function (Child-Pugh B) is 20 mg every 4 weeks and the maximum recommended dose is 40 mg every 4 weeks. Avoid the use in patients with severe hepatic impairment (Child Pugh C).

## 2.2 General clinical pharmacology

### 2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

An extensive Clinical Pharmacology (CP) program has been conducted for pasireotide s.c. and pasireotide LAR in healthy volunteers and patient populations. The PK of pasireotide LAR in healthy volunteers was characterized in five Phase 1 single-dose studies (Table 3).

**Table 3. Phase 1 clinical studies providing PK data for pasireotide LAR in healthy volunteers**

Study	Objectives	Pasireotide LAR Dose	No. of subjects
[C2101]	PK, safety, tolerability (Western HV)	40 mg, 60 mg single dose	12 <sup>a</sup> (M)
[C2111]	PK (BE), safety (Western HV)	60 mg single dose	114 <sup>b</sup> (M)
[B2116]	Ethnic PK, safety (Chinese HV)	20 mg, 40 mg, 60 mg single dose	45 (M)
[C2112]	Ethnic PK, safety (Taiwanese HV)	20 mg, 40 mg, 60 mg single dose	45 (M)
[G1101]	Ethnic PK, safety (Japanese HV)	10 mg, 20 mg, 40 mg, 60 mg single dose	32 (M)

BE: bioequivalence; HV: healthy volunteers; M: male

<sup>a</sup> Only data on the LAR formulation variant 2b were included from Study C2101 because it was the only formulation variant selected for clinical development

<sup>b</sup> Only data on the Basel batch were included from Study C2111 because the LAR Basel batches were used in clinical studies in healthy volunteers and acromegaly patients, and because the LAR Schaftebau batch failed to demonstrate bioequivalence (BE) versus the Basel batch.

Source: Sponsor's Summary of Clinical Pharmacology, Table 1-2, Page 11

The TQT studies B2113 and B2125, hepatic impairment Study B2114 and DDI Study B2127 were conducted with the s.c. formulation. A study of renal impairment (Study B2126) is ongoing with the s.c. formulation. Since pasireotide is the same active entity in both the s.c. and LAR formulations, results for the s.c. formulation were used to bridge to the LAR formulation by the sponsor, and studies where relevant information was available with the s.c. formulation were not repeated with the LAR formulation. The approach of bridging results from human absorption, distribution, metabolism and excretion (ADME), TQT, renal impairment, hepatic impairment, and drug-drug interactions (DDI) studies conducted with the s.c. formulation to the LAR formulation was agreed at pre-submission meetings with FDA.

The PK and PK/PD (pharmacokinetics/pharmacodynamics) of pasireotide LAR in acromegaly patients were characterized in one Phase 1 study and two Phase 3 studies (**Table 4**). The PK and PK/PD of pasireotide s.c. in acromegaly patients were characterized in one Phase 1 and one Phase 2 study (**Table 5**). The dose selection was based on bridging the dose-response of LAR and SC formulation by matching PK from study B2201 (SC) and C2110 (LAR), assuming the same exposure-response relationship exists for these two formulations. There was no dose finding study.

**Table 4. Summary of Phase 1 and Phase 3 clinical studies with PK and PK/PD components for pasireotide LAR in acromegaly patients**

Study	Objectives	Pasireotide LAR dose	No. of subjects
[C2110] (Phase I)	Safety, tolerability, PK, PD	20, 40, 60 mg monthly (q28d) Dose up- and down-titration allowed	35 <sup>a</sup> (23 M, 12 F)
[C2110E] (Phase I)	Safety, tolerability, PK, PD	20, 40, 60 mg monthly (q28d) Dose up- and down-titration allowed	29 <sup>a</sup> (20 M, 9 F)
[C2305] (Phase III)	Efficacy, safety, PK, PD	40 mg monthly (q28d) Dose up- and down-titration allowed	176 <sup>b</sup> (85 M, 91 F)
[C2402] (Phase III)	Efficacy, safety, PK, PD	40, 60 mg monthly (q28d) Dose down-titration allowed	130 <sup>c</sup> (57 M, 73 F)

M: male; F: female

<sup>a</sup> Both acromegaly patients and carcinoid patients were enrolled in Study C2110 and its extension Study C2110E, but only data from patients with acromegaly were included in the present report for the target indication of acromegaly. No new patients were enrolled in Study C2110E

<sup>b</sup> Study C2305 included both pasireotide LAR and octreotide LAR arms, but only data from patients treated with pasireotide LAR were included in this table.

<sup>c</sup> Study C2402 included pasireotide LAR, octreotide LAR and lanreotide ATG arms, but only data from patients treated with pasireotide LAR were included in this table.

Source: Sponsor's Summary of Clinical Pharmacology, Table 1-3, Page 13

**Table 5. Summary of Phase 1 and Phase 2 clinical studies with PK and PK/PD components for pasireotide s.c. in acromegaly patients**

Study	Objectives	Pasireotide sc dose	No. of subjects
[B2103] (Phase I)	Efficacy, safety, PK, PD	100, 250 µg single dose	12 (6 M, 6 F)
[B2201] (Phase II)	Efficacy, safety, PK, PD	200, 400, 600 µg bid x 4 weeks	60 (33 M, 27 F)
[B2201E] (Phase II)	Safety, efficacy, PK, PD	200, 400, 600 µg bid	30 (14 M, 16 F)

M: male; F: female

Source: Sponsor's Summary of Clinical Pharmacology, Table 1-4, Page 14

### 2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The primary and secondary efficacy endpoints in Phase 3 studies C2305 and C2402 were chosen based on the biochemical markers of the disease and the clinical manifestations of acromegaly. GH and IGF-I (adjusted for age and sex) are the most important biochemical variables for diagnosis and for monitoring progression or treatment response in acromegaly. The standard biochemical goals of therapy are to reduce GH levels to <2.5 µg/L, and to reduce IGF-1 levels to normal levels for age and sex.

Because GH secretion is pulsatile in nature and therefore variable, a patient's GH level should be assessed based on the mean of multiple samples collected over at least 2 hours. In studies C2305 and C2402, all GH assessments were based on the mean of a 5-point 2-hour profile. All assays for GH and IGF-1 were performed at a central laboratory to minimize assay variability.

## 2.3 Exposure-Response

### 2.3.1 *Does the exposure-response relationship for efficacy (GH and IGF-1) support the proposed initial dose of 40 mg every 4 weeks?*

Yes. The proposed initial dose appears reasonable given the lack of evidence of exposure-response for efficacy in study C2305 and modest trend in study C2402. Dose titration from 40 mg to 60 mg provided some benefit in patients who did not respond by the first 3 months. However it should be noted that there was no control arm for the titration effect. Patients with higher baseline GH and IGF-1 levels tend to have lower probability of response, and higher likelihood of requiring higher dose.

The efficacy and safety of pasireotide LAR in acromegaly patients are primarily derived from two phase 3 studies comparing pasireotide LAR with active controls (superiority design).

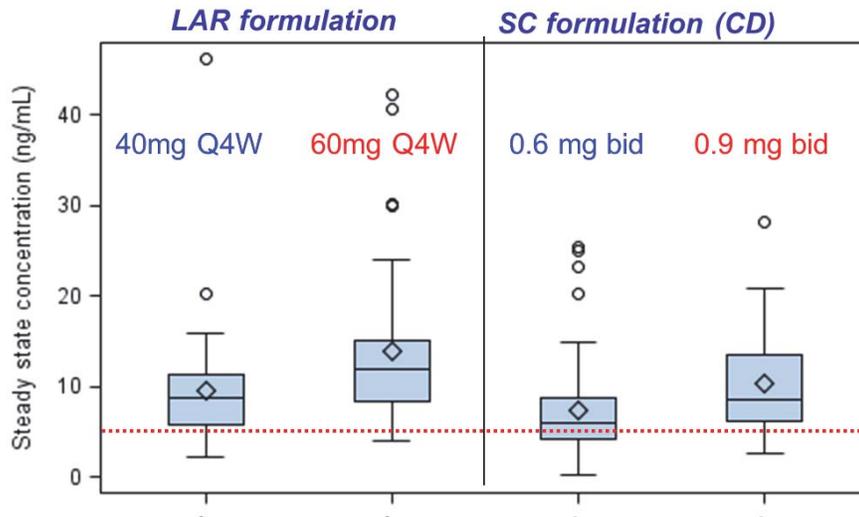
- In medically naïve patients (Study C2305), the primary endpoint was met at the end of the 12-month blinded core phase: 31.3% responders (patients with GH below 2.5 µg/L and normalized IGF-1) in the pasireotide LAR arm, vs. 19.2% in the octreotide LAR arm, with an odds ratio (95% CI) of 1.942 (1.190, 3.168) in favor of pasireotide LAR ( $p=0.007$ ).
- In the inadequately controlled patients (Study C2402), superiority of both pasireotide LAR 40 mg and 60 mg over active control (octreotide LAR 30 mg or lanreotide ATG 120 mg) was demonstrated. The proportion of responders at month 6 was 15.4% in the 40 mg arm, 20% in the 60 mg arm, and 0% in the active control arm. The comparison was statistically significantly higher for both pasireotide LAR doses vs. active control. The results of additional analysis across demographic subgroups (race, ethnicity and age) showed a treatment effect consistently favoring pasireotide LAR.

### **Rationale of dose selection for Phase 3 study**

Phase 2 dose-response Study B2201 with the s.c. formulation showed that higher response (GH < 2.5 µg/L and normalized IGF-1) (12.7%, 24.1% and 31.5%) was associated with higher dose (0.2, 0.4 and 0.6 mg bid, respectively), suggesting higher doses might provide better efficacy and should be explored further. An effective concentration required for complete GH normalization ( $C_{\text{effective}} = 5.09 \pm 4.19$  ng/mL) was estimated based on PKPD modeling analysis.

In Study C2110 with LAR formulation (Q4W), observed steady-state trough concentrations were above  $C_{\text{effective}}$  for GH normalization with 40 mg ( $5.92 \pm 2.85$  ng/mL) and 60 mg LAR ( $8.87 \pm 4.53$  ng/mL), but not 20 mg ( $2.74 \pm 1.33$  ng/mL). As the 40 mg LAR dose is the closest to the dose strength of the pasireotide s.c. 0.6 mg bid dose in terms of monthly dose ( $1.2$  mg/day  $\times$  28 days = 33.6 mg Q4W), 40 mg Q4W was chosen as the starting dose in Study C2305, and as one of two doses tested in Study C2402. This is also supported by comparison of PK between LAR formulation in study

C2402 and s.c. formulation in Cushing's Disease patients (see **Figure 1**). The mean steady state trough concentration was slightly lower for the s.c. formulation. But the range of distribution was generally comparable between 40 mg Q4W vs 0.6 mg bid, and between 60 mg Q4W vs 0.9 mg bid. The mean trough concentrations on both the 40 mg Q4W and 0.6 mg bid dose were above the  $C_{\text{effective}}$ .



**Figure 1. PK Comparison between LAR and s.c. formulation**

Since some patients may require doses higher than 40 mg of pasireotide LAR, a dose increase to 60 mg Q4W was permitted in Study C2305 for patients who did not achieve biochemical control (GH levels to  $<2.5 \mu\text{g/L}$ , and to reduce IGF-1 levels to normal levels for age and sex) after 3 months (at steady-state) of treatment, and the 60 mg Q4W dosing regimen was included as a randomized treatment in Study C2402.

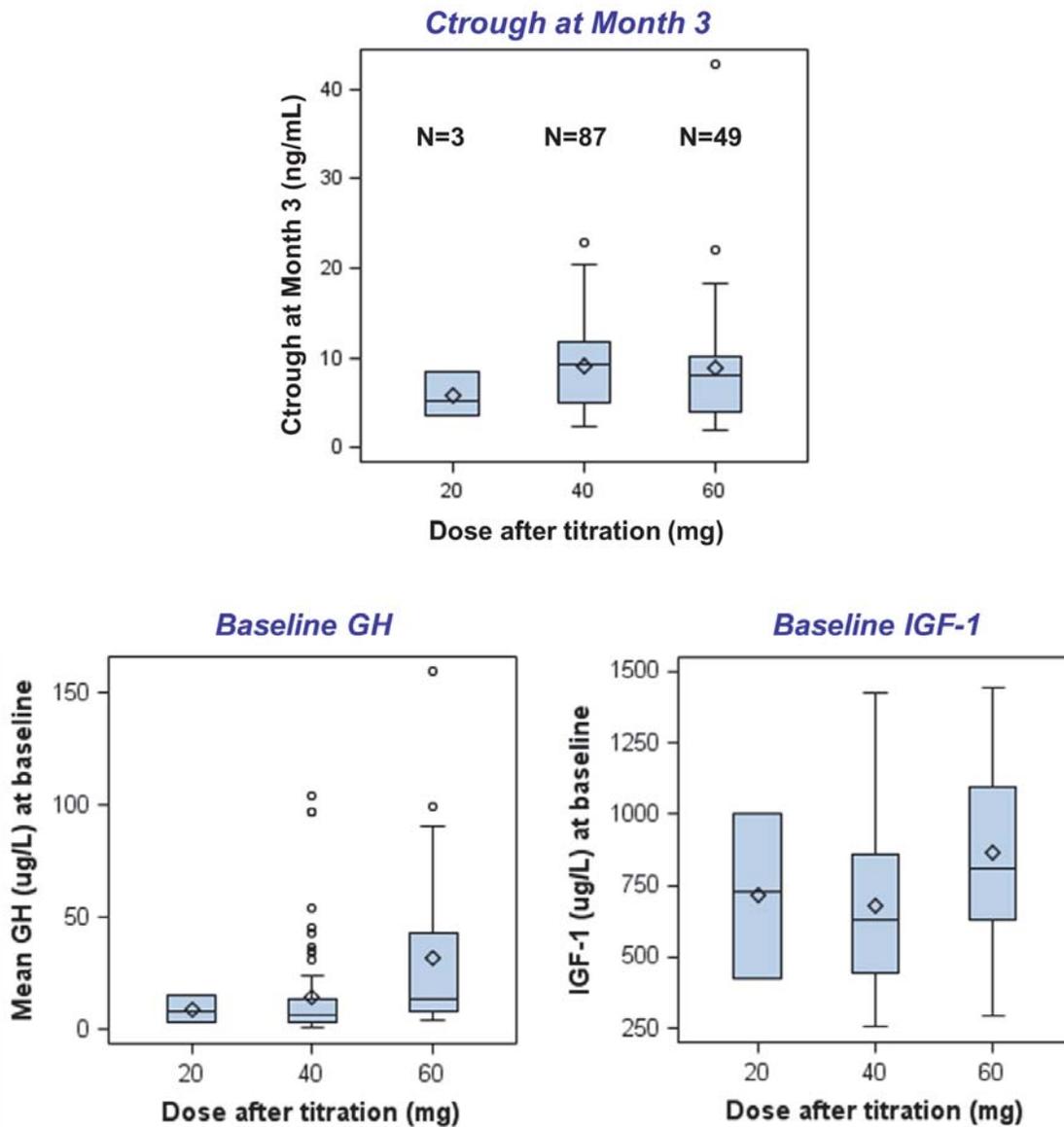
### **Exposure-response relationship**

Exposure-response analysis for efficacy was conducted for Study C2305 and C2402 separately, to link the probability of achieving biochemical control (GH below  $2.5 \mu\text{g/L}$  and normalized IGF-1) with pasireotide exposure. ER relationships were assessed at month 3 and month 6 for Study C2402 and only at month 3 for Study C2305, in which case dose escalations from 40 mg LAR were permitted after that which may confound the ER relationship. It is also because that the plateau of response is reached by 3 months. For analyses conducted at month 3, the average trough concentration over the first 3 months for each patient was used as the exposure variable.

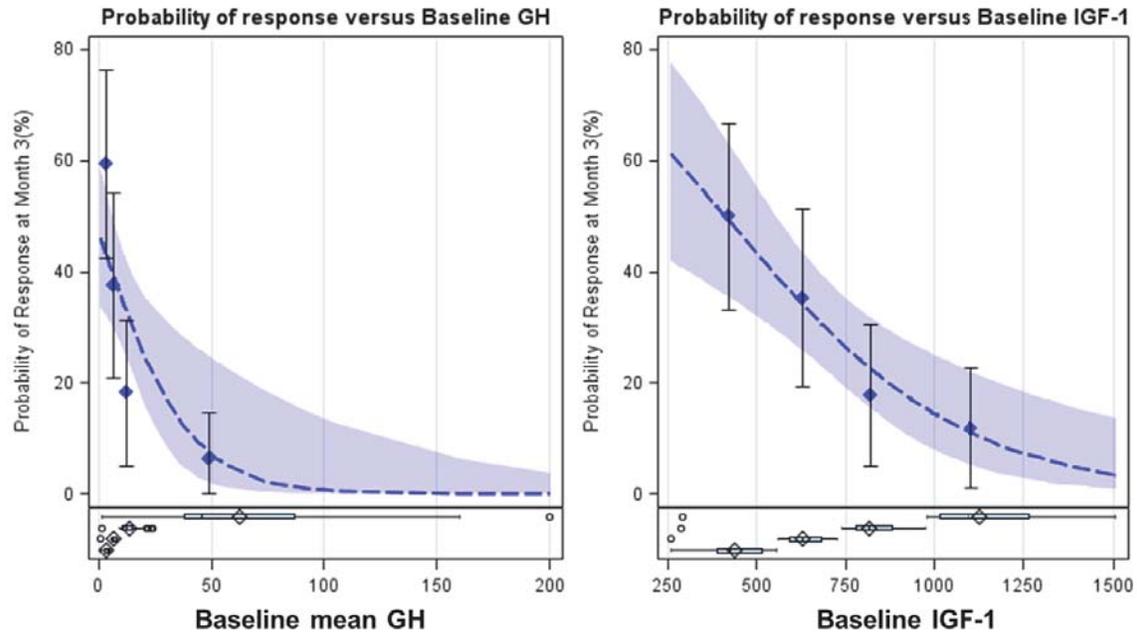
In dose-titration Study C2305, the distribution pasireotide trough concentrations at month 3 before dose titration was plotted across titration groups, as shown in **Figure 2**

**Figure 2.** Comparable exposure was observed between patients who stayed on 40 mg and those who got up-escalated to 60 mg after month 3, indicating lower concentration was not the reason for lack of biochemical control by month 3.

It was noticed that patients who were up-titrated after month 3 had higher baseline GH and IGF-1 levels (**Figure 2**). From the logistic regression results, it was observed that the probability of response decreases with the increase in baseline GH and IGF-1 levels (**Figure 3**). In other words, patients with higher baseline had lower probability of response as they have to undergo greater reduction to go below the threshold in order to be defined as a responder. Therefore, baseline GH and IGF-1 levels were accounted for using multivariate analysis.

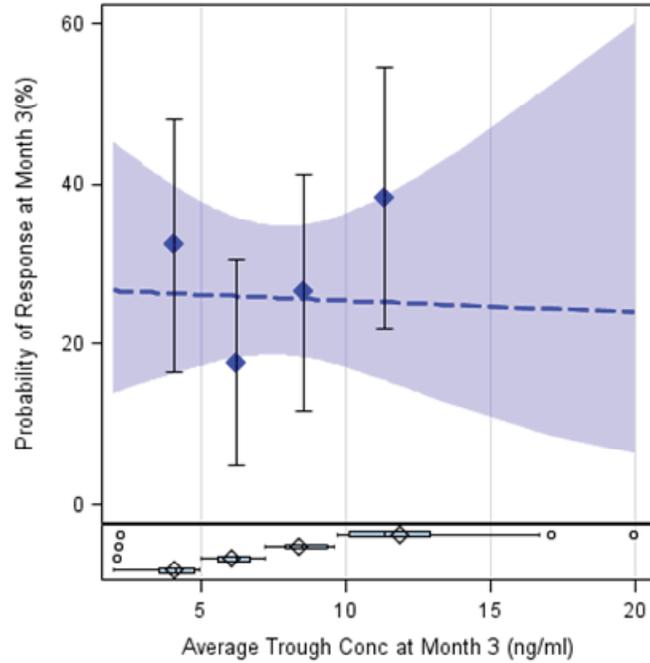


**Figure 2. Distribution of pasireotide trough concentrations at month 3 before dose titration, and baseline GH and IGF-1 levels across dose-titration groups**

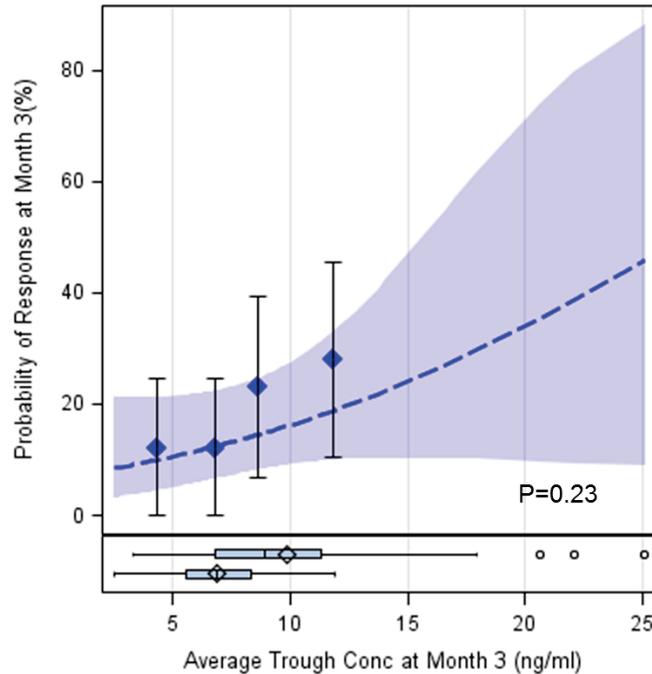


**Figure 3. Patients with higher baseline GH-1 and IGF-1 levels have lower probability of Response (Study C2305). Logistic regression model includes the probability of response at month 3 as a function of baseline GH and IGF-1. The observed mean and 95% CI of the response rate versus mean baseline levels is represented by blue square and black bar while dashed blue line and purple band represent the model predicted mean and 95% CI. The box plots at the bottom represent the distribution of baseline values in each quartile.**

The exposure-response relationship was not evident in Study C2305 (**Figure 4**), with or without adjusting for baseline GH and IGF-1. In Study C2402, where 40 mg and 60 mg were studied in parallel, there was a shallow trend showing higher probability of response with increasing exposure (**Figure 5**). Even though the relationship was not statistically significant ( $p = 0.23$ ), this suggests potential benefit might be gained by 60 mg over 40 mg, which is consistent with the observed dose-response results. It should be noted that the results are consistent if response at month 6 is used as the response variable and steady state concentration at month 6 as the exposure variable. In addition, exposure-response analysis was also conducted using GH and IGF-1 as continuous variables for efficacy and conclusions regarding the exposure-response relationship for efficacy remain the same.



**Figure 4.** No evident relationship is shown between exposure and response rate (GH below 2.5  $\mu\text{g/L}$  and normalized IGF-1) at month 3 (Study C2305). Logistic regression model includes the probability of responder at month 3 as a function of average pasireotide concentration at month 3 after adjusting for baseline GH and IGF-1 (Ctrough p-value=0.81; baseline GH p-value=0.044; baseline IGF-1 p-value=0.0122). The observed mean and 95% CI of the response rate versus mean concentration in four average trough concentration quartiles is represented by blue square and black bar while dashed blue line and purple band represent the model predicted mean and 95% CI. The box plots at the bottom represent the distribution of trough concentration in each concentration quartiles.



**Figure 5. A shallow trend of increase in response rate (GH below 2.5  $\mu$ g/L and normalized IGF-1) with increasing exposure is shown at month 3 (Study C2402). Logistic regression model includes the probability of responder at month 3 as a function of average pasireotide concentration at month 3 after controlling for baseline GH and IGF-1 (Ctrough p-value=0.23; baseline GH p-value=0.52; baseline IGF-1 p-value=0.02). The observed mean and 95% CI of the response rate versus mean concentration in four average trough concentration quartiles is represented by blue square and black bar while dashed blue line and purple band represent the model predicted mean and 95% CI. The box plots at the bottom represent the distribution of trough concentration in each concentration quartiles.**

**Is there evidence to support dose increase from 40 mg to 60 mg Q4W if biochemical control not achieved by month 3?**

Yes. For patients who did not achieve biochemical control, there is evidence for additional benefits with dose increase from 40 mg to 60 mg Q4W.

In Study C2305, dose escalation from pasireotide LAR 40 mg to 60 mg was permitted after month 3 if biochemical control was not achieved. The proportion of patients with dose increase during the core is summarized by month 12 response status in **Table 6**. More than half of all patients had a dose increase prior to month 12 (50.6% on pasireotide LAR and 67.6% on octreotide LAR), which allowed additional patients to achieve response. Following dose increase, 12.4% (11/89) and 18% (16/89) of the patients who did not respond by the initial 3 months achieved full response and achieved partial response respectively, at month 12 with pasireotide LAR. However, it should be noted

that this titration effect was not supported by a control arm where patients stay at the initial 40 mg dose.

**Table 6. Patients with at least one dose increase by GH and IGF-1 response at Month 12**

Response status	Pasireotide LAR		Octreotide LAR	
	Total	Dose increase n (%)	Total	Dose increase n (%)
Overall	176	89 (50.6%)	182	123 (67.6%)
Full response	63	11 (17.5%)	38	11 (28.9%)
Partial response	24	16 (66.7%)	33	18 (54.5%)
No response	89	62 (69.7%)	111	94 (84.7%)

Full response (FR) included patients who achieved biochemical response. Patients were not considered responders if their IGF-1 was below normal limits. Partial response (PR) was defined as GH <5 µg/L and IGF-1 ≤ 1.3xULN and not achieving FR criteria. No response (NR) was defined as neither FR nor PR.

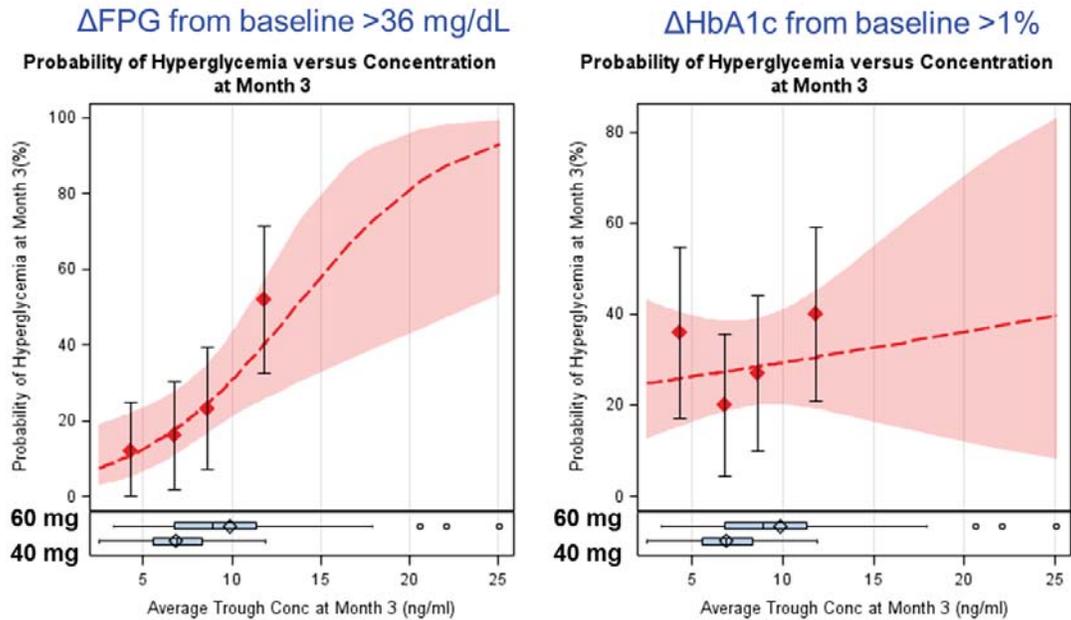
Source: Sponsor's Clinical Study Report for Study C2305, Table 11.6.

2.3.2 *Does the exposure-response relationship for safety (post-baseline Hyperglycemia) support the proposed initial dose of 40 mg every 4 weeks?*

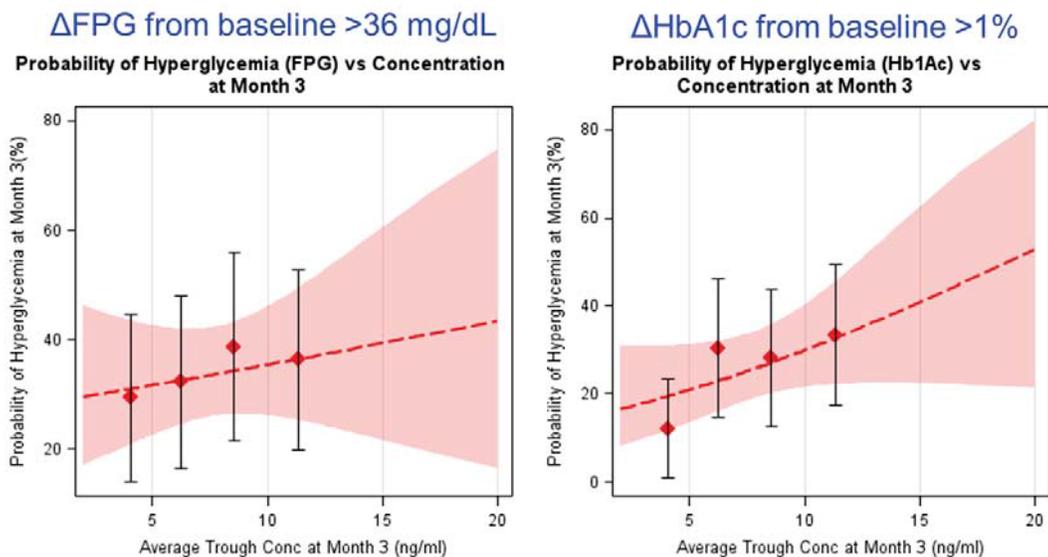
Yes. The starting dose of 40 mg Q4W is reasonable given potential risk of elevated plasma glucose levels at higher dose.

One of the main safety concerns for pasireotide is hyperglycemia. Two definitions for the occurrence of hyperglycemia were used in the analysis. One was defined as change in free plasma glucose (FPG) from baseline >36 mg/dL as used in sponsor's analysis, while another was as change in HbA1c from baseline >1% as previously used for Cushing's disease.

As hyperglycemia effect caused by pasireotide reached plateau at month 3 at population level, exposure-response analysis was conducted at month 3 separately for each definition after accounting for baseline HbA1c levels (baseline FPG levels was not identified as a significant risk factor). For Study C2402 as shown in **Figure 6**, there is a clear trend showing increased probability of experiencing >36 mg/dL post-baseline glucose with increasing exposure, suggesting that 60 mg will result in a higher risk of post-baseline hyperglycemia than 40 mg. Therefore, starting with lower dose of 40 mg Q4W is reasonable. In Study C2305, the trend was similar, but shallower with glucose and slightly steeper with HbA1c increase (**Figure 7**).



**Figure 6. Increase in probability of developing post-baseline hyperglycemia at month 3 with the increase of pasireotide exposure after adjusting for baseline HbA1c (Study C2402). Logistic regression model includes the probability of post-baseline hyperglycemia at month 3 as a function of average pasireotide concentration at month 3 after controlling for baseline HbA1c. For definition by glucose ( $\Delta$ FPG from baseline >36 mg/dL): Ctrough p-value=0.003; Baseline HbA1c p-value=0.067). For definition by HbA1c ( $\Delta$ HbA1c from baseline >1%): Ctrough p-value=0.66; Baseline HbA1c p-value=0.0002).**



**Figure 7. Increase in probability of developing post-baseline hyperglycemia at month 3 with the increase of pasireotide exposure after adjusting for baseline HbA1c (Study C2305). Logistic regression model includes the probability of post-baseline hyperglycemia at month 3 as a function of average pasireotide concentration at month 3 after controlling for baseline HbA1c. For definition by glucose ( $\Delta$ FPG from baseline >36 mg/dL): Ctrough p-value=0.53; Baseline HbA1c p-value=0.04). For definition by HbA1c ( $\Delta$ HbA1c from baseline >1%): Ctrough p-value=0.10; Baseline HbA1c p-value=0.24).**

### 2.3.3 Does this drug prolong the QT or QTc interval?

Yes, pasireotide prolongs QT interval and results of a TQT study performed with the s.c. formulation are included in the current approved label. The exposures expected in the worst case scenario with the LAR formulation are anticipated to be covered by those observed in the TQT studies with the s.c. formulation. QT-IRT concluded that TQT studies performed with pasireotide s.c. formulation would cover the potential effect of pasireotide LAR formulation on QT interval. For details refer to QT-IRT review under NDA203255 (dated July 17, 2014).

## 2.4 PK Characteristics of Pasireotide LAR

### 2.4.1 What are the single and multiple dose PK characteristics of the drug?

#### Single dose PK- Healthy volunteers

A summary of PK parameters after a single dose of 10 to 60 mg LAR pasireotide in male healthy volunteers by study (Study C2101, Study C2111, Study B2116, Study C2112 and Study G1101) is shown in **Table 7**. 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 (**Figure 8**). The PK exposures are approximately dose proportional in the 10 to 60 mg range. The extended release of pasireotide LAR is suitable for every-4-week 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 s.c. formulation is 100%. Pasireotide is excreted mainly in feces as unchanged form.

**Table 7. Summary of PK parameters after a single dose of 10-60 mg pasireotide LAR in healthy volunteers by study [C2101 (Western), C2111 (Western), B2116 (Chinese), C2112 (Taiwanese), G1101 (Japanese)]**

Study*	Dose (mg)	N	Cmax,P1 (ng/mL)	Cmax,P2 (ng/mL)	AUCinf (ng.h/mL)	CL/F (L/h)	RBA <sup>a</sup>
C2101 <sup>b</sup>	40	5	6.1 ± 3.9 (63.9)	9.6 ± 5.1 (53.4)	4959 ± 1068 (21.5)	8.5 ± 2.4 (28.0)	1.48 ± 0.15 (10.2)
	60	5	5.5 ± 1.2 (21.8)	15.8 ± 3.3 (20.8)	7971 ± 651 (8.2)	7.6 ± 0.6 (8.1)	1.33 ± 0.23 (17.4)
C2111 <sup>b</sup>	60	110	8.0 ± 5.7 (70.6)	20.0 ± 7.4 (37.0)	10394 ± 3091 (29.7)	6.2 ± 1.7 (27.4)	NA
B2116 <sup>b</sup>	20	15	6.7 ± 2.5 (37.7)	6.1 ± 1.5 (25.0)	3260 ± 720 (22.1)	6.4 ± 1.3 (19.9)	1.18 ± 0.23 (19.1)
	40	14	9.4 ± 3.2 (34.5)	12.0 ± 4.8 (40.1)	6274 ± 1777 (28.3)	6.8 ± 1.8 (25.7)	1.20 ± 0.22 (18.1)
	60	13	11.9 ± 2.9 (24.7)	19.6 ± 5.3 (26.9)	9915 ± 2596 (26.2)	6.4 ± 1.6 (25.2)	1.32 ± 0.35 (26.3)
C2112 <sup>b</sup>	20	15	2.8 ± 2.1 (73.0)	6.9 ± 2.5 (36.9)	3300 ± 710 (21.5)	6.3 ± 1.1 (17.1)	1.15 ± 0.27 (23.3)
	40	15	6.2 ± 2.9 (46.7)	14.0 ± 5.2 (37.5)	6944 ± 2168 (31.2)	6.1 ± 1.3 (21.3)	1.06 ± 0.16 (15.0)
	60	15	5.8 ± 3.5 (60.2)	18.7 ± 9.2 (49.0)	8951 ± 3013 (33.7)	7.2 ± 1.6 (22.3)	1.14 ± 0.36 (31.8)
G1101 <sup>c</sup>	10	8	1.7 ± 0.4 (22.0)	4.4 ± 1.1 (24.5)	1953 ± 272 (13.9)	5.2 ± 0.7 (13.3)	NA
	20	8	3.1 ± 1.6 (52.4)	8.2 ± 1.7 (20.6)	4069 ± 1184 (29.1)	5.2 ± 1.3 (24.9)	NA
	40	8	10.6 ± 4.1 (38.5)	19.8 ± 10.4 (52.4)	10259 ± 4844 (47.2)	4.5 ± 1.5 (33.9)	NA
	60	8	9.7 ± 4.4 (45.0)	29.0 ± 9.0 (30.9)	13395 ± 1468 (11.0)	4.5 ± 0.5 (10.8)	NA

NA: not applicable; RBA: relative bioavailability

\*Data are presented as mean ± SD (CV%) for all parameters, where CV% = coefficient of variation (%) = SD/mean\*100%

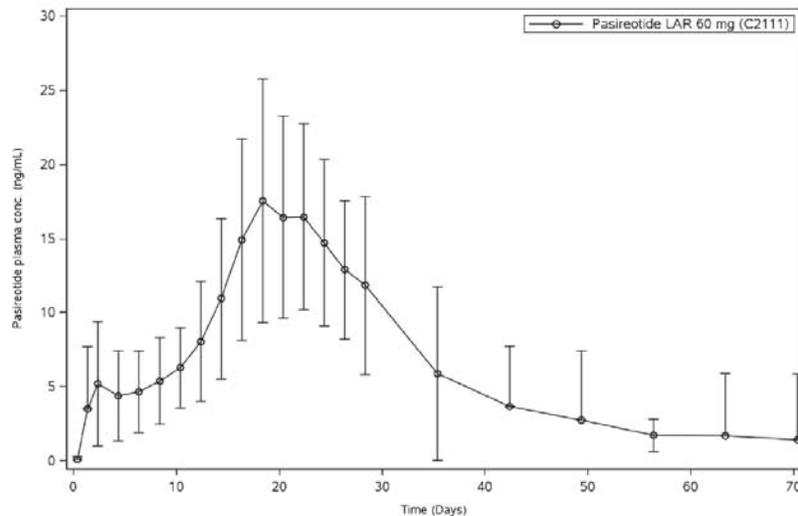
<sup>a</sup> RBA = (AUCinf,LAR/LAR dose)/(AUCinf,sc/sc dose)

<sup>b</sup> PK parameters AUCinf, Cmax,p1 and Cmax,p2 are adjusted based on the exact doses in studies C2101, C2111, B2116 and C2112

<sup>c</sup> PK parameters AUCinf, Cmax,p1 and Cmax,p2 are based on the planned doses in study G1101 because no exact dose data were available.

Source: [\[Appendix 1-Table 3-3\]](#)

Source: Sponsor's Summary of Clinical Pharmacology, Table 2-1, Page 31

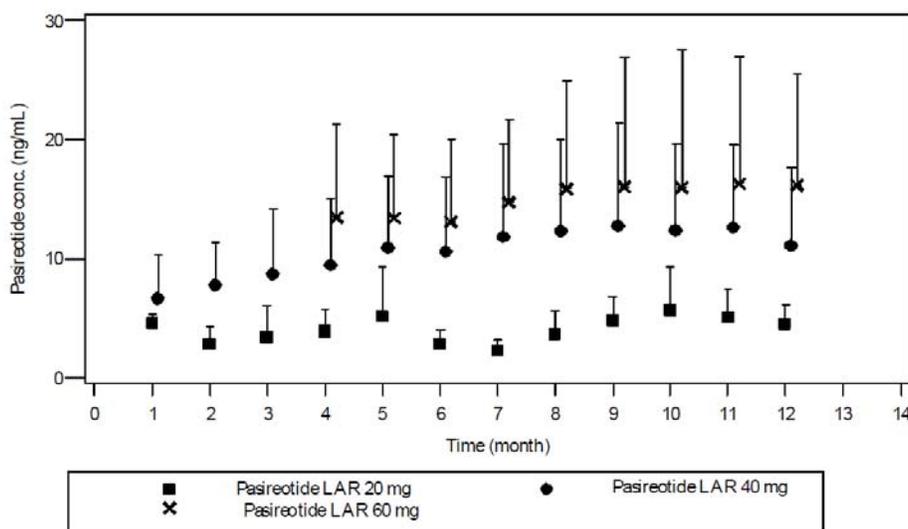


Source: Clinical Study Report No. C2111, Figure 14.2-3.2

**Figure 8. Mean (SD) plasma concentration versus time profile for pasireotide LAR 60 mg in healthy volunteers (Study C2111)**

### Multiple dose PK (Q4W)- Acromegaly patients

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. Mean (SD) pasireotide trough concentration versus time profiles following twelve monthly i.m. injections of 20, 40 or 60 mg pasireotide LAR in medically naïve acromegaly patients (Study C2305, 12-months core phase) are shown in **Sponsor's Summary of Clinical Pharmacology, Figure 3-3, Page 44** **Figure 9**.



Source: *Sponsor's Summary of Clinical Pharmacology, Figure 3-3, Page 44*

**Figure 9. 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, core phase)**

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  $C_{max}$ , and 8.2-47.2% for  $AUC_{inf}$ . 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.

### Protein binding

The distribution of pasireotide between blood cell and plasma showed that pasireotide was primarily located in the plasma component (91%), and distribution in blood was independent of concentration. As binding of pasireotide to human plasma protein was moderate (88%) and concentration-independent, a DDI due to protein-binding displacement is not expected for pasireotide LAR in acromegaly patients.

## Metabolism

Pasireotide was mainly excreted as unchanged drug in healthy volunteers (Study B2112). The non-clinical and clinical data suggested that no DDI between pasireotide and co-medications (such as CYP450 inhibitors) would be expected.

## Excretion

Results from the human ADME study in healthy volunteers (Study B2112) indicate that pasireotide is mainly eliminated via hepatic clearance, with renal clearance playing a minimal role in the elimination of pasireotide in humans.

### 2.4.2 *Dose the body weight, age, race, gender have effect on PK parameters?*

Population PK analysis suggests that age, body weight, race, gender have no clinically meaningful influence on PK of pasireotide.

## **3 Labeling Recommendations**

(Please refer attached file for clinical pharmacology labeling comments. ~~Strikethrough~~ indicates deletion and red underlined text indicates addition.)

Labeling addendum will be added later.

## **4 Appendices**

### **4.1 RESULTS OF SPONSOR'S ANALYSIS**

Sponsor assessed the exposure-response relationship for efficacy (GH, IGF-1 and overall response) and safety endpoints (FPG and HbA1c) through population PK/PD modeling. The summary of the results is presented here. For details please refer to sponsor's Summary of Clinical Pharmacology.

#### 4.1.1 *Exposure-response relationship for Efficacy*

PK/PD relationships of pasireotide plasma concentrations with GH and IGF-1 were assessed by two modeling approaches:  $E_{max}$  modeling and logistic regression modeling. The former approach was used to establish the concentrations at which a 50% reduction or complete normalization of GH and IGF-1 would be expected, as well as the maximum possible extent of reduction. The latter approach modeled the probabilities of normalization (GH, IGF-1 and GH+IGF-1) as a function of exposure. Parameter estimates from the  $E_{max}$  models in Phase 3 studies C2305 and C2402 are displayed in **Error! Reference source not found.** and Error! Reference source not found..

**Table 8. Parameter estimates (+/- SE) from the  $E_{max}$  model for pasireotide concentration vs. GH in Phase 3 studies C2305 and C2402**

Parameter	Study C2305	Study C2402
Emax ( $\mu\text{g/L}$ )	10.58 $\pm$ 0.32	7.68 $\pm$ 1.95
E0 ( $\mu\text{g/L}$ )	1.55 $\pm$ 0.17	1.30 $\pm$ 0.29
(Emax-E0)/Emax (%)	85.3 $\pm$ 1.67	83.0 $\pm$ 6.47
EC50 (ng/mL)	0.73 $\pm$ 0.16	2.83 $\pm$ 1.06
Ceffective (ng/mL)	6.25 $\pm$ 1.12	12.28 $\pm$ 3.32

Source: [Study C2305-Table 14.2-3.36]; [Study C2402-Table 14.2-3.8]

Source: Sponsor's Summary of Clinical Pharmacology, Table 1-5

**Table 9. Parameter estimates (+/- SE) from the  $E_{max}$  model for pasireotide concentration vs. IGF-1 in Phase 3 studies C2305 and C2402**

Parameter	Study C2305	Study C2402
Emax ( $\times$ Upper Limit of Normal [ULN])	2.83 $\pm$ 0.05	2.29 $\pm$ 0.14
E0 ( $\times$ ULN)	0.75 $\pm$ 0.05	0.75 $\pm$ 0.12
(Emax-E0)/Emax (%)	73.6 $\pm$ 1.86	67.1 $\pm$ 5.76
EC50 (ng/mL)	1.84 $\pm$ 0.28	8.13 $\pm$ 1.81
Ceffective (ng/mL)	13.45 $\pm$ 2.39	42.30 $\pm$ 16.57

Source: [Study C2305-Table 14.2-3.37]; [Study C2402-Table 14.2-3.9]

Source: Sponsor's Summary of Clinical Pharmacology, Table 1-6

The primary output of the repeated measures logistic regression model was in terms of the increase in odds of response when concentration increases by 50% (expected for a dose increase from 40 mg to 60 mg). Significant increases in response rate are obtained by an increase in concentration that would be expected with an increase of dose from 40 mg to 60 mg (**Table 10**).

**Table 10. Percent increase in odds of response for a 50% increase in pasireotide LAR concentration in Phase 3 studies C2305 and C2402**

Response: Normalization of	Study C2305	Study C2402
GH	25% (9%-43%)	44% (13%-85%)
IGF-1	37% (17%-59%)	51% (21%-88%)
GH and IGF-1	27% (9%-48%)	54% (22%-94%)

Note: Results are expressed as Estimate (95% CI)

Source: [Appendix 1-Table 4-5] to [Appendix 1-Table 4-7] and [Study C2402-Table 14.2-3.10].

Source: Sponsor's Summary of Clinical Pharmacology, Table 1-7

*Reviewer's Comments: The finding of sponsor's ER analysis is generally consistent with reviewer's independent assessment. It is noted that the estimated EC50 and Ceffective for GH and IGF-1 were much higher and the baseline for GH and IGF-1 were slightly lower in Study C2402 compared to Study C2305. These differences may be due to different underlying disease status of these two patient populations. The PK/PD results suggest that higher concentrations of pasireotide were required to achieve similar efficacy, especially to normalize IGF-1, in Study C2402 compared to Study C2305.*

#### 4.1.2 Exposure-response relationship for Safety

Repeated measures logistic regression model was used to quantify the rate of occurrence of hyperglycemia, which was defined as FPG change from baseline >36 mg/dL. The primary outcome of was the change in odds of hyperglycemia associated with a 50% increase in pasireotide trough concentration (**Table 11**). The models adjusted for baseline FPG.

**Table 11. Repeated measures logistic regression model: percent increase in odds of hyperglycemia for a 50% increase in concentration**

Study C2305	Study C2402	Study C2305 and Study C2402 <sup>a</sup>
21%	36%	33%

<sup>a</sup>Pooled inadequately controlled patients from two studies  
Source: [Appendix 1–Table 4-8], [Study C2402-Table 14.2-3.13] and [Appendix 1-Table 7-9]

Source: Sponsor's Summary of Clinical Pharmacology, Table 1-8

*Reviewer's Comments: The finding of sponsor's analysis is consistent with reviewer's independent assessment. In both medically naïve and inadequately controlled acromegaly patients, there is a statistically significant association between pasireotide trough concentration and probability of developing hyperglycemia, with baseline FPG levels as significant covariates.*

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LIAN MA  
08/15/2014

SANG M CHUNG  
08/15/2014

IMMO ZADEZENSKY  
08/15/2014

NITIN MEHROTRA  
08/15/2014

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## ONDQA BIOPHARMACEUTICS REVIEW

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**NDA#:** 203-255/S-000  
**Submission Date:** 11/15/2013, 2/14/2014, 6/12/2014  
**Drug Name:** Signifor LAR (pasireotide pamoate) Injection  
**Formulation:** Powder for Injection  
**Strength:** 20, 40, and 60 mg  
**Applicant:** Novartis  
**Reviewer:** John Duan, Ph.D.  
**Submission Type:** Original NDA 505(b)(1)

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### BACKGROUND

Pasireotide (SOM230) is a second generation somatostatin analogue proposed for the treatment of patients with acromegaly (b)(4) SOM230 Powder for suspension for injection, is a long acting release dosage form for parenteral (intramuscular) administration. This review will focus on the dissolution and IVIVC studies.

### COMMENTS

1. The proposed dissolution acceptance criteria based on the Agency's recommendation are acceptable. However, the Applicant needs to update the product specification table and other relevant documentations of the NDA.
2. There is a concern for the method of establishment of the IVIVC. The Applicant needs to provide justification (b)(4)

### RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed NDA 203-255 and the recommendation is pending on the update of the product specification table and other relevant documentations of the NDA.

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John Duan, Ph.D.  
Reviewer  
ONDQA Biopharmaceutics

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Date

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Tapash Ghosh, Ph.D.  
Team Leader  
ONDQA Biopharmaceutics

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Date

cc: NDA 203-255 *DARRTS*

# BIOPHARMACEUTICS EVALUATION

## 1. Introduction

Pasireotide (SOM230) is a second generation somatostatin analogue proposed for the treatment of patients with acromegaly (b) (4) SOM230 Powder for suspension for injection, is a long acting release dosage form for parenteral (intramuscular) administration. It is a slightly yellowish to yellowish powder in a 6 ml brownish glass vial, consisting of drug loaded poly(D,L-lactide-co-glycolide) microparticles to be suspended in an aqueous vehicle prior to injection.

## 2. Physiological properties of the drug substance

**Physical description:** The active ingredient, Pasireotide (SOM230), is a cyclic hexapeptide presented as the pamoate salt. Pasireotide pamoate is an (b) (4) white to yellowish powder which has been developed into a long acting release intramuscular formulation.

**Solubility:** The drug substance pasireotide pamoate is practically insoluble in water as shown in the following table.

SOM230 salt solubility data (mg/ml in water at 25 °C)

(b) (4)

**Stability:** The stability of SOM230 salts in poly(D,L-lactide-co-glycolide) (b) (4) is shown in the following table.

(b) (4)

**Reviewer's Comments:** The pamoate salt was selected for the long acting release formulation based on its low solubility in water as well as stability in poly(D,L-lactide-co-glycolide) (b) (4)

## 3. Pharmacokinetics

Following a single LAR dose of 60 mg in healthy volunteers, the PK profile showed an initial burst release (C<sub>max,p1</sub>) at 12 hours post-injection on Day 1 (T<sub>max, p1</sub>), followed by a dip from Day 2 to Day 7, a slow increase to maximum concentration (C<sub>max,p2</sub>) around Day 20 (Week 3; T<sub>max, p2</sub>), and a slow declining phase over the next 7 weeks. PK exposures (C<sub>max,p2</sub> and AUC<sub>inf</sub>) were approximately dose proportional for 10-60 mg of pasireotide LAR in healthy volunteers. The inter-subject variability (CV%) of C<sub>max,p2</sub> ranged from 23.2% to 70.5% and CV% of AUC<sub>inf</sub> ranged from 10.9% to 41.0% in different studies, suggesting moderate to high inter-individual variability of PK exposure among healthy volunteers after a single LAR dose. The relative bioavailability of the LAR formulation to the sc formulation is complete, ranging from 106% to 148%. The PK release profiles and exposures were comparable in acromegaly

patients and healthy volunteers following repeated q28d dosing of pasireotide LAR. PK steady state was achieved subsequent to the third injection. Ctrough were approximately dose proportional for the tested levels of 20-60 mg in patients with acromegaly. High inter-patient variability and moderate intra-patient variability were observed for pasireotide LAR trough concentration.

The extent of plasma protein binding observed with pasireotide was moderate (88%) and concentration-independent. These results are applicable to both the sc and the LAR formulations. Following a single dose of 10-60 mg of pasireotide LAR in healthy volunteers, the apparent volume of distribution ( $V_z/F$ ) was large (>2000 L). However, this  $V_z/F$  value was most likely over-estimated due to the flip-flop PK characteristics of pasireotide LAR. The actual volume of distribution should be better estimated by the sc formulation data with  $V_z/F >100L$ , which is more than 2.5-fold of total body water volume in humans (~42 L).

Following sc administration in healthy volunteers, pasireotide was metabolically stable and was the main circulating component in the blood. No first-pass metabolism is expected. These results are also applicable to the LAR formulation.

In healthy volunteers, following sc administration pasireotide was mainly eliminated via hepatic clearance; in the total radioactivity recovery (~56%, over a 10 day excreta collection period), most of the excretion was via the fecal route (~48%) with a minimal amount detected in urine (~8%). Pasireotide was excreted mainly as unchanged form in both feces and urine. These results are also applicable to the LAR formulation, considering that the systemic elimination of pasireotide is independent of the formulation, as evidenced by similar  $CL/F$  values between the LAR formulation (range: 4.5 – 8.5 L/h) and the sc formulations (range: 4.3-9.0 L/h). The  $CL/F$  (4.5 – 8.5 L/h) for pasireotide LAR is low and about 5-9% of liver blood flow in humans (~90 L/h). The mean apparent terminal half-life ( $T_{1/2}$ ) for pasireotide LAR was long (14 – 15 days).

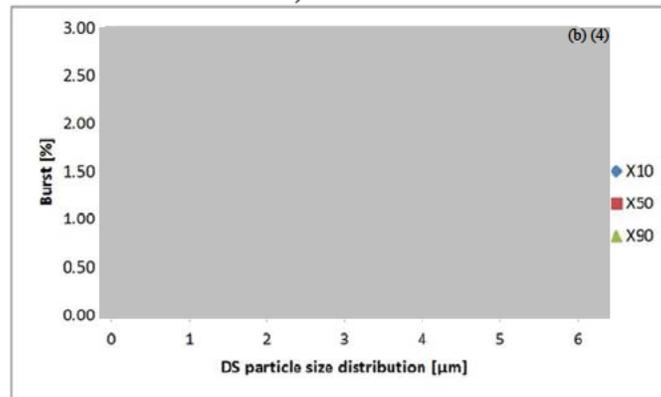
*Reviewer's Comments: The q28d dosing is related to the long acting release and the long half-life of the product. It seems that the solubility of the drug plays a role for the long acting release. High inter-patient variability were observed for pasireotide LAR trough concentration, and even the intra-patient variability is moderate, indicating the drug quality may contribute to the exposure variability.*

#### **4. Factors affecting product performance**

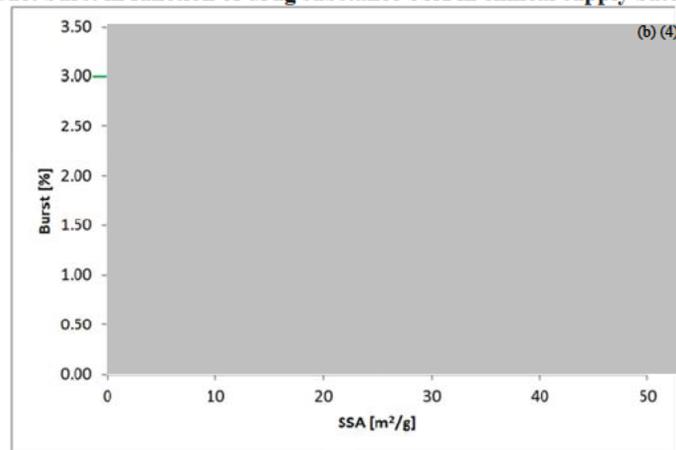
Beside the solubility, the drug substance particle size distribution (PSD) and specific surface area (SSA) are potential critical physical properties for the drug product performance. They are routinely controlled as follows:



**Figure: Drug product burst as a function of drug substance PSD in clinical batches (drug substance X10, X50 and X90 in different colors)**



**Figure: Drug product burst in function of drug substance SSA in clinical supply batches**



*The Reviewer's Comments: The data show that SSA and PSD are critical quality attributes. The drug substance PSD should be strictly controlled.*

## 5. The compositions of the drug products

The composition of the drug product is shown in the following table. The composition of the product (powder and solvent for suspension for injection) used in all clinical studies with pasireotide LAR is identical to the intended market form.

Ingredients	Theoretical amount (mg) per strength			Function	Reference to standards
	20mg	40mg	60mg		
<b>Drug substance</b>					
SOM230 pamoate	27.420 <sup>1</sup>	54.840 <sup>1</sup>	82.260 <sup>1</sup>	Active ingredient	Novartis
<b>Excipients</b>				(b) (4)	
Poly(D,L-lactide-co-glycolide) (50-60:40-50) <sup>2</sup>	26.290	52.580	78.870		Novartis
Poly(D,L-lactide-co-glycolide) (50:50) <sup>3</sup>	26.290	52.580	78.870		Novartis
(b) (4)	--	--	--		Ph. Eur./ NF
(b) (4)	--	--	--		Ph. Eur./ NF
(b) (4)	--	--	--		Ph. Eur./ NF
(b) (4)	--	--	--		Ph. Eur./ NF
(b) (4)	--	--	--		Ph. Eur./ USP
(b) (4)	--	--	--		Ph. Eur./ NF
(b) (4)	q.s.	q.s.	q.s.		Ph. Eur./ NF
<b>Theoretical fill weight <sup>5</sup></b>	80.00 <sup>5</sup>	160.00 <sup>5</sup>	240.00 <sup>5</sup>		

<sup>1</sup> Corresponding to 20mg, 40mg and 60mg of SOM230 base (active moiety), respectively. The salt/base ratio

(b) (4)

(b) (4)

<sup>5</sup> Note: Each vial contains (b) (4) overfill (20ma, 40ma, 60ma strengths), which is not included in the table.

(b) (4)

A listing of the SOM230 LAR formulation variants leading to the final proposed market formulation, LAR 2b, is shown in the following table.

(b) (4)

**Reviewer's Comments:**

(b) (4)

All dosage strengths (b) (4), and differ only in the amount of powder filled in the vials. Therefore, the strengths are considered compositionally similar.

**6. Dissolution method development**

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*Reviewer's Comments:* The proposed acceptance criteria based on (b) (4) are not appropriate. See comments at the end of this section.

**3) Justification of the dissolution medium**

During method development of the accelerated drug release method different test media, apparatus and test conditions (temperature, stirring speed) have been investigated.

(b) (4)  
Good solubility has been observed in the acidic range of pH 2 of phosphate buffer which therefore has been chosen as preferred choice for the medium and pH value.

To increase the wettability of the microparticles surfactant screening has been performed including (b) (4)

(b) (4)

*Reviewer's Comments:* The medium and surfactant selections seem reasonable.

**4) Justification of the rotation speed and volume**

Different dissolution apparatus and testing conditions (stirring speed) have been tested, i.e. (b) (4). From those the paddle method at 50 rpm has been selected (b) (4)

(b) (4)

*Reviewer's Comments: The rotation speed of 50 rpm is appropriate.*

**5) Discriminating ability**

The (b) (4) test method has been shown to discriminate batches (b) (4) For investigations on discriminatory power technical challenge batches have been prepared.

(b) (4)

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immediately following this page

On 6/12/2014, the Applicant provided a response, which acknowledges FDA's view on (b) (4) setting acceptance criteria on in vitro drug release. Based on the data available, the Applicant made a new proposal as shown in the following table.

Time point	Originally proposed	FDA recommendation	Newly proposed
1 h			(b) (4)
24 h			
48 h			
96 h			
144 h			

**The Reviewer's Comments:** *The Applicant's proposal has two differences compared to the Agency's recommendation: (b) (4) difference for the time point of 48 h and (b) (4) difference for the time point of 96 h. The proposal is considered acceptable based on the consideration of the available data, which showed that the tighter acceptance criteria may not be met. The following comments were sent to the Applicant.*

*The dissolution acceptance criteria you proposed in your response dated 6/12/2014 are acceptable. Update and resubmit the specification table and other relevant documents in your NDA.*

The response is pending.

## 7. IVIVC study

(b) (4)

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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.**  
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/s/  
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JOHN Z DUAN  
08/11/2014

TAPASH K GHOSH  
08/11/2014