

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203255Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

**Application number:** 203255  
**Supporting document/s:** eCTD 0000  
**Applicant's letter date:** October 15, 2013  
**CDER stamp date:** October 15, 2013  
**Product:** Signifor® LAR Pasireotide injection (SOM230)  
**Indication:** Acromegaly  
**Applicant:** Novartis  
**Review Division:** DMEP  
**Reviewer:** Miyun Tsai-Turton, PhD, MS  
**Supervisor/Team Leader:** Karen Davis-Bruno, PhD  
**Division Director:** Jean-Marc Guettier, MD  
**Project Manager:** Jennifer Johnson

*Primary review is due on August 11, 2014*

*PDUFA goal date: September 15, 2014*

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203255 are owned by Novartis or are data for which Novartis has obtained a written right of reference. Any information or data necessary for approval of NDA 203255 that Novartis does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203255.

## TABLE OF CONTENTS

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>5</b>
1.1	INTRODUCTION .....	5
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS .....	5
1.3	RECOMMENDATIONS .....	6
<b>2</b>	<b>DRUG INFORMATION .....</b>	<b>10</b>
2.1	DRUG .....	10
2.2	RELEVANT INDS, NDAs, BLAs AND DMFs .....	11
2.3	DRUG FORMULATION .....	11
2.4	COMMENTS ON NOVEL EXCIPIENTS .....	12
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN .....	12
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN .....	13
2.7	REGULATORY BACKGROUND .....	13
<b>3</b>	<b>STUDIES SUBMITTED.....</b>	<b>14</b>
3.1	STUDIES REVIEWED.....	14
3.2	STUDIES NOT REVIEWED .....	14
3.3	PREVIOUS REVIEWS REFERENCED.....	14
<b>4</b>	<b>PHARMACOLOGY .....</b>	<b>14</b>
4.1	PRIMARY PHARMACOLOGY .....	15
4.2	SECONDARY PHARMACOLOGY .....	27
4.3	SAFETY PHARMACOLOGY .....	27
<b>5</b>	<b>PHARMACOKINETICS/ADME/TOXICOKINETICS .....</b>	<b>30</b>
5.1	PK/ADME.....	30
5.2	TOXICOKINETICS .....	35
<b>6</b>	<b>GENERAL TOXICOLOGY.....</b>	<b>35</b>
<b>7</b>	<b>GENETIC TOXICOLOGY .....</b>	<b>49</b>
<b>8</b>	<b>CARCINOGENICITY .....</b>	<b>50</b>
<b>9</b>	<b>REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY .....</b>	<b>50</b>
<b>10</b>	<b>SPECIAL TOXICOLOGY STUDIES.....</b>	<b>51</b>
<b>11</b>	<b>INTEGRATED SUMMARY AND SAFETY EVALUATION.....</b>	<b>59</b>
<b>12</b>	<b>APPENDIX/ATTACHMENTS .....</b>	<b>63</b>

## Table of Tables

Table 1 Proposed clinical doses and their formulations. ....	11
Table 2 Study No rd-2011-00248: Expt 1 – Effect of 4 and 8 mg/kg pasireotide LAR up to 35 days in rats .....	16
Table 3 Study No rd-2011-00248: Experiment #2 – Effect of 8 and 80 mg/kg pasireotide LAR up to 49 days in rats .....	19
Table 4 Study No pcs-r1270349-01: hERG-lite assay results .....	28
Table 5 Study No pcs-r1270473: IC50 results.....	29
Table 6 Study No dmpk-r1200248-01: P-gp and BCRP inhibitors.....	32
Table 7 Study No dmpk-r1200761: OCT1 and OCT2 inhibitors .....	33
Table 8 Study No dmpk-r1200835: OAT1 and OAT3 inhibitors.....	34
Table 9 Study No r0470138: 6 month rat tox study with LAR formulation – study design .....	37
Table 10 Study No r0470138: 6 month rat tox study with LAR formulation – TK data...	38
Table 11 Study No r0470138: 6 month rat tox study with LAR formulation – anti drug resposne .....	39
Table 12 Study No r0470138: 6 month rat tox study with LAR formulation – microscopic findings.....	40
Table 13 Study No r0770082: 3 month rat tox study with LAR formulation – study design .....	42
Table 14 Study No r0770082: 3 month rat tox study with LAR formulation – TK data...	48
Table 15 Immunotox memo-27523: cell counts for rat MLN cell suspensions.....	52
Table 16 Studies with SOM230 LAR formulation .....	61
Table 17 Safety Margin for Signifor LAR formulation .....	63

## Table of Figures

Figure 1 Study No rd-2011-00248: Experiment #1 – Effect of 4 and 8 mg/kg pasireotide LAR on body weight, glucose, insulin, and glucagon in rats.....	17
Figure 2 Study No rd-2011-00248: Experiment #2 – Effect of 8 and 80 mg/kg pasireotide LAR on unstimulated GH and IGF-1 rats .....	20
Figure 3 Study No rd-2011-00248: Experiment #3 – Effect of 4 and 8 mg/kg pasireotide LAR on unstimulated GH and IGF-1 rats.....	21
Figure 4 Study No rd-2011-00248: Experiment #4 – Effect of octreotide and pasireotide on GHRH induced GH secretion in rats.....	23
Figure 5 Study No rd-2011-00248: Experiment #5 – Plasma level of octreotide and pasireotide in rats .....	27

# 1 Executive Summary

## 1.1 Introduction

Pasireotide (SOM230) is a somatostatin analog. Pasireotide powder for suspension for injection (long acting release) is a depot formulation administered intramuscularly once a month to treat acromegaly. It comes three strengths – 20 mg, 40 mg, and 60 mg.

Acromegaly is a rare disease that is caused by neuroendocrine tumors where growth hormone is excessively secreted. Besides surgery and radiotherapy, currently the medical treatment options for acromegaly include SSAs (octreotide and lanreotide), growth hormone (GH) antagonists (pegvisomant), and dopamine agonists.

Other somatostatin analogs such as octreotide and lanreotide have been approved for as first-generation SSAs to treat acromegaly. These analogs can inhibit corticotropin-releasing hormone (CRH)-induced ACTH release, GH, IGF, glucagon and insulin secretion. They have a high affinity to the sst subtype 2 (sst2) with moderate or no affinity to the remaining subtypes (sst1, sst3, sst4, and sst5). On the other hand, pasireotide (SOM23) has higher receptor affinities to the sst1, sst2, sst3, and sst5 receptors when compared to those currently approved somatostatin analogues. Based on this SSTR binding profile, pasireotide should be expected to be more efficacious than the first generation SSAs in acromegaly.

Signifor® LAR is not approved in any country. However, the pasireotide sc formulation (Signifor®) was approved in the US in Dec 2012 for treatment of Cushing's disease. In this NDA submission, there are two pivotal Phase III trials – Study CSOM230C2305 (blinded study comparing pasireotide intramuscular use with octreotide intramuscular use in patients with active acromegaly) and CSOM230C2402 (parallel-group study comparing the efficacy and safety of double-blind pasireotide intramuscular use 50 mg and pasireotide intramuscular use 60 mg vs. open-label octreotide intramuscular use of lanreotide ATG in patients with inadequately controlled acromegaly). The maximum recommended clinical dose of pasireotide LAR for acromegaly is up to 60 mg/28 days im.

## 1.2 Brief Discussion of Nonclinical Findings

Most nonclinical studies were submitted previously for the NDA 200677 – pasireotide sc formulation for Cushing's disease. Under NDA 200677, the majority of the findings (i.e. pituitary gland, reduced cellularity in the hematopoietic organs, prolongation of the estrus cycle in rats, pituitary, thyroid, large intestine, and injection sites in the monkeys) were considered related to the pharmacological effects of pasireotide.

There were few new nonclinical data submitted under NDA 203255 with SOM230 LAR formulation.

One PD study in male rats showed that SOM230 LAR (a single sc injection) strongly inhibited plasma IGF-1 but only transiently inhibited GH and glucose. When compared

to octreotide, pasireotide caused a stronger inhibition of GH and IGF-1 and showed less tachyphylaxis (small hyperglycemia was only seen in Day 1). Based on these data, by different effects seen with pasireotide and octreotide, one can speculate that the non-desensitizing effects of pasireotide on GH, insulin, and IGF-1 might be mediated primarily via sstr5 whereas the desensitizing effect of pasireotide on glucagon is mediated primarily via sstr2.

Two safety pharmacology studies in vitro showed that SOM230 could inhibit hERG trafficking at high concentration ( $\geq 100 \mu\text{M}$ ) and also inhibit hNCX1 ion channel ( $\text{IC}_{50} = 21.7 \mu\text{M}$ ).

Three PK studies in vitro also showed that SOM230 was an inhibitor of P-gp/BCRP and OAT1/OAT3 but was not an inhibitor of OCT1/OCT2, indicating that there were some potential of P-gp mediated and/or transporter mediated drug-drug interaction between pasireotide and co-medications in vivo.

Lastly, under NDA 200677, there were several local toxicity studies and repeated dose studies (i.e. 3 or 6 month study in rats once daily IM administration) conducted with SOM230 LAR formulation. All in all, there were no new safety concerns with SOM230 LAR formulation. Based on the repeat dose toxicity studies with pasireotide LAR formulation in rats (at doses up to 6 mg/animal) had an estimated systemic exposure ( $\text{AUC}_{0-28\text{day}}$ ) at 2.3x of the estimated human exposure for pasireotide LAR at 60 mg/28 days.

### 1.3 Recommendations

#### 1.3.1 Approvability

Pharm/tox recommends approval.

#### 1.3.2 Additional Non Clinical Recommendations

No additional nonclinical study is requested.

#### 1.3.3 Labeling

##### Proposed labeling by the sponsor

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits (b) (4)

(b) (4) showed evidence of (b) (4) harm to the (b) (4) fetus due to pasireotide.

(b) (4) SIGNIFOR LAR should be used during pregnancy only i (b) (4)

#### 8.2 Labor and Delivery

No data in humans are available. Studies in rats with pasireotide via subcutaneous route have shown no effects on labor and delivery [see *Nonclinical Toxicology* (13)].

#### 8.3 Nursing Mothers

It is not known whether pasireotide is excreted in human milk. (b) (4)

As a risk to the breast-fed child cannot be excluded, SIGNIFOR LAR should not be used by the nursing mother.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

##### *Carcinogenesis*

A life-time carcinogenicity study was conducted in rats and transgenic mice. Rats were given daily subcutaneous doses of pasireotide at 0.01, 0.05, and 0.3 mg/kg/day for 104 weeks. There were no drug-related tumors in rats at exposures up to (b) (4)-times higher than the maximum recommended clinical exposure of the pasireotide LAR 60mg dose. Mice were given subcutaneous doses of pasireotide at 0.5, 1.0, and 2.5 mg/kg/day for 26 weeks and did not identify any carcinogenic potential.

##### *Mutagenesis*

Pasireotide was not genotoxic in a battery of in vitro assays (Ames mutation test in *Salmonella* and *E coli*. and mutation test in human peripheral lymphocytes). Pasireotide was not genotoxic in an in vivo rat bone marrow nucleus test.

##### *Impairment of Fertility*

Subcutaneous dosing at 0.1 mg/kg/day before mating and continuing into gestation in rats at exposures less than the human clinical exposure based on body surface area comparisons across species resulted in statistically significant increased implantation loss and decreased viable fetuses, corpora lutea, and implantation sites. Abnormal cycles or acyclicity were observed at 1 mg/kg/day (4 (b) (4)-fold higher than the maximum therapeutic exposure of pasireotide LAR based on surface area, comparisons across species).

#### Recommended labeling by the FDA

Under Sections 8, the sponsor proposed the same Pregnancy Category C as Signifor®. However the proposed language was different. Since this section is based solely based on studies under NDA 200677, the language should stay close to Signifor®'s labeling. Under Section 13, the sponsor proposed almost identical language to Signifor®.

For labeling purposes, the exposure multiples are calculated based on studies from the pasireotide NDA 200677 for Cushing's disease. The clinical dose for this indication was 0.9 mg BID given SC whereas the clinical dose for this acromegaly indication is 60 mg IM of a long-acting pasireotide formulation (i.e. Signifor® LAR). The AUC for the Signifor 0.9 mg BID SC dose AUC<sub>0-24 h</sub> Signifor® = 291 ng\*hr/ml. The AUC for Signifor® LAR is 1.3-times higher or AUC<sub>0-t</sub> Signifor LAR = 390 ng\*hr/ml (the value was derived from the AUC<sub>0-t</sub> = 463 ng\*d/ml → 463 ng\*d/ml x 24 h/d = 11112 ng\*h/ml / 28 = 390 ng\*h/ml as estimated daily average AUC over 28 days). Therefore the exposure multiples in labeling based on AUC comparisons are adjusted accordingly

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits which showed evidence of harm to the fetus due to pasireotide at therapeutic exposures. Animal reproduction studies are not always predictive of human response. (b) (4) should be used during pregnancy only if clearly needed.

Dosing in rats before mating and continuing into gestation at exposures less than the human clinical exposure based on body surface area comparisons across species, resulted in adverse fertility effects including: statistically significant increased implantation loss and decreased viable fetuses, corpora lutea, and implantation sites. Abnormal cycles or acyclicity were observed at systemic exposure 4-fold higher than the maximum therapeutic exposure based on surface area, comparisons across species [see Nonclinical Toxicology (13.1)].

In embryofetal development studies in rats given 1, 5, and 10 mg/kg/day subcutaneously throughout organogenesis, maternal toxicity was observed at all doses, including the lowest dose tested which had exposures (b) (4) times higher than that at the maximum therapeutic dose based on AUC comparisons across species.

In embryofetal development studies in rabbits given 0.05, 1, and 5 mg/kg/day subcutaneously through organogenesis, maternal toxicity was observed at 1 mg/kg/day at an exposure 5-times higher than the maximum therapeutic exposure. Treatment related increased incidence of skeletal malformations were observed at 0.05 mg/kg/day, exposures less than the maximum therapeutic exposure based on AUC comparisons across species.

In pre- and post-natal developmental studies in rats given subcutaneous doses of 2, 5, and 10 mg/kg/day during gestation through lactation and weaning, maternal toxicity was observed at all doses including the lowest dose (9-times higher than the maximum therapeutic dose based on surface area comparisons across species). Retardation of physiological growth, attributed to GH inhibition was observed at 2 mg/kg/day during a pre- and postnatal study in rats. After weaning, body weight gains in the rat pups (F1 generation) exposed to pasireotide were comparable to controls, showing reversibility of this developmental delay.

### **8.2 Labor and Delivery**

No data in humans are available. Studies in rats have shown no effects on labor and delivery [see Nonclinical Toxicology (13.1)].

### **8.3 Nursing Mothers**

It is not known whether (b) (4) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SIGNIFOR is administered to a nursing woman [see Nonclinical Toxicology (13.1)].

Pasireotide was excreted into rat milk at levels 30% of the plasma level. As a risk to the breastfed child cannot be excluded, SIGNIFOR should not be used by the nursing mother.

## **13 NONCLINICAL TOXICOLOGY**

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenesis*

A life-time carcinogenicity study was conducted in rats and transgenic mice. Rats were given daily subcutaneous doses of pasireotide at 0.01, 0.05, and 0.3 mg/kg/day for 104 weeks. There were no drug-related tumors in rats at exposures up to 5-times higher than the maximum recommended clinical exposure of the pasireotide LAR 60mg dose. Mice were given subcutaneous doses of pasireotide at 0.5, 1.0, and 2.5 mg/kg/day for 26 weeks and did not identify any carcinogenic potential.

#### *Mutagenesis*

Pasireotide was not genotoxic in a battery of in vitro assays (Ames mutation test in *Salmonella* and *E coli*. and mutation test in human peripheral lymphocytes). Pasireotide was not genotoxic in an in vivo rat bone marrow nucleus test.

#### *Impairment of Fertility*

Subcutaneous dosing at 0.1 mg/kg/day before mating and continuing into gestation in rats at exposures less than the human clinical exposure based on body surface area comparisons across species resulted in statistically significant increased implantation loss and decreased viable fetuses, corpora lutea, and implantation sites. Abnormal cycles or acyclicity were observed at 1 mg/kg/day (4-fold higher than the maximum therapeutic exposure of pasireotide LAR based on surface area, comparisons across species).

### Signifor® Labeling

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

###### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits which showed evidence of harm to the fetus due to pasireotide at therapeutic exposures. Animal reproduction studies are not always predictive of human response. (b) (4) should be used during pregnancy only if clearly needed.

Dosing in rats before mating and continuing into gestation at exposures less than the human clinical exposure based on body surface area comparisons across species, resulted in adverse fertility effects including: statistically significant increased implantation loss and decreased viable fetuses, corpora lutea, and implantation sites. Abnormal cycles or acyclicity were observed at systemic exposure 5-fold higher than the maximum therapeutic exposure based on surface area, comparisons across species [see *Nonclinical Toxicology (13.1)*].

In embryofetal development studies in rats given 1, 5, and 10 mg/kg/day subcutaneously throughout organogenesis, maternal toxicity was observed at all doses, including the lowest dose tested which had exposures 4-times higher than that at the maximum therapeutic dose based on AUC comparisons across species.

In embryofetal development studies in rabbits given 0.05, 1, and 5 mg/kg/day subcutaneously through organogenesis, maternal toxicity was observed at 1 mg/kg/day at an exposure 7-times higher than the

maximum therapeutic exposure. Treatment related increased incidence of skeletal malformations were observed at 0.05 mg/kg/day, exposures less than the maximum therapeutic exposure based on AUC comparisons across species.

In pre- and post-natal developmental studies in rats given subcutaneous doses of 2, 5, and 10 mg/kg/day during gestation through lactation and weaning, maternal toxicity was observed at all doses including the lowest dose (12-times higher than the maximum therapeutic dose based on surface area comparisons across species). Retardation of physiological growth, attributed to GH inhibition was observed at 2 mg/kg/day during a pre- and postnatal study in rats. After weaning, body weight gains in the rat pups (F1 generation) exposed to pasireotide were comparable to controls, showing reversibility of this developmental delay.

## 8.2 Labor and Delivery

No data in humans are available. Studies in rats have shown no effects on labor and delivery [see *Nonclinical Toxicology (13.1)*].

## 8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SIGNIFOR is administered to a nursing woman [see *Nonclinical Toxicology (13.1)*]. Pasireotide was excreted into rat milk at levels 30% of the plasma level. As a risk to the breastfed child cannot be excluded, SIGNIFOR should not be used by the nursing mother.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### *Carcinogenesis*

A life-time carcinogenicity study was conducted in rats and transgenic mice. Rats were given daily subcutaneous doses of pasireotide at 0.01, 0.05, 0.3 mg/kg/day for 104 weeks. There were no drug-related tumors in rats at exposures up to 7-fold higher than the maximum recommended clinical exposure at the 1.8 mg/day dose. Mice were given subcutaneous doses of pasireotide at 0.5, 1.0, 2.5 mg/kg/day for 26 weeks and did not identify any carcinogenic potential.

### *Mutagenesis*

Pasireotide was not genotoxic in a battery of in vitro assays (Ames mutation test in Salmonella and E coli and mutation test in human peripheral lymphocytes). Pasireotide was not genotoxic in an in vivo rat bone marrow nucleus test.

### *Impairment of Fertility*

Subcutaneous dosing at 0.1 mg/kg/day before mating and continuing into gestation in rats at exposures less than the human clinical exposure based on body surface area comparisons across species resulted in statistically significant increased implantation loss and decreased viable fetuses, corpora lutea, and implantation sites. Abnormal cycles or acyclicity were observed at 1 mg/kg/day (5-fold higher than the maximum therapeutic exposure based on surface area, comparisons across species).

# 2 Drug Information

## 2.1 Drug

**CAS Registry Number:** 396091-79-5

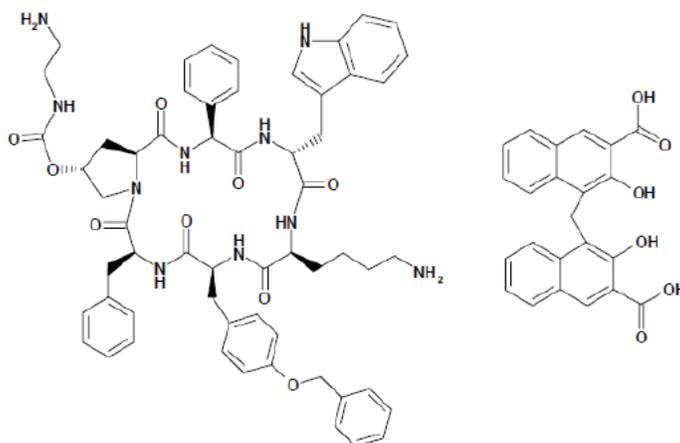
**Generic Name:** Pasireotide pamoate

**Code Name:** SOM230C, SOM230-BFA, SOM230-BFA.001, SOM230 pamoate

**Chemical Name:**

The CAS name is Cyclo[(2S)-2-phenylglycyl-D-tryptophyl-L-lysyl-O-(phenylmethyl)-L-tyrosyl-L-phenylalanyl-(4R)-4-[[[(2-aminoethyl)amino]carbonyl]oxy]-L-prolyl]4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylate] (1:1).

**Molecular Formula/Molecular Weight:** C<sub>58</sub>H<sub>66</sub>N<sub>10</sub>O<sub>9</sub> · C<sub>23</sub>H<sub>16</sub>O<sub>6</sub> and 1435.58  
**Structure or Biochemical Description**



**Pharmacologic Class:** pasireotide

**2.2 Relevant INDs, NDAs, BLAs and DMFs**

IND (b) (4) 068635, DMFs (b) (4)

**2.3 Drug Formulation**

Pasireotide pamoate (API) + inactive ingredients ( (b) (4) sodium, mannitol, poloxamer 188, water)

**Table 1 Proposed clinical doses and their formulations.**

Ingredients	Declared content of one vial of SOM230 20mg, 40mg and 60mg Powder for suspension for injection			Function	Reference to standards
	Theoretical amount (mg) per strength				
	20mg	40mg	60mg		
<b>Drug substance</b>					
SOM230 pamoate	27.420 <sub>1</sub>	54.840 <sub>1</sub>	82.260 <sub>1</sub>	Active ingredient	Novartis
<b>Excipients</b>					
Poly(D,L-lactide-co-glycolide) (50-60:40-50) <sup>2</sup>	26.290	52.580	78.870	(b) (4)	Novartis
Poly(D,L-lactide-co-glycolide) (50:50) <sup>3</sup>	26.290	52.580	78.870	(b) (4)	Novartis

Ingredients	Theoretical amount (mg)			Function	Reference to standards
	20mg	40mg	60mg		
(b) (4)	--	--	--	(b) (4)	Ph. Eur./ NF
	--	--	--		Ph. Eur./ NF
	--	--	--		Ph. Eur./ NF
	--	--	--		Ph. Eur./ NF
	--	--	--		Ph. Eur./ USP
	--	--	--		Ph. Eur./ NF
	q.s.	q.s.	q.s.		Ph. Eur./ NF
<b>Theoretical fill weight <sup>5</sup></b>	<b>80.00<sup>5</sup></b>	<b>160.00<sup>5</sup></b>	<b>240.00<sup>5</sup></b>		

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

(b) (4)

(b) (4)

<sup>5</sup> Note: Each vial contains a (b) (4)% overfill (20mg, 40mg, 60mg strengths), which is not included in the table. The overfill allows removal of the labeled content from the vial. Also, a correction to the amount of powder filled into the vial is made when the active ingredient content of the powder differs from 250mg (SOM230 base) per g.

## 2.4 Comments on Novel Excipients

There are no novel excipients.

## 2.5 Comments on Impurities/Degradants of Concern

Under NDA 20067, there were 11 impurities identified by the applicant and there were within acceptable limits. Some product-related substances were further qualified by in vitro genotoxicity (i.e. Ames and chromosome aberration assays) and in vivo repeat dose studies (i.e. 4-week repeat dose toxicity rat studies). A series of impurity genotoxicity studies (tested three lots in 6 in vitro assays and 2 in vivo studies) showed that SOM230 (with impurities including (b) (4)) was not genotoxic and that there was no difference in exposure or toxicity from those of SOM230 seen in the absence of these impurities.

With drug substance (pasireotide pamoate) under NDA 203255, the specifications were considered qualified for clinical/commercial use with an estimated daily dose up to 2.14 mg (60 mg/28 days) pasireotide LAR. They are also within the requirements of Ph. Eur. general monograph for 'Substances for pharmaceutical use' which defines for synthetic peptides an identification threshold of (b) (4)% and a qualification threshold of (b) (4)%.

**Specifications of pasireotide pamoate (drug substance)**

With drug product under NDA 203255, most of the degradation products were set a levels of  $\leq$  (b) (4) %, which is the identification threshold for drug products with daily intake of 1 – 10 mg (maximum average intake for pasireotide LAR is (b) (4) mg (60 mg/28 days)) per ICH Q3B(R2). For individual degradation products (b) (4) and cluster including (b) (4), the specifications for shelf life were set at (b) (4) %. These levels are considered qualified as higher levels were presented in toxicology batch ( (b) (4) % and (b) (4) % in batch TOX3/SOM230 05/2 batch for (b) (4) and cluster including (b) (4), respectively).

**Specifications of pasireotide LAR (drug product)****2.6 Proposed Clinical Population and Dosing Regimen**

Clinical population: patients with acromegaly

Dose Regimen: 20, 40, and 60 mg for IM injection once a month

**2.7 Regulatory Background**

- March 2006 – IND 74642 new IND submission
- April 2006 – FCH hold due to insufficient information to assess the risk to human with LAR formulation 2b and in vitro genotox data needed based on the concern for methylene chloride.
- Oct 2006 – Novartis complete response to FCH

- Nov 2006 – pt supervisor’s memo stating deficiencies in FCH letter were not addressed adequately.
- March 2007 – FCH removed - pt memo reviewing a single IM dosing TK study in rats (Study No JK06011), local toxicity study of the two formulation 2 and 2b, and one 6-cycle monthly tox study (Study No 0470138) in rats with formulation 2.
- Feb 2011 – EOP2 mtg
- Nov 2011 – pre-NDA mtg
- Oct 2013 – NDA 203255 submission

### 3 Studies Submitted

#### 3.1 Studies Reviewed

- PD (rd-2011-00248) and safety pharmacology studies (pcs-r1270349-01 and pcs0r1270473)
- PK studies: drug-drug interaction (dmpk-r1200248-01, dmpk-r1200761, dmpk-r1200835)
- Toxicology studies: genotox (pcs-r0412410-01), carci (pcs-r0670694-802088-02), and immunotox (memo-27523)

#### 3.2 Studies Not Reviewed

n/a

#### 3.3 Previous Reviews Referenced

There are several pharm/tox memo and meeting minutes (i.e. EOP2 and pre-NDA mtgs) under IND 74642 and they can be found in DARRTS.

There is also a comprehensive review for NDA 20067 (Signifor®) in DARRTS.

### 4 Pharmacology

Under NDA 200677, a series of in vitro and in vivo studies was conducted to establish the PD profile of Signifor®.

- SOM230 had the highest binding affinity to sst5 receptors (which are highly expressed in pituitary tumors from Cushing’s patients) and simultaneously a high affinity to sst2, sst3, and sst1.
- Pasireotide had a stronger inhibitory effect on ACTH secretion, membrane binding, GTP $\gamma$ S activation and/or cAMP production when compared to octreotide, which acts predominately via sst2.
- Pasireotide also had an inhibitory effect on proliferation.
- Pasireotide had an inhibitory effect on GH/IGF-1 secretion observed in animals, which was the basis for treating acromegaly as well as having potential side effect in Cushing’s patients.
- Pasireotide had an inhibitory effect on insulin vs. glucagon secretion in rats but not in monkeys, leading to transient hyperglycemia.

Under NDA 200677, a series of safety pharmacology studies were also conducted to evaluate the safety profile of Signifor®.

- Pasireotide did not have adverse effects on respiratory function in rats and cardiac function in monkeys but have some adverse effects on CNS in mice (i.e. decreased locomotor activity, hypothermia, decreased grip strength, and loss of righting reflex at greater than clinical exposure). This is inconsistent with drug distribution studies indicating a limited ability to penetrate the CNS, suggesting some toxicity rather than an off-target effect on CNS receptors.
- Even though there were no pasireotide-related findings on blood pressure or electrocardiogram in animals, other somatostatin analog, lanreotide and octreotide, and pasireotide itself have been shown to cause bradycardia in patients and/or healthy volunteers.

**One new PD study and two other safety pharmacology studies in vitro for Signifor LAR were conducted which are discussed below.**

#### 4.1 Primary Pharmacology

##### ***rd-2011-00248: binding affinity study 01***

Study title: SOM230 LAR: Effect of long acting SOM230 LAR (pasireotide LAR) on hormone secretion in rats

Study design: The pasireotide LAR formulation (PKF227-230) was injected sc in male rats and the effect of GH, IGF-1, glucose, insulin, glucagon, and body weight was determined over a one month time period. Several experiments were included into one study.

- Experiment #1 – effect of 4 and 8 mg/kg SOM230 on glucose, insulin, glucagon, IGF-1 and PK up to 35 days in rats
- Experiment #2 – effect of 8 and 80 mg/kg SOM230 LAR on glucose, IGF-1, and PK up to 49 days in rats
- Experiment #3 – Effect of 4 mg/kg and 8 mg/kg SOM230 LAR on unstimulated GH and IGF-1 in rats
- Experiment #4 – Effect of octreotide and pasireotide (10 µg/kg/h) applied continuously by osmotic minipumps on GHRH induced GH secretion in rats
- Experiment #5 – Plasma level of octreotide and pasireotide (3 and 10 µg/kg/h) applied continuously by osmotic minipumps in rats

##### Key findings:

- 24 hrs after a single injection at 4, 8, and 80 mg/kg, plasma levels of 17, 49, and 132 ng/ml were recorded respectively. Plasma levels remained relatively stable during the first 10 days. On Days 20-28, they started to increase and reached peak concentrations of 43, 94, and 510 ng/ml. On Day 49, 8 and 80 mg pasireotide LAR, plasma levels were 13 and 87 ng/ml.
- A single injection of pasireotide LAR at 4, 8, and 80 mg/kg resulted in peak inhibition of IGF-1 (to 44, 22, and 18% of the control value respectively) on Days 3-4. A relatively stable level of inhibition to 62, 40, and 44% of the control

respectively was reached on Days 7-15 and remained at this level up to 49 days at the 8 and 80 mg/kg.

- Pasireotide also caused a stronger inhibition of GH and IGH-1 than octreotide and showed less tachyphylaxis.
- Pasireotide LAR did cause a small but significant increase in glucose only on Day 1. There was no effect on plasma glucose in rats for the remaining 48 days.

#### Study results:

- **Experiment #1** - First 10 days, pasireotide LAR 4 and 8 mg/kg resulted in plasma values between 5-20 ng/ml. On Days 15-30, plasma values ranged between 20-60 ng/ml for 8 mg/kg dose which was slightly higher than the values obtained with the 4 mg/kg. There was a significant inhibition of IGF-1 for the entire treatment period of 35 days. In addition, Pasireotide LAR resulted in a stabilization of the body weight and pasireotide caused a small and transient elevation of plasma glucose.

**Table 2 Study No rd-2011-00248: Expt 1 – Effect of 4 and 8 mg/kg pasireotide LAR up to 35 days in rats**

<b>Plasma level of 4 and 8 mg pasireotide LAR</b>		
	pasireotide LAR 4 mg/kg	pasireotide LAR 8 mg/kg
time after treatment [day]	[ng/ml ± SEM]	[ng/ml ± SEM]
1	17.4 ± 5.8	13.4 ± 3.4
4	18.2 ± 7.1	17.9 ± 7.0
10	21.9 ± 20.1	8.1 ± 1.6
15	7.1 ± 1.9	24.2 ± 8.4
20	43.5 ± 39.7	39.6 ± 7.2
25	36.6 ± 17.5	60.1 ± 15.6
30	32.7 ± 15.8	43.5 ± 17.8
35	33.5 ± 16.4	17.7 ± 6.2

Plasma level of pasireotide after a single injection of 4 and 8 mg/kg pasireotide LAR s.c. from 6 animals. Mean ± SEM at indicated days.

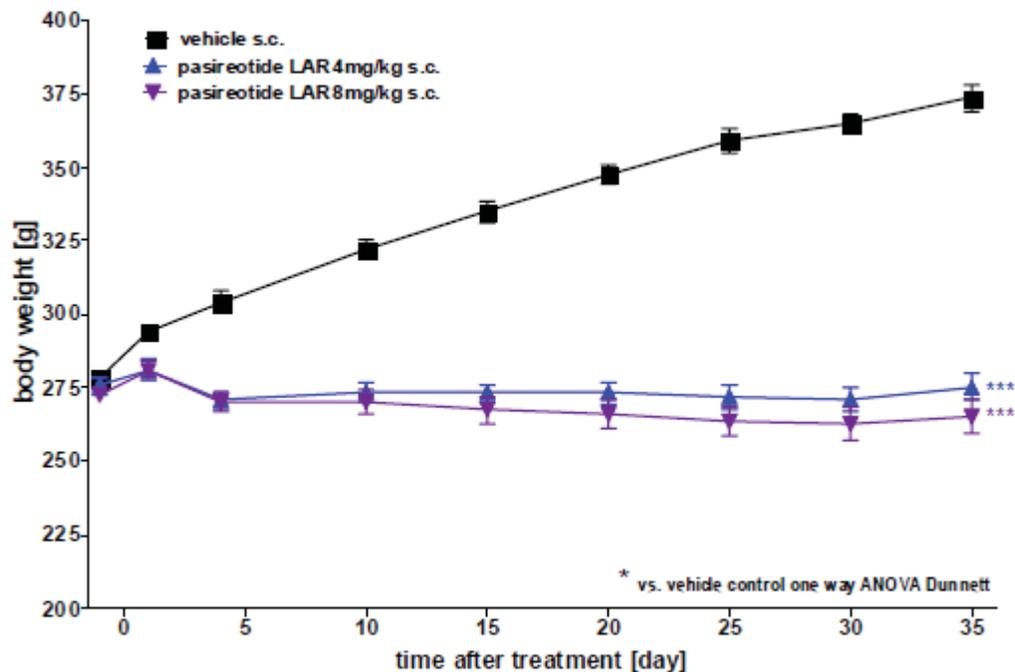
#### **IGF-1 plasma levels after 4 and 8 mg/kg pasireotide LAR**

	vehicle	pasireotide LAR 4 mg/kg	pasireotide LAR 8 mg/kg
time after treatment [day]	[ng/ml ± SEM]	[ng/ml ± SEM]	[ng/ml ± SEM]
-1	1065±21	1102±27	1098±23
1	1113±63	626±24	671±30
4	1097±76	487±116	407±21
15	1105±25	694±78	596±32
25	1083±43	706±116	524±9
35	1158±63	709±75	588±29

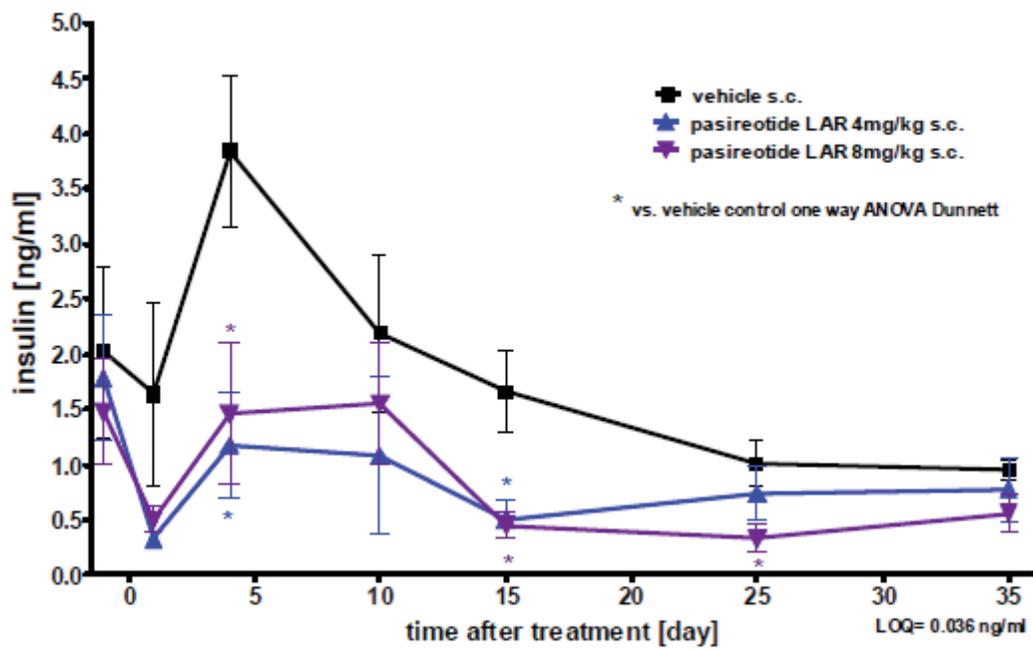
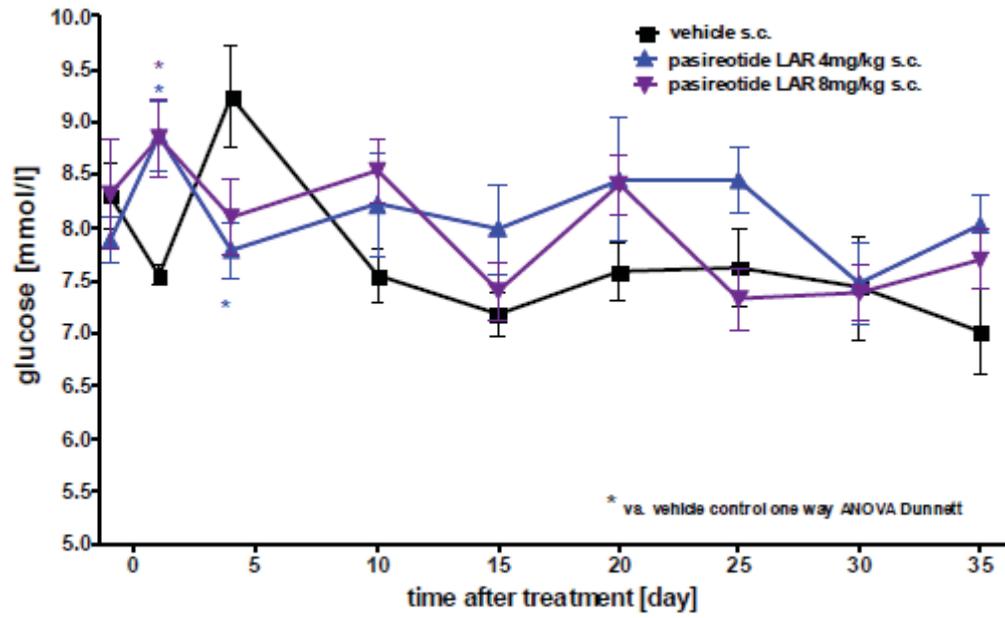
Plasma values of IGF-1 after a single injection of 4 and 8 mg/kg pasireotide LAR s.c. from 6 animals. Mean ± SEM at indicated days.

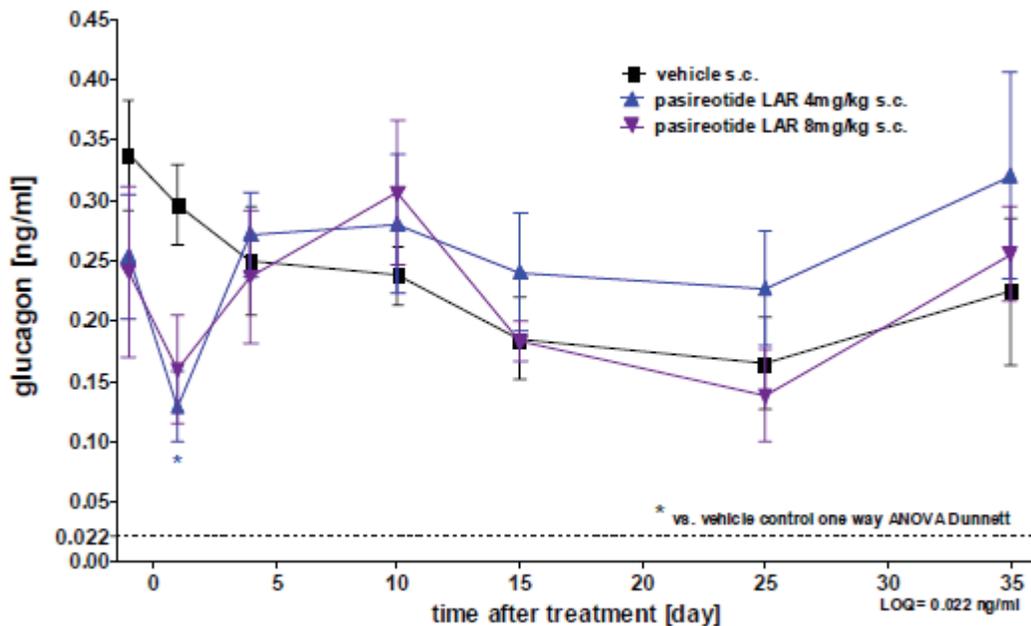
Figure 1 Study No rd-2011-00248: Experiment #1 – Effect of 4 and 8 mg/kg pasireotide LAR on body weight, glucose, insulin, and glucagon in rats

**Effect of 4 and 8 mg/kg pasireotide LAR s.c. on body weight in rats**



**Effect of 4 and 8 mg/kg pasireotide LAR s.c. on glucose, insulin and glucagon in rats**





- Experiment #2** – On Day 1, pasireotide LAR 8 and 80 mg/kg resulted in plasma values of 49 and 132 ng/ml. At 8 mg dose, plasma level reached their max plasma concentration of 93 ng/ml on Day 21 and gradually fell to 13 ng/ml on Day 49. At 80 mg dose, plasma level reached their max plasma concentration of 516 ng/ml on Day 28 and gradually fell to 86 ng/ml on Day 49. There was a significant inhibition of IGF-1 for the entire treatment period of 49 days. In addition, Pasireotide LAR did not affect significantly glucose levels except for the small increase on Day 1.

Table 3 Study No rd-2011-00248: Experiment #2 – Effect of 8 and 80 mg/kg pasireotide LAR up to 49 days in rats

time after treatment [day]	Plasma level of 8 and 80 mg/kg pasireotide LAR	
	pasireotide LAR 8 mg/kg [ng/ml ± SEM]	pasireotide LAR 80 mg/kg [ng/ml ± SEM]
1	49.1 ± 9.4	132.0 ± 4.5
3	44.0 ± 5.8	128.2 ± 9.8
7	47.7 ± 7.2	167.4 ± 16.9
14	73.1 ± 12.3	333.6 ± 84.4
21	93.8 ± 5.0	492.8 ± 64.2
28	39.2 ± 8.1	516.2 ± 43.8
35	30.9 ± 8.5	289.8 ± 71.6
42	23.2 ± 8.5	169.8 ± 39.3
49	13.2 ± 3.1	86.9 ± 15.2

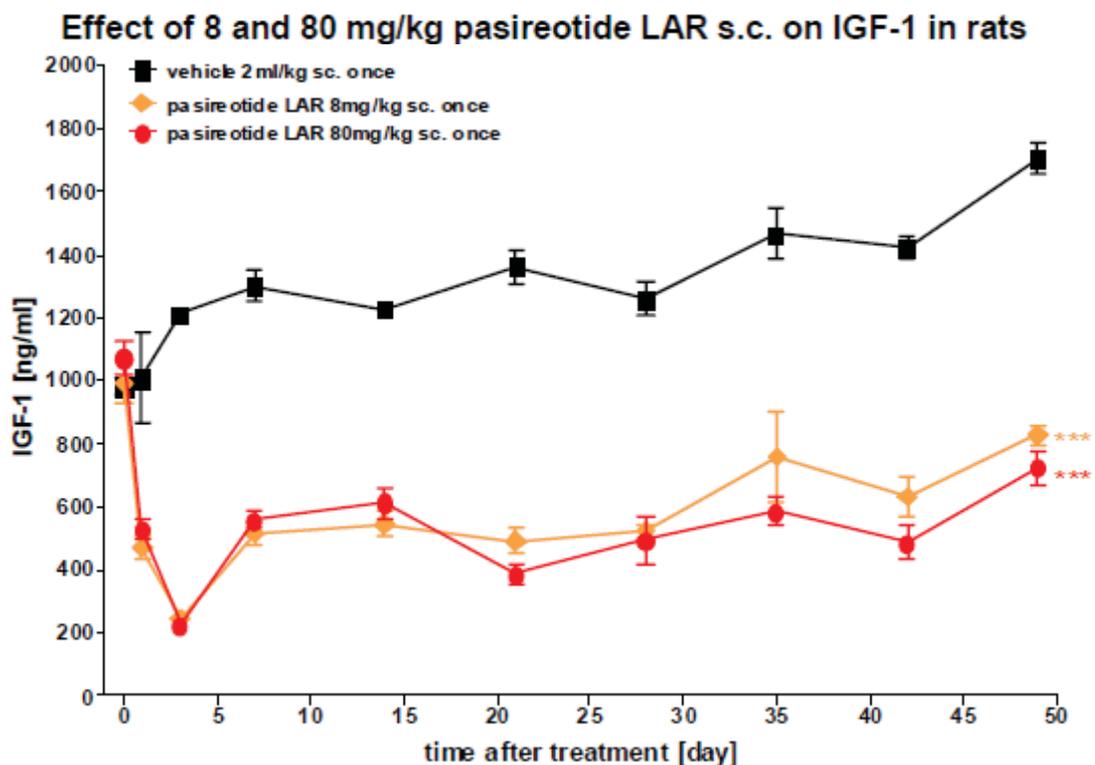
Plasma values of pasireotide after a single injection of 8 and 80 mg/kg pasireotide LAR s.c. from 6 animals. Mean ± SEM at indicated days.

**IGF-1 plasma levels after 8 and 80 mg/kg pasireotide LAR**

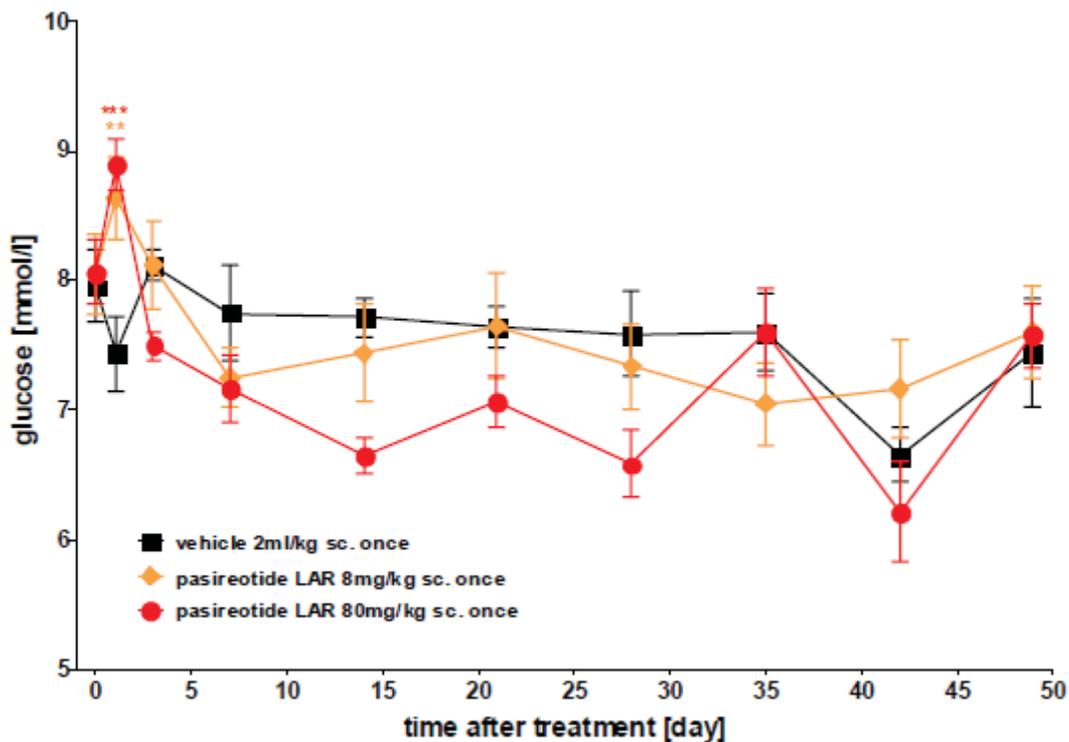
time after treatment [day]	vehicle s.c.once [ng/ml ± SEM]	pasireotide LAR 8 mg/kg [ng/ml ± SEM]	pasireotide LAR 80 mg/kg [ng/ml ± SEM]
0	984 ± 28	995 ± 67	1074 ± 51
1	1011 ± 44	473 ± 34	531 ± 31
3	1216 ± 19	246 ± 8	227 ± 5
7	1302 ± 48	518 ± 38	560 ± 29
14	1229 ± 14	546 ± 40	614 ± 50
21	1362 ± 54	494 ± 37	388 ± 31
28	1260 ± 53	524 ± 24	496 ± 79
35	1467 ± 79	758 ± 140	584 ± 45
42	1423 ± 39	635 ± 64	486 ± 54
49	1707 ± 45	828 ± 34	726 ± 53

Plasma values of IGF-1 after a single injection of 8 and 80 mg/kg pasireotide LAR s.c. from 6 animals. Mean ± SEM at indicated days.

Figure 2 Study No rd-2011-00248: Experiment #2 – Effect of 8 and 80 mg/kg pasireotide LAR on unstimulated GH and IGF-1 rats



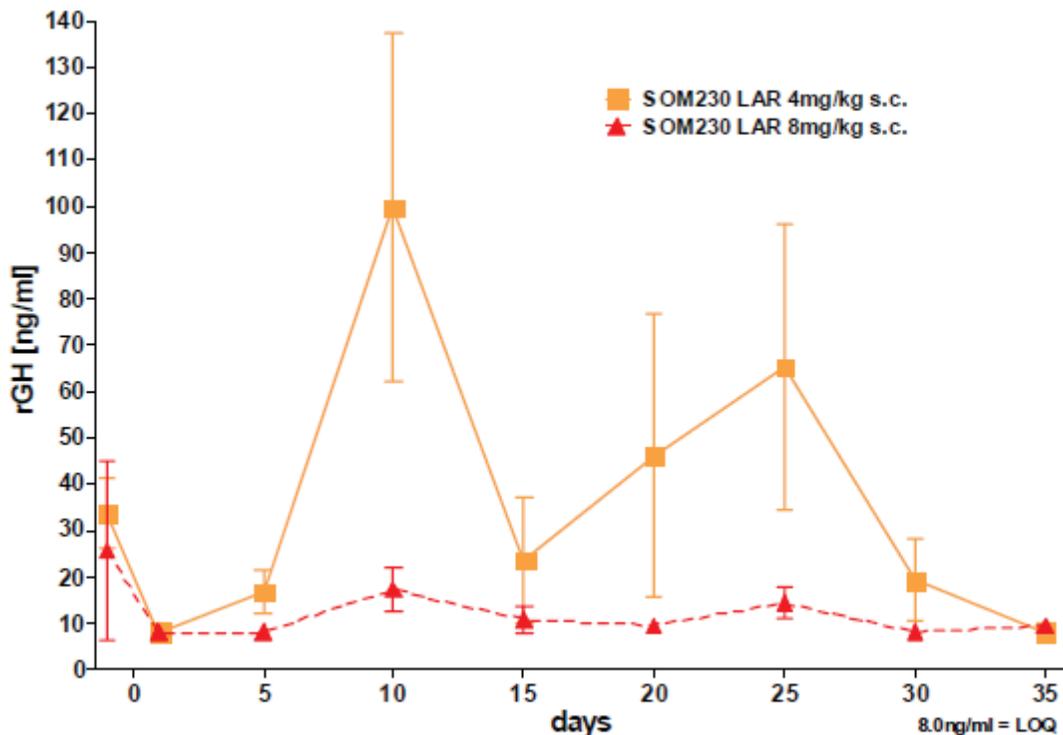
**Effect of 8 and 80 mg/kg pasireotide LAR s.c. on glucose in rats**



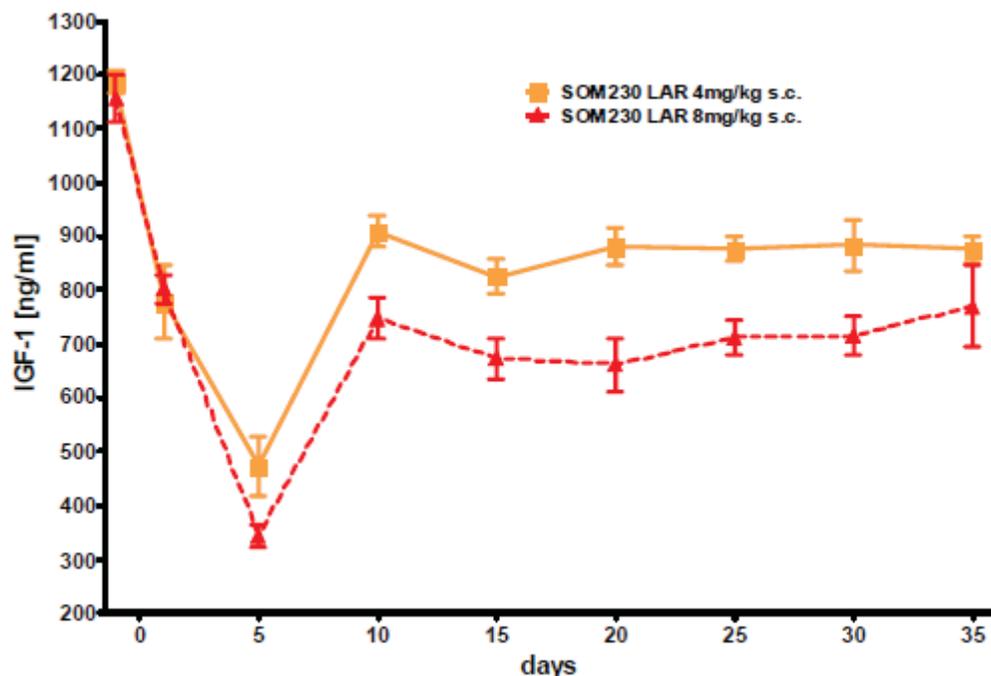
- **Experiment #3** – Pasireotide LAR at 8 mg/kg prevented the detection of GH peaks. The IGF-1 plasma values were more stable than the GH values and showed a dose dependency in the response.

Figure 3 Study No rd-2011-00248: Experiment #3 – Effect of 4 and 8 mg/kg pasireotide LAR on unstimulated GH and IGF-1 rats

**Effect of 4 and 8 mg/kg pasireotide LAR s.c. on GH in rats**



**Effect of 4 and 8 mg/kg pasireotide LAR s.c. on IGF-1 in rats**

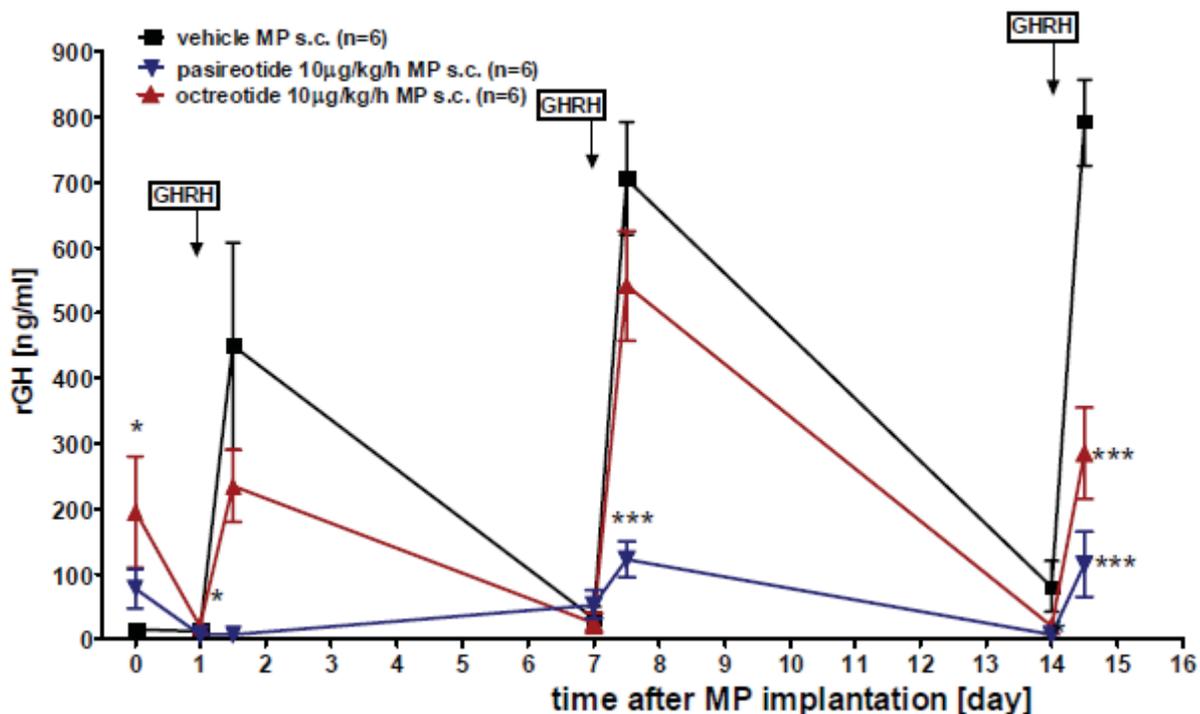


- Experiment #4** – GHRH strongly increased plasma GH on Days 1, 7, and 14 in VH-treated rats. Pasireotide strongly and significantly reduced GHRH stimulated GH on each experimental day whereas octreotide was less consistent (significant only on Day 14). In addition, a separate analysis of the stimulated and the unstimulated response of pasireotide and octreotide showed that IGF-1 levels

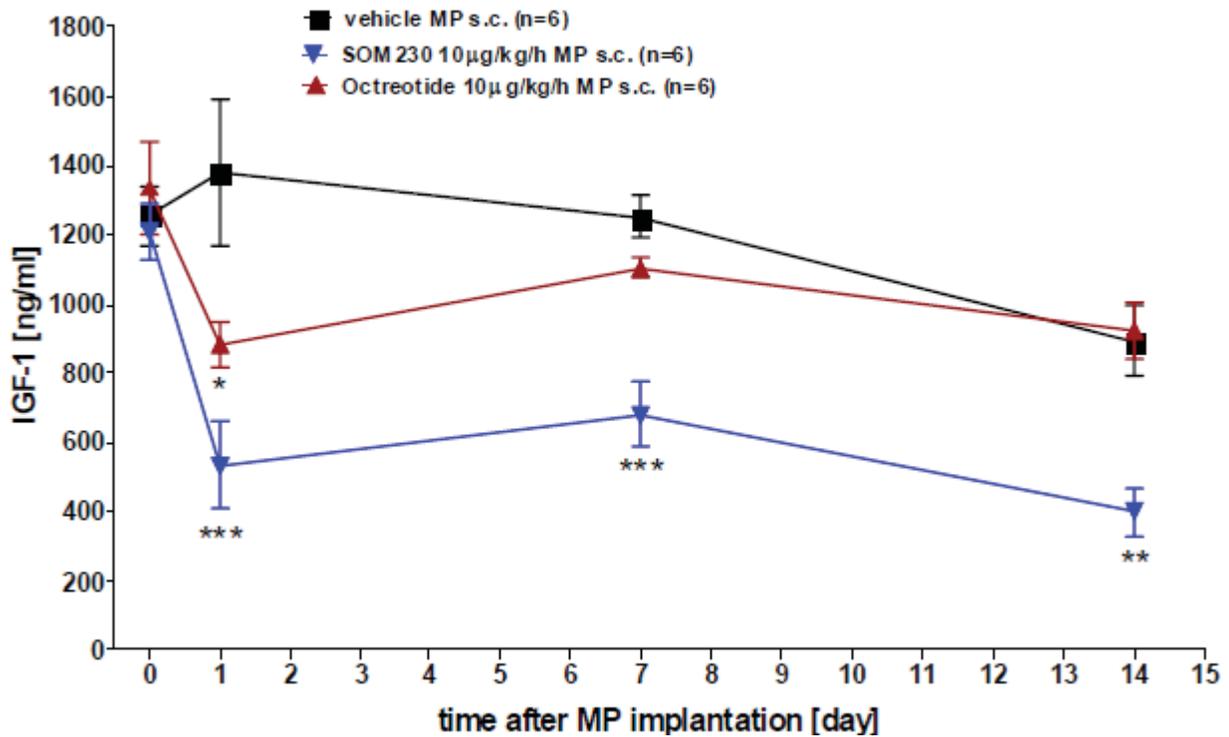
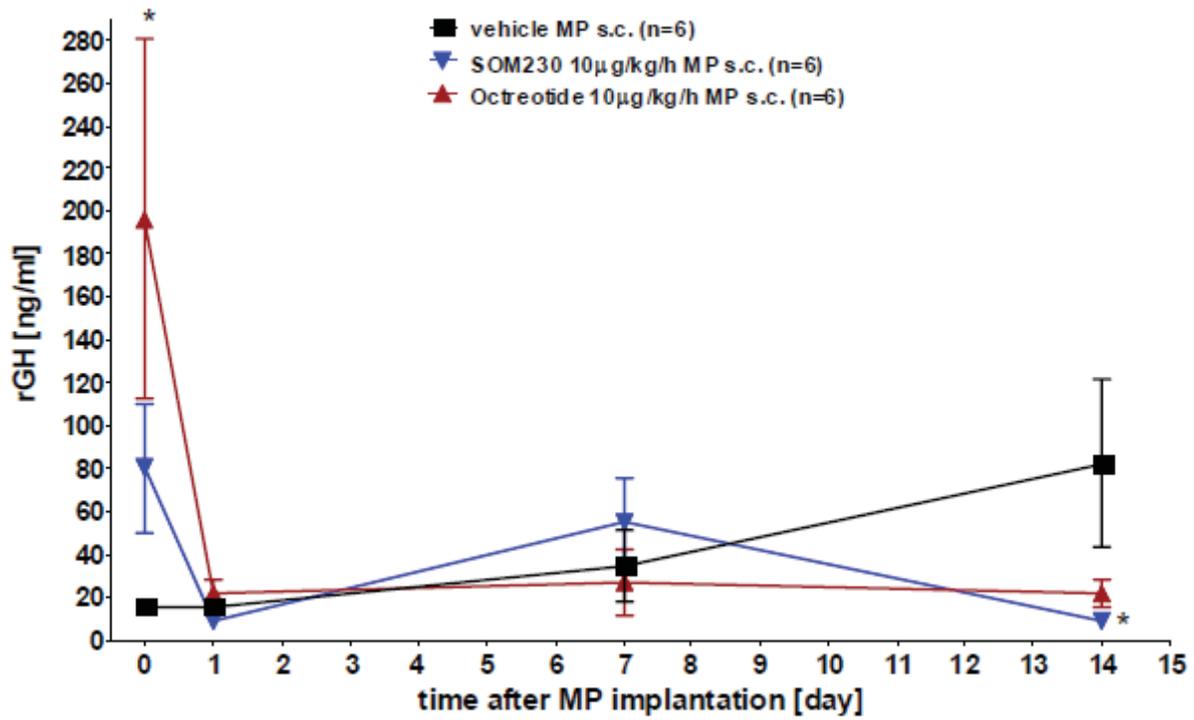
were inhibited some more strongly and consistently with pasireotide than with octreotide. Moreover, a slight inhibition in glucose was seen with octreotide. GHRH stimulation rapidly increased plasma glucose values. However, these values were not affected by the pasireotide whereas in the octreotide group, there was no increase in the GHRH stimulated as well as in the GHRH unstimulated group.

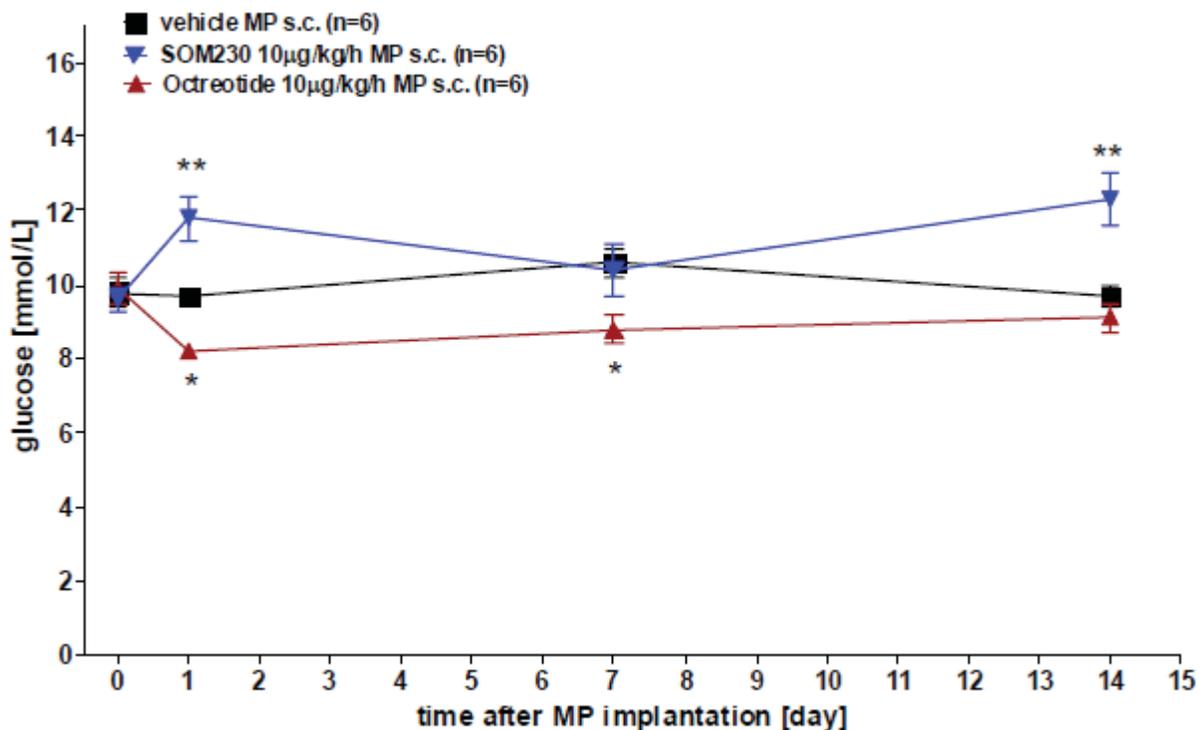
Figure 4 Study No rd-2011-00248: Experiment #4 – Effect of octreotide and pasireotide on GHRH induced GH secretion in rats

**Effect of GHRH (5 mg/kg i.v.) on plasma GH during continuous infusion of pasireotide and octreotide using minipumps in male rats**

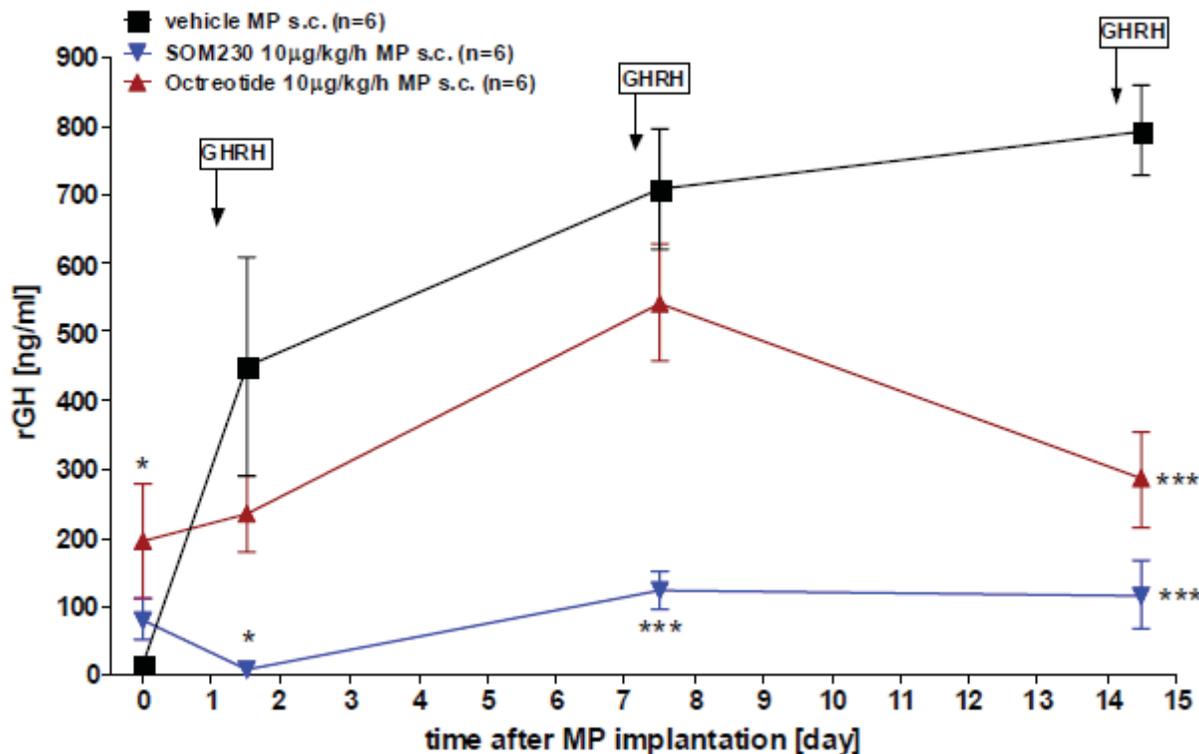


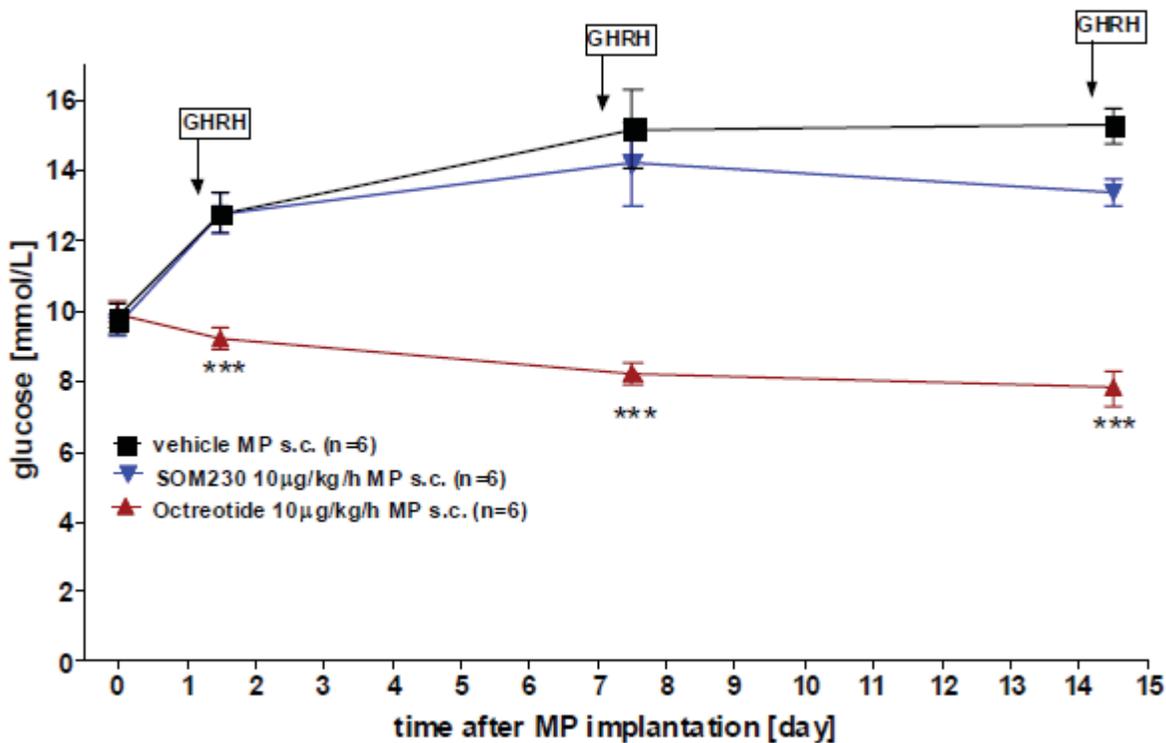
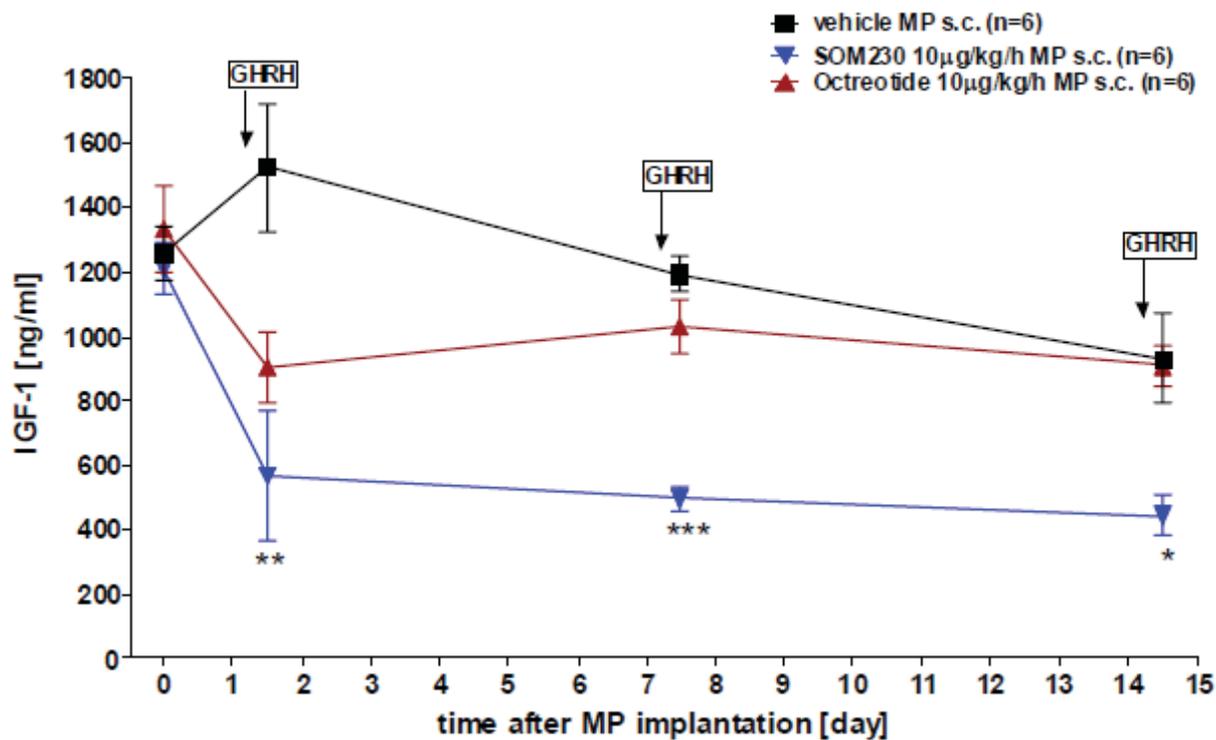
Separate analysis of the unstimulated effect of long term SOM230 and octreotide applied via osmotic minipumps on GH, IGF-1 and glucose





**Separate analysis of the GHRH stimulated effect of long term SOM230 and octreotide applied via osmotic minipumps on GH, IGF-1 and glucose**

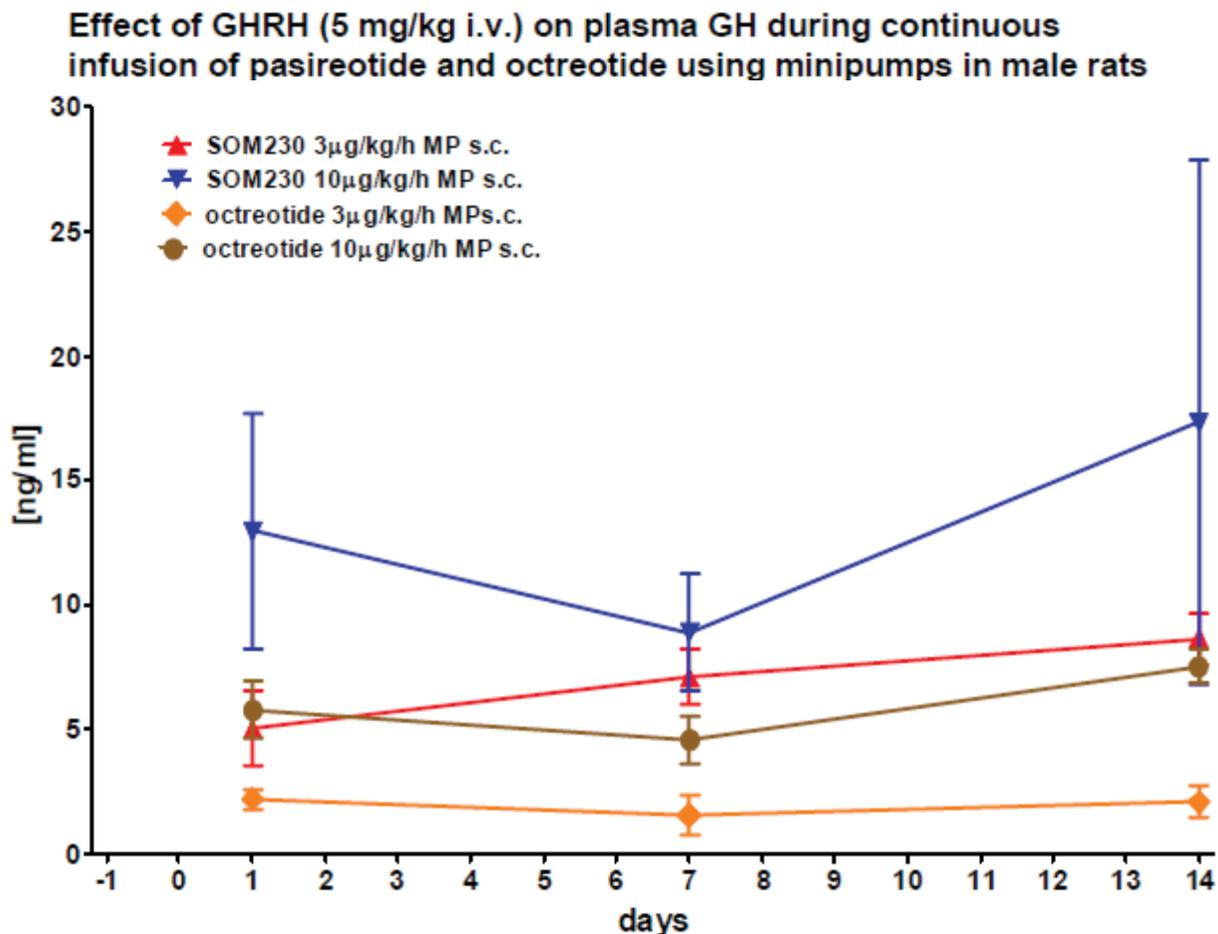




- **Experiment #5** – Mean plasma levels of both pasireotide and octreotide applied via osmotic minipumps resulted in stable mean plasma concentrations throughout 14 days. With pasireotide at 3 µg/kg/h, it remained in a narrow range

of 5-8 ng/ml throughout the 14 days period, whereas the higher dose of 10 µg/kg/h resulted in mean plasma values between 9-18 ng/ml.

Figure 5 Study No rd-2011-00248: Experiment #5 – Plasma level of octreotide and pasireotide in rats



#### 4.2 Secondary Pharmacology

n/a

#### 4.3 Safety Pharmacology

#### **pcs-r1270349-01: in vitro hERG assay**

Study title: Effect of Test Article SOM230 on Cloned hERG Channel Surface Expression in Mammalian Cells (by (b) (4))

Study design: This study assessed the effect of SOM230 (Test Article ID - SOM230-BTA.002 and Batch Number R002) on hERG current in HEK293 cells transfected with hERG cDNA. There are three treatment groups: 1) vehicle (0.3% DMSO), 2) reference item (1 µM geldanamycin or 1 µM astemizole), and 3) SOM230 (0.0003 -100 µM). The hERG-Lite assay was used to evaluate changes in relative surface expression of the hERG potassium channel. Trafficking inhibition was assessed by monitoring surface

expression of the wild-type (WT) channel, while channel block was predicted based on the rescue of surface expression of a hERG single mutant (SM).

Study results:

- SOM230 showed a significant decrease in hERG-WT surface expression at the highest concentration tested (YES in the trafficking inhibition column). SOM230 however did not show a significant increase hERG-SM surface expression at any concentration tested.
- The positive control, geldanamycin for hERG-WT and astemizole for hERG-SM, showed a ~34% decrease in hERG-WT surface expression and greater than a 5X increase in hERG-SM surface expression, respectively.

Table 4 Study No pcs-r1270349-01: hERG-lite assay results

**Relative Surface Expression of the hERG Channel**

Test Article ID	Test Conc. (µM)	hERG-SM Relative Surface Expression			hERG-WT Relative Surface Expression			Predicted hERG Risk	
		AVG	SD	Plate	AVG	SD	Plate	Channel Block	Trafficking Inhibition
SOM230-BTA.002	0.0003	NS/0.98	0.17	2	NS/1.08	0.05	1	no	YES
	0.0010	NS/0.91	0.12		NS/1.04	0.02			
	0.0030	NS/0.97	0.07		NS/1.01	0.09			
	0.0100	NS/1.02	0.17		NS/1.03	0.08			
	0.0300	NS/0.91	0.16		NS/0.98	0.08			
	0.1000	NS/0.97	0.13		NS/0.95	0.02			
	0.3000	NS/1.04	0.25		NS/1.13	0.28			
	1.0000	NS/1.03	0.06		NS/0.97	0.06			
	3.0000	NS/1.22	0.52		NS/0.98	0.10			
	10.0000	NS/0.81	0.04		NS/0.84	0.05			
	30.0000	NS/0.76	0.06		NS/0.97	0.08			
100.0000	NS/1.02	0.33	0.62	0.01					

**Positive Controls for the hERG-Lite Assay**

Positive Control Article	Test Conc. (µM)	hERG-SM Relative Surface Expression			hERG-WT Relative Surface Expression		
		AVG	SD	Plate #	AVG	SD	Plate #
Astemizole	1	9.06	0.70	2			
Geldanamycin	1				0.66	0.06	1

**pcs-r1270473: in vitro assay**

Study title: Effects of SOM230 on ten cloned ion channels expressed in mammalian cells (by (b) (4))

Study design: This study examined the in vitro effect of SOM230 (Test Article ID SOM230-BTA.002 Batch No R0002; up to 30 µM) on 10 cloned ion channels expressed in mammalian cells, HEK293 or CHO cell lines. With patch clamp recording, the IC50 for the inhibitory effect of SOM230 on each channel current was measured.

Study results:

- SOM230 inhibited the hNCX1 current (IC<sub>50</sub> = 21.7 μM).
- With other channels, IC<sub>50</sub> could not be determined since the highest test concentration did not inhibit more than 50%.

Table 5 Study No pcs-r1270473: IC<sub>50</sub> results

<b>Summary of effects of SOM230 on ten channels</b>				
<b>Channel</b>	<b>Concentration (μM)</b>	<b>% Inhibition</b>	<b>SD</b>	<b>n</b>
hCav3.2	10	3.1	2.4	5
	30	36.6	3.0	4
hHCN2	10	0.6	0.1	3
	30	-0.8	2.3	5
hHCN4	10	-3.7	1.8	3
	30	-4.5	2.2	4
hKir2.1	10	3.1	1.8	3
	30	4.6	1.0	3
hKir3.1/hKir3.4	10	3.2	2.3	4
	30	2.6	1.2	3
hKir6.2/SUR2A	10	1.1	1.6	3
	30	-1.3	1.3	4
hKvLQT1/hminK	10	0.8	1.8	4
	30	0.7	1.8	3
hKv1.5	10	1.5	0.5	3
	30	2.9	3.0	4
hKv4.3	10	7.0	1.5	3
	30	2.6	3.4	3
hNCX1	3	7.0	1.1	3
	10	21.0	20.4	3
	30	63.2	10.7	3

**Summary of effects of positive controls on ten channels**

Channel	Positive Control	Concentration (µM)	% Inhibition	SD	n
hCav3.2	Nickel (II)	100	85.7	2.7	2
hHCN2	Zatebradine	100	81.2	1.3	2
hHCN4	Zatebradine	10	60.6	11.7	2
hKir2.1	Barium Chloride	100	96.8	0.4	2
hKir3.1/hKir3.4	Barium Chloride	300	72.8	5.5	2
hKir6.2/SUR2A	Glybenclamide	1	89.8	5.2	2
hKvLQT1/hminK	Chromanol 293B	30	83.9	0.8	2
hKv1.5	4-AP	2000	86.3	1.6	2
hKv4.3	Flecainide	100	78.0	7.6	3
hNCX1	KB-R7943	3	62.4	4.4	2

## 5 Pharmacokinetics/ADME/Toxicokinetics

Under NDA 200677, ADME studies demonstrated several key findings:

- Pasireotide was well absorbed
- It had moderate plasma protein binding.
- It was somewhat well distributed to tissues such as kidney, lymph nodes, spleen, liver, injection site, and small intestinal wall (with some distribution to reproductive system and minimal distribution to CNS).
- It was present in the milk and could be absorbed into the fetus (milk and plasma AUC ratio in rats ~ 0.28).
- It was metabolized by CYP3A4 (formation of P24) and CYP3A5 (formation of P30 or M27, an oxidative product) with low turnover rate.
- It remained mostly unchanged in the plasma.
- It was excreted (mainly the parent drug) via feces and urine.
- It would have minimal drug and drug interactions with its co-medications based on a series of enzyme inhibition and induction (i.e. weak inhibitions on CYP2B6 and UGT1A1), and transporters studies (i.e. no inhibition on hepatic uptake transporters OATP1B1/OATP1B3 and inhibition on bile transporters MRP2/hBSEP).

**Few PK (drug interaction) studies in vitro were conducted which are discussed below.**

### 5.1 PK/ADME

#### **DRUG INTERACTIONS**

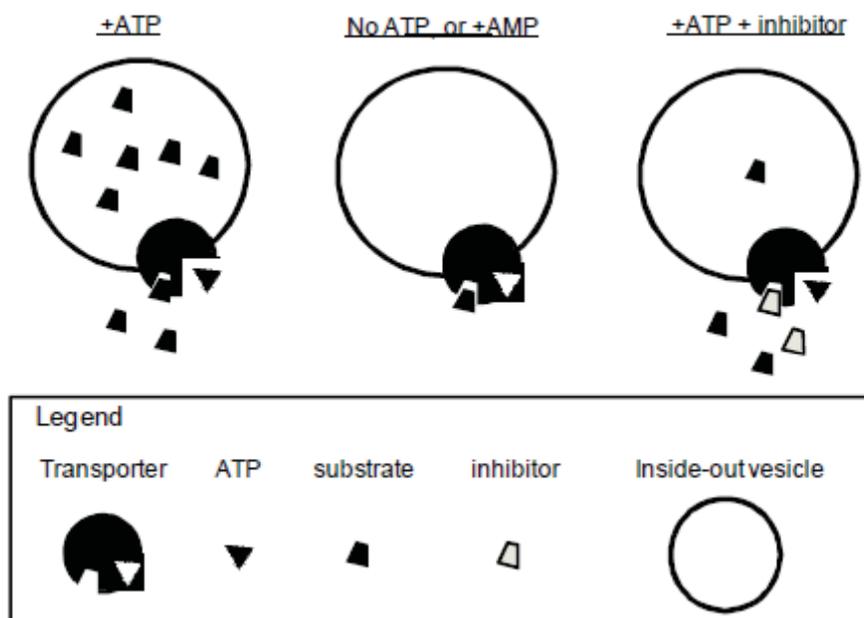
**dmpk-r12002481-01: inhibitor of P-gp and BCRP**

### Assessment of SOM230 as an inhibitor of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)

This study studied the potential of SOM230 (SOM230 diacetate; Lot No NVP-PKF227-230-AK-5) to inhibit P-gp or BCRP activity using inside-out membrane vesicles expressing P-gp or BCRP. The potential inhibitory effect of SOM230 was tested based on the accumulation of radiolabeled P-gp or BCRP substrate in the membrane vesicles. For P-gp, the effect of SOM230 (0.5-10  $\mu\text{M}$ ) or CsA (model P-gp inhibitor; 40  $\mu\text{M}$ ) on [3H]NMV ATP-dependent accumulation in vesicles was examined. For BCRP, the effect of SOM230 (0.5-10  $\mu\text{M}$ ) or FTC (model BCRP inhibitor; 10  $\mu\text{M}$ ) on [3H]NMV ATP-dependent accumulation in vesicles was examined. The IC<sub>50</sub> values for inhibition of transport was determined by scintillation and luminescence counter.

#### inside-out membrane vesicle methodology

Inside-out membrane vesicles expressing P-gp or BCRP are commercially available. The inside-out orientation renders the ATP binding site and ligand binding site(s) of the transporter accessible from the external media. The transporter mediates the intravesicular accumulation of substrate in the presence of ATP. Inhibition of the expressed transporter would result in reduced intravesicular accumulation of the test substrate.



#### Findings:

- CsA completely inhibited the [3H]NMV accumulation in P-gp expressing cells. The transport of [3H]NMV by P-gp vesicles was maximally inhibited (~91%) by SOM230 at 10  $\mu\text{M}$  (IC<sub>50</sub> = 0.851  $\pm$  0.41  $\mu\text{M}$ ). This suggests that SOM230 could inhibit P-gp activity provided that high enough concentrations can be achieved at the P-gp active site.

- FTC inhibited (~98%) the [<sup>3</sup>H]NMV accumulation in BCRP expressing cells. The transport of [<sup>3</sup>H]NMV by BCRP vesicles was maximally inhibited (~48%) by SOM230 at 10 μM (IC<sub>50</sub> ~ 10 μM).

Table 6 Study No dmpk-r1200248-01: P-gp and BCRP inhibitors

**Effect of SOM230 and the model inhibitor CsA on P-gp-mediated [<sup>3</sup>H]NMV transport**

Substrate, concentration	Inhibitor	Inhibitor concentration, μM	P-gp-mediated transport (pmol/mg protein/min) <sup>a</sup>	% inhibition
[ <sup>3</sup> H]NMV, 0.4 μM	None	-	1.38 ± 0.34	0
	CsA	40 <sup>b</sup>	-0.160 ± 0.30	~100%
	SOM230	0.50	1.04 ± 0.26	24.6
		1.0	0.471 ± 0.12	65.9
		2.5	0.425 ± 0.036	69.3
		5.0	0.229 ± 0.018	83.4
		10	0.124 ± 0.0080	91.0

<sup>a</sup> P-gp mediated activity was calculated as the average difference in [<sup>3</sup>H]E<sub>3</sub>S accumulation in vesicles in the presence ATP from that in the absence ATP

<sup>b</sup> Nominal concentration

**Effect of SOM230 and the model inhibitor FTC on BCRP-mediated [<sup>3</sup>H]E<sub>3</sub>S transport**

Substrate, concentration	Inhibitor	Inhibitor concentration, μM	BCRP mediated transport (pmol/mg protein/min) <sup>a</sup>	% Inhibition
[ <sup>3</sup> H] E <sub>3</sub> S, 1 μM	None	-	114 ± 4.5	0
	FTC	10	2.44 ± 1.1	97.9
	SOM230	0.50	107 ± 13	6.28
		1.0	105 ± 16	7.80
		2.5	90.5 ± 2.4	20.6
		5.0	77.4 ± 2.3	32.1
		10	58.8 ± 0.93	48.4

<sup>a</sup> BCRP-mediated activity was calculated as the average difference in [<sup>3</sup>H] E<sub>3</sub>S accumulation in vesicles in the presence ATP from that in the presence AMP

**dmpk-r1200761: non-inhibitor of transporters OCT1/2**

**Assessment of SOM230 as an inhibitor of human organic cation transporters 1 and 2**

This study studied the potential of SOM230 (Batch No PKF227-230-BF-2) to inhibit OCT1 and OCT2 (important determinants in the hepatic and renal elimination of a number of therapeutic drugs) in HEK cells. The inhibition of OCT1 uptake of [<sup>3</sup>H]MPP+ and the inhibition of OCT2 uptake of [<sup>14</sup>C]metformin were conducted. The protein content was then measured using the BCA protein determination assay kit.

Findings:

- For OCT1, SOM230 did not inhibit OCT-1 mediated [3H]methyl-4-phenylpyridinium ([3H]MPP+) transport with the concentration tested (0.1-10  $\mu\text{M}$ ). The uptake of [3H]MPP+ into HEK-OCT1 cells was much greater than uptake into parental HEK cells (9.2 fold higher). With decynium 22 (OCT inhibitor at 20  $\mu\text{M}$ ), the uptake activity was reduced 84.4%.
- For OCT2, SOM230 also did not inhibit OCT2-mediated [14C]metformin transport with the concentration tested (0.1-10  $\mu\text{M}$ ). The uptake of [14C]metformin into HEK-OCT2 cells was much greater than uptake into parental HEK cells (41 fold higher). With decynium 22 (OCT inhibitor at 20  $\mu\text{M}$ ), the uptake activity was reduced 99.7%.
- This data suggests that the cell lines used were appropriate for assessing the inhibitory effect of SOM230 toward OCT1 and OCT2.

Table 7 Study No dmpk-r1200761: OCT1 and OCT2 inhibitors

**Effect of SOM230 and decynium 22 on [<sup>3</sup>H]MPP<sup>+</sup> accumulation in control or OCT1-expressing cells**

Inhibitor	Inhibitor concentration, $\mu\text{M}$	[ <sup>3</sup> H]MPP <sup>+</sup> accumulation, <sup>a</sup> (fmol-mg protein <sup>-1</sup> ·min <sup>-1</sup> )		% Inhibition <sup>b</sup>
		OCT1 cells	Control cells	
None	-	154 ± 4.6	16.6 ± 1.9	0.0
Decynium 22	20	32.6 ± 1.4	11.3 ± 0.47	84.4
SOM230	0.10	145 ± 1.0	16.5 ± 0.63	6.29
	0.50	149 ± 0.79	17.6 ± 0.25	3.98
	1.0	147 ± 6.1	17.5 ± 0.58	5.58
	5.0	156 ± 2.2	17.5 ± 1.3	NI <sup>c</sup>
	7.5	149 ± 4.2	18.0 ± 1.4	4.04
	10	155 ± 17	18.0 ± 0.51	NI

<sup>a</sup> [<sup>3</sup>H]MPP<sup>+</sup> was added to a final concentration of 7.9 nM

<sup>b</sup> % inhibition was calculated as described by Equation 1 in Section 2.5

<sup>c</sup>NI: No Inhibition

**Effect of SOM230 and decynium 22 on [<sup>14</sup>C]metformin accumulation in control or OCT2-expressing cells**

Inhibitor	Inhibitor concentration, $\mu\text{M}$	[ <sup>14</sup> C]metformin accumulation, <sup>a</sup> (pmol-mg protein <sup>-1</sup> ·min <sup>-1</sup> )		% Inhibition <sup>b</sup>
		OCT2 cells	Control cells	
None	-	119 ± 7.9	2.89 ± 0.13	0.0
Decynium 22	20	1.51 ± 0.25	1.20 ± 0.11	99.7
SOM230	0.10	123 ± 4.5	2.89 ± 0.36	NI <sup>c</sup>
	0.50	115 ± 1.8	2.49 ± 0.15	3.12
	1.0	116 ± 4.5	2.46 ± 0.25	2.34
	5.0	111 ± 3.6	2.04 ± 0.40	6.45
	7.5	105 ± 1.4	1.81 ± 0.13	11.8
	10	106 ± 1.2	1.49 ± 0.16	10.7

<sup>a</sup> [<sup>14</sup>C]Metformin was added to a final concentration of 10.5  $\mu\text{M}$

<sup>b</sup> % inhibition was calculated as described by Equation 1 in Section 2.5

<sup>c</sup>NI: No Inhibition

**dmpk-r1200835: inhibitor of transporters OAT1/3****Assessment of SOM230 as an inhibitor of human organic anion transporters 1 and 3**

This study studied the potential of SOM230 (Batch No PKF227-230-BF-2) to inhibit OAT1 and OAT3 (active and rate-limiting step in the renal tubular secretion of numerous organic anions, including those that are therapeutic drugs, for final elimination in the urine) in HEK cells. The inhibition of OAT1 uptake of [<sup>3</sup>H]cidofovir and the inhibition of OAT3 uptake of [<sup>3</sup>H]estrone-3-sulfate were conducted. The protein content was then measured using the BCA protein determination assay kit.

**Findings:**

- For OAT1, SOM230 inhibit OAT-1 mediated [<sup>3</sup>H]cidofovir transport with the concentration tested (0.1-10 μM). The uptake of [<sup>3</sup>H]cidofovir into HEK-OAT1 cells was much greater than uptake into parental HEK cells (142 fold higher). At 10 μM, SOM230 had 50.6% inhibition of OAT1 activity (IC<sub>50</sub> = ~10 μM). With probenecid (OAT1/3 inhibitor at 100 μM), the uptake activity was greatly reduced.
- For OAT3, SOM230 also inhibited OAT3-mediated of [<sup>3</sup>H]estrone-3-sulfate transport with the concentration tested (0.1-10 μM). The uptake of [<sup>3</sup>H]estrone-3-sulfate into HEK-OCT2 cells was much greater than uptake into parental HEK cells (10 fold higher). At 10 μM, SOM230 had 84.0% inhibition of OAT3 activity (IC<sub>50</sub> = 1.7±0.3 μM). With probenecid (OAT1/3 inhibitor at 100 μM), the uptake activity was greatly reduced.
- This data suggests that SOM230 could increase the systemic exposure of co-medications whose clearance is mediated by OAT1 or OAT3 transport activity.

**Table 8 Study No dmpk-r1200835: OAT1 and OAT3 inhibitors**

<b>Effect of SOM230 and the model inhibitor probenecid on [<sup>3</sup>H]cidofovir accumulation in control or OAT1-expressing HEK293 cells</b>				
Inhibitor	Inhibitor concentration, μM	[ <sup>3</sup> H]cidofovir accumulation <sup>a</sup> (pmol/mg protein/min)		% inhibition <sup>b</sup>
		Control cells	OAT1 cells	
None	0	0.0759 ± 0.021	9.38 ± 1.1	0
Probenecid	100	0.0920 ± 0.034	0.879 ± 0.076	91.6
SOM230	0.10	0.0558 ± 0.024	8.66 ± 0.071	7.60
	0.50	0.0576 ± 0.024	8.31 ± 0.49	11.3
	1.0	0.0323 ± 0.018	7.60 ± 0.26	18.6
	2.5	0.0447 ± 0.010	7.22 ± 0.35	22.9
	5.0	0.0547 ± 0.014	5.81 ± 0.35	38.1
	10	0.0438 ± 0.070	4.64 ± 0.54	50.6

<sup>a</sup> Final [<sup>3</sup>H]cidofovir concentration in the incubation mixture was 1.6 μM

<sup>b</sup> % Inhibition was calculated from the effect of inhibitor concentration on the difference in level of [<sup>3</sup>H]cidofovir accumulation in OAT1 cells compared to that in control cells relative to the same difference in the absence of inhibitors as described in Section 2.3

**Effect of SOM230 and the model inhibitor probenecid on [<sup>3</sup>H]estrone-3-sulfate accumulation in control or OAT3-expressing HEK293 cells**

Inhibitor	Inhibitor concentration, $\mu\text{M}$	$[^3\text{H}]\text{E}_3\text{S}$ accumulation <sup>a</sup> (fmol/mg protein/min)		% Inhibition <sup>b</sup>
		Control cells	OAT3 cells	
None	0	0.629 $\pm$ 0.024	6.28 $\pm$ 0.059	0
Probenecid	100	0.579 $\pm$ 0.045	0.961 $\pm$ 0.068	93.2
SOM230	0.10	0.614 $\pm$ 0.070	5.74 $\pm$ 0.32	9.19
	0.50	0.597 $\pm$ 0.056	4.63 $\pm$ 0.053	28.8
	1.0	0.565 $\pm$ 0.036	3.97 $\pm$ 0.13	39.7
	2.5	0.573 $\pm$ 0.0040	3.13 $\pm$ 0.026	54.7
	5.0	0.516 $\pm$ 0.031	1.87 $\pm$ 0.10	76.0
	10	0.498 $\pm$ 0.020	1.40 $\pm$ 0.011	84.0

<sup>a</sup> Final  $[^3\text{H}]\text{E}_3\text{S}$  concentration in the incubation mixture was 0.75  $\mu\text{M}$

<sup>b</sup> % Inhibition was calculated from the effect of inhibitor concentration on the difference in level of  $[^3\text{H}]\text{E}_3\text{S}$  accumulation in OAT3 cells compared to that in control cells relative to the same difference in the absence of inhibitors as described in Section 2.3

## 5.2 Toxicokinetics

n/a

## 6 General Toxicology

Somatostatin decreases IFG-1 and GH so expected particular target organ toxicities include pituitary (mice/rats/monkeys), bone (mice/rats), liver (mice/rats), coagulation (rats), female reproductive tract (mice/rats), bone marrow (rats/monkeys), , spleen (rats), thyroid (monkeys), and GI (monkeys/dogs), and injection sites (mice/rats/monkeys).

In NDA 200677, most of these exaggerated pharmacological effects of SOM230 described above were consistent across species. A few rat findings (i.e. CV effects of edema and hyperemia or  $\uparrow$  AST/ALT) were noted in shorter duration studies (i.e. < 4 weeks) but not in the 26 week study. Few monkey findings (i.e. in GI and thyroid glands) were not seen in mice/rats, whereas few rat findings (i.e. in bone, ovary/uterine, liver, and coagulation factors) were not seen in monkeys. Despite some species differences with SOM230, the toxicological profile of SOM230 was similar to other somatostatin analogues.

### Single dose toxicity studies with Signifor® (reviewed under NDA 200677)

Single dose toxicity studies were done in mice and rats showed that SOM230 at 30 mg/kg was not lethal. In mice, SOM230 caused crust formation at the injection site in 1 female from Days 8-15. In rats, SOM230 caused sores at injection site in all females at 15 mg/kg and all animals at 30 mg/kg from Days 4/5-15. Body weight loss was observed during 1<sup>st</sup> week after treatment.

### Pivotal repeat-dose studies with Signifor® (reviewed under NDA 200677)

Repeat dose toxicity studies were done in mice, rats, dogs, and monkeys. The pivotal studies were conducted for up to 26 weeks in rats and up to 39 weeks in monkeys with SOM230 administered sc either b.i.d. or once daily. Majority of SOM-230 related

findings (i.e. in pituitary, pancreas, spleen, bone marrow, thyroid, ovary/uterine, or bone) were exaggerated pharmacological effects of pasireotide.

- The 26 week rat sc study (0, 0.008, 0.024, 0.08, and 0.24 mg/kg once daily) resulted in reduced body weight gain was noted, altered hematological/clotting factor parameters (i.e. decreased WBC/lymphocytes and increased PT/APTT), clinical chemistry parameters (i.e. decreased serum proteins), and urinary parameters (i.e. volume/pH). Microscopic findings were noted in pituitary (decreased eosinophilia of the somatotrophs), pancreas (decreased zymogene granules), spleen (lymphoid and hematopoietic cell depletion), bone marrow (hypocellularity), ovary (interstitial cell hyperplasia and decreased number of corpora lutea), uterine/vagina (uterine dilation and vaginal mucosal proliferation), and injection site (inflammation). Other shorter duration ( $\leq 26$  weeks) rat sc studies also showed that SOM230 had effects on vascular system (edema and hyperemia), bone formation (lack of new bone formation in ribia/femur), liver wt/functional changes (decreased weight and increased ALT). These organ-specific findings were related to the pharmacology of pasireotide and recoverable. The NOAEL was  $< 0.008$  mg/kg/day (applicant NOAEL = 0.024 mg/kg/day based on histopath).
- The 39 week monkey sc study (0, 0.4, 1.6, and 3.2 mg/kg once daily) resulted in injection site findings (swelling, redness, scabs mostly in HD group). Microscopic findings were noted in pituitary (increased acidophilia in the pars distalis, vacuolar change with proteinaceous materials), thyroid (minimal or slight small follicles), GI (proteinaceous material present in the crypts of the mucosa in the cecum and colon), and injection site (edema, inflammation). The NOAEL was  $< 0.4$  mg/kg/day (applicant NOAEL = 1.6 mg/kg/day based on histopath).

#### **Local tolerance/repeated dose toxicity studies with Signifor LAR (reviewed under NDA 200677)**

A series of local tolerance studies (in rats: single dose at 5/6 mg/kg and in rabbits: 28, 34, 40 mg/kg) and repeat dose toxicity studies (in rats: 3 monthly at 0, 10, 12.5 mg/kg and 6 monthly at 0, 3.125, 6.25 mg/kg) were done to evaluate LAR (long acting release) formulation of SOM230.

- These studies showed the LAR formulation was tolerable.
- The findings of LAR pasireotide were similar to those observed after sc administration (i.e. decreased body weight, increased PTT, target organs including adrenals/pituitary/thyroid glands). However, injection site findings (erythema and granulomas) were noted in microparticle placebo- and SOM230-treated animals, attributed to microparticles contained in the LAR formulation.

#### **r0470138: 6 mo (once monthly) rat IM study (reviewed under NDA 200677)**

Study title: 6-cycle intramuscular (one injection/month) toxicity study in male rats with recovery using a new long acting release (LAR) formulation

**Study designs:** This study was to establish the toxicity of SOM230 when administered to male rats as an IM injection for 6 cycles (1 injection per month for 6 months) with a long lasting release (LAR) formulation. SOM230 (batch no 0321003) was administered by IM injection as a LAR micro-particle 50/50 polymer mixture. IM injections of the SOM230 formulation were given once every 4 weeks for 6 cycles (Weeks 1, 5, 9, 13, 17, and 21) to two troupes of male rats at 3.125 mg (dose volume of 0.25 ml) and 6.25 mg (dose volume of 0.5 ml) base per injection. Two additional groups of rats were given either vehicle for microparticles or SOM230 placebo (microparticles) at a dose volume of 0.5 ml. Some animals were designated to sacrifice at the end of the dosing period (Week 25) or at the end of 14 or 21 weeks recovery. The endpoints included clinical signs, injection site observations, body weights, food consumption, ophthalmoscopic exam, macroscopic and microscopic exams, organ weight, antibody analysis and TK analysis.

**Table 9 Study No r0470138: 6 month rat tox study with LAR formulation – study design**

<b>Study design, animal allocation and test article doses</b>					
Group	Number (males)	Animal Numbers	Dose(mg free base/animal)	Concentration (mg/mL)	Necropsy
1 Vehicle control	10	1001-10	0	0	Week 25
	10	1011-20			Recovery week 14
	10	1021-30			Recovery week 21
2 Placebo control	10	2001-10	0	0	Week 25
	10	2011-20			Recovery week 14
	10	2021-30			Recovery week 21
3 Low	10	3001-10	3.125	12.5*	Week 25
	10	3011-20			Recovery week 14
	10	3021-30			Recovery week 21
4 High	10	4001-10	6.25	12.5*	Week 25
	10	4011-20			Recovery week 14
	10	4021-30			Recovery week 21

\*Doses corrected for active moiety.

#### **Findings:**

- No mortality was noted. A slight increase in erythema in microparticle placebo and SOM230-treated animals, attributable to the microparticle formulation. Most cases of erythema resolved within 5 days after injection. One single HD male had thin appearance, hunched posture, staining of the fur, slightly decreased locomotor activity, and etc.
- Slight transit body weight loss was seen in SOM230-treated animals which generally coincided with monthly injections. Significant decreases in mean body weight (36.4 and 37.3% on Day 168; partially reversible after 21 week recovery period) and food consumption (23.6 and 23.1% on Day 168; reversible) were observed in SOM230-

treated animals at 3.125 and 6.25 mg/injection respectively, starting on Day 8 or 15 (and till the end of dosing period Day 168).

- Most changes were noted in hematological parameter (i.e. minimal decreases in the lymphocyte and platelet counts and plasma fibrinogen levels; recoverable) and clinical chemistry parameter (i.e. minimal decreases in serum globulin, creatinine, calcium, and phosphorus levels and minimal increases in cholesterol, chloride and urea; increases in sodium, AST and APT – only at 6.25 mg; recoverable) at  $\geq 3.125$  mg/injections.

**Clinical chemistry changes in male rats receiving SOM230**

Analyte	Dose	Time point
↑AST activity (U/L)	6.25 mg/injection (mild)	d125 and d163
↑ALP activity (U/L)	6.25 mg/injection (mild)	d125 and d163
↓Globulins (g/dL)	$\geq 3.125$ mg/injection (mild)	d125, d163 and R*d90
↑Urea (mg/dL)	$\geq 3.125$ mg/injection (mild)	d125 and d163
↓Creatinine (mg/dL)	$\geq 3.125$ mg/injection (mild)	d125 (6.25 mg only), d163 and Rd90 (6.25 mg only)
↑Sodium (mEq/L)	6.25 mg/injection (mild)	d125
↑Chloride (mEq/L)	$\geq 3.125$ mg/injection (mild)	d125, d163 and Rd90 (6.25 mg only)
↓Calcium (mg/dL)	$\geq 3.125$ mg/injection (mild)	d125 and d163
↓Phosphorus (mg/dL)	$\geq 3.125$ mg/injection (mild)	d125 and d163
↑Cholesterol (mg/dL)	$\geq 3.125$ mg/injection (mild)	d125 and d163

\*R= recovery phase

- Microscopic findings were noted in injection sites (i.e. microphages and giant cell granulomas all groups), pituitary (i.e. decreased acidophilia; partially reversible), pancreas (i.e. increased retention of zymogen; reversible) and, thyroid glands (i.e. follicular dilation with attenuation of follicular epithelium at 6.25 mg/injection; reversible), bones (i.e. lack of new bone formation beneath the epiphyseal plate of the tibia and femur) and bone marrow (i.e. hypocellularity, fatty; partially to fully reversible) in SOM-230 treated animals.
- The release of SOM230 LAR formulation was slow after first injection (Tmax 648 hr). For cycles 2-6, the apparent Tmax was 2 hr at first time point collected at 3.125 mg (Cmax = 1740 ng/ml and AUC2-168hr = 388000 ng\*hr/ml) and 168 hr at 6.25 mg/injection (Cmax = 2050 ng/ml and AUC2-168hr = 682000 ng\*hr/ml). Exposure was generally dose proportional. After 21 week recovery period, SOM230 can be detected in approx. 30% animals for both dose levels.

**Table 10 Study No r0470138: 6 month rat tox study with LAR formulation – TK data**

**Mean toxicokinetic parameters of SOM230 in male rat plasma, during the treatment phase**

Toxicokinetic parameter	Dose level of SOM230 (mg/injection)	
	3.125 mg (Group 3)	6.250 mg (Group 4)
<b>Day 1 (cycle 1)</b>		
$t_{max}$	648	648
$C_{max}$	68.8	133
$C_{max}/dose$	22.0	21.3
$AUC_{(2-648h)}$	14900	25500
$AUC_{(2-648h)}/dose$	4780	4080
<b>Day 29(cycle 2)</b>		
$t_{max}$	2	168
$C_{max}$	87	354
$C_{max}/dose$	27.8	56.6
$AUC_{(2-648h)}$	42900	172000
$AUC_{(2-648h)}/dose$	13700	27600
<b>Day 57(cycle 3)</b>		
$t_{max}$	2	168
$C_{max}$	521	1900
$C_{max}/dose$	167	304
$AUC_{(2-648h)}$	164000	710000
$AUC_{(2-648h)}/dose$	52600	114000
<b>Day 85(cycle 4)</b>		
$t_{max}$	2	168
$C_{max}$	1410	2820
$C_{max}/dose$	451	451
$AUC_{(2-648h)}$	320000	919000
$AUC_{(2-648h)}/dose$	102000	147000
<b>Day 113(cycle 5)</b>		
$t_{max}$	2	168
$C_{max}$	1800	2690
$C_{max}/dose$	576	430
$AUC_{(2-648h)}$	403000	834000
$AUC_{(2-648h)}/dose$	129000	133000
<b>Day 141(cycle 6)</b>		
$t_{max}$	2	168
$C_{max}$	1740	2050
$C_{max}/dose$	557	328
$AUC_{(2-648h)}$	388000	682000
$AUC_{(2-648h)}/dose$	124000	109000
Units : $t_{max}$ [h]. $C_{max}$ [ng/mL]. $C_{max}/dose$ [(ng/mL)/mg] $AUC_{(2-648h)}$ [h-ng/mL]. $AUC_{(2-648h)}/dose$ [(h-ng/mL)/mg]		

- There was anti-SOM230 antibody detected in 26/59 SOM230-treated animals. However, these antibodies did not appear to have neutralizing effect on SOM230.

Table 11 Study No r0470138: 6 month rat tox study with LAR formulation – anti drug response

**Anti-SOM230 antibody response in SOM230-treated animals**

Number of animals with positive response	Dose level of SOM230 (mg/injection)	
	3.125 mg (Group 3)	6.250 mg (Group 4)
Treatment Week 25	9/10	4/10
Recovery week 14	4/10	3/10
Recovery week 21	3/9	3/10

<sup>a</sup>Samples with mean non specific binding (NSB) signal above 0.068 (OD) were set as positive for immunogenicity.

- NOAEL was < 3.125 mg/injected (applicant's NOAEL = 3.125 mg/injection based on increased AST and ALP at 6.25 mg/injection).

Table 12 Study No r0470138: 6 month rat tox study with LAR formulation – microscopic findings

**Compound-related microscopic findings**

Tissue/finding	Treatment group											
	Vehicle control			Placebo control			SOM230 3.125 mg/injection			SOM230 6.25 mg/injection		
	Term	Recovery (week)		Term	Recovery (week)		Term	Recovery (week)		Term	Recovery (week)	
		14	21		14	21		14	21		14	21
<b>Injection site- R<sup>a</sup></b>												
Granuloma	0	0	0	0	0	0	7 <sup>c</sup>	2	3	9	8	6
Eosinophilic granular material	0	0	0	0	0	0	7 <sup>c</sup>	2	3	9	8	6
<b>Injection site- L<sup>b</sup></b>												
Granuloma	0	0	0	7	0	0	10 <sup>c</sup>	3	4	10	7	3
Eosinophilic granular material	0	0	0	0	0	0	10 <sup>c</sup>	3	4	10	7	3
<b>Pancreas</b>												
Retention zymogen	0	0	0	0	0	0	11 <sup>c</sup>	0	0	10	0	0
<b>Pituitary</b>												
Acidophilia decreased	0	0	0	0	0	0	11 <sup>c</sup>	4	2	9 <sup>d</sup>	10	2
<b>Thyroid</b>												
Dilation follicular + attenuated epithelia	0	0	0	0	0	0	2 <sup>c</sup>	1	0	8	2	0
<b>Bone Marrow</b>												
Hypocellularity (increased fat)	0	0	0	0	0	0	11 <sup>c</sup>	0	0	10	9	5
<b>Femur/ Sternum</b>												
↓primary spongiosa	0	0	0	0	0	0	11 <sup>c</sup>	0	0	10	0	0

<sup>a</sup>The final injection to the right hind limb was administered on Day 113 (13-Jan-2005).

<sup>b</sup>The final injection to the left hind limb was administered on Day 141 (10-Feb-2005).

<sup>c</sup>Animal 3023, sacrificed for humane reasons on day 166, had compound-related findings similar to terminal sacrifice animals.

<sup>d</sup>Animal 4003, pituitary missing at processing  
N=10/timepoint/group

### **r0770082: 3 mo (once monthly) rat IM study (reviewed under NDA 200677)**

**Study title:** A 3-cycle (1 injection per month) toxicity study of SOM230 administered by the intramuscular route to rats with a 21-week recovery phase (by (b) (4) study no. BLA00175)

**Study designs:** This study was to establish the toxicity of SOM230 when administered to male rats as an IM injection for 3 cycles (1 injection per month for 3 months) with a long lasting release (LAR) formulation. SOM230 (A: lot 0321003; B: lot C0001) was administered by IM injection as a LAR micro-particle 50/50 polymer mixture. IM injections of the SOM230 formulation A were given to one group of rats at 12.5 mg/ml

(0.66 ml/animal) once every 4 weeks for 3 cycles (Weeks 1, 5, and 9). IM injections of the SOM230 formulation B were given to two other groups at 10.0 mg/ml (0.41 or 0.82 ml/animal) for the 1<sup>st</sup> dose and 12.5 mg/ml (0.33 or 0.66 ml/animal) for the 2<sup>nd</sup> and 3<sup>rd</sup> doses. One other group of rats was given vehicle once monthly for 3 months. The endpoints included clinical signs, injection site observations, body weights, food consumption, ophthalmoscopic exam, macroscopic and microscopic exams, organ weight, antibody analysis and TK analysis.

**Table 13 Study No r0770082: 3 month rat tox study with LAR formulation – study design**

Study design. animal allocation and test article doses								
Group	Number of animals		Animal numbers		SOM230 <sup>a</sup>			
					Dose (mL)		Concentration (mg/mL)	
	Males	Females	Males	Females	1 <sup>st</sup> dose	2 <sup>nd</sup> and 3 <sup>rd</sup> dose	1 <sup>st</sup> dose	2 <sup>nd</sup> and 3 <sup>rd</sup> dose
1	10	10	5187-5206	5267-5286	0.82	0.66	0	0
	10	10						
2	10	10	5207-5226	5287-5306	0.41	0.33	10	12.5
	10	10						
3	10	10	5227-5246	5307-5326	0.82	0.66	10	12.5
	10	10						
4	10	10	5247-5266	5327-5346	0.66	0.66	12.5	12.5
	10	10						

<sup>a</sup>Dose levels in terms of salt were as follows: Group 1, 0 mg/animal/month; Group 2, 4.113 mg/animal/month; and Groups 3 and 4, 8.226 mg/animal/month.

Group number	No. of animals		Formulation	Dose Level (mg/animal/month)	Dose concentration (mg/mL)		Necropsy
	Males	Females			1 <sup>st</sup> dose	2 <sup>nd</sup> and 3 <sup>rd</sup> doses	
1	10	10	Control article	0	0	0	W 13
	10	10					W 34
2	10	10	Formulation B low	3	10	12.5	W 13
	10	10					W 34
3	10	10	Formulation B high	6	10	12.5	W 13
	10	10					W 34
4	10	10	Formulation A high	6	12.5	12.5	W 13
	10	10					W 34

W: week  
(W34 – Recovery Week 21)

### Formulation A

SOM230C LAR microparticle filled in vial MPVI: 50/50 polymer mixture (also identified as SOM230 250 mg/g MR MICRO PARTICLES PARENTERAL, SOM230 LAR MPPA 250 MG/G.002)

Lot no./batch no.:

Y024 0204

#### Formulation B

SOM230 10 mg MR microparticles in vial 40 mg (also identified as SOM230 LAR MPVI 10 mg 22GLW 40 MG.007)

Lot no./batch no.:

U019 0706

#### Findings:

- 4 females were found dead (1 Group 2 and 2 Group 3 females on Day 86 – blood collection procedures, 1 Group 3 recovery female on Day 214 – lung/ovary inflammation).

#### Necropsy findings – found dead animals

Sex	Finding	Group 2	Group 3
	Injection site – discoloration	--	2/3
Females	Liver – discoloration	1/1	--
	Ovary – enlarged	--	1/3
Group 2 (SOM230 B, 3 mg/animal/month)		Group 3 (SOM230 B, 6 mg/animal/month)	

- Slight erythema was observed in both sexes across all treated groups following each monthly dose. A higher incidence was observed in 6 mg/animal/month-treated animals. Edema and erythema were also noted on a few occasions.
- Decreases in body weight were seen during the 1<sup>st</sup> week and decreases in body weight gain were noted throughout the dosing period in a dose-dependent manner. The reduced body weight gains resulted in absolute body weight differences up to 35.8%. Correlating decreases up to 23.8% in mean food consumption were seen. After 21 week recovery period, reduced weight gains and food consumption were still evident but to a much lesser extent. Formulation B treated animals had less affected than formulation A treated animals.

#### Statistically significant differences in body weight/body weight changes

Sex	Parameter	Group 2 (SOM230 B, 3 mg/animal/month)	Group 3 (SOM230 B, 6 mg/animal/month)	Group 4 (SOM230 A, 6 mg/animal/month)
Male	Body weight	Days 8-231 ↓	Days 8-231 ↓	Days 8-231 ↓
	Body weight changes	Days 1-84 ↓	Days 1-84 ↓	Days 1-78 ↓
		Days 92-106 ↓	Days 92-99 ↓	Days 92-106 ↓
		Days 120-127 ↑	Days 141-148 ↑	Days 120-127 ↑
		Days 134-148 ↑	Days 155-162 ↑	Days 134-218 ↑
		Days 155-162 ↑	Days 169-190 ↑	
		Days 169-211 ↑	Days 204-211 ↑	
Days 218-225 ↑	Days 218-225 ↑			
Female	Body weight	Days 8-204 ↓	Days 8-231 ↓	Days 8-231 ↓
	Body weight changes	Days 1-43 ↓	Days 1-22 ↓	Days 1-22 ↓
		Days 57-64 ↓	Days 29-43 ↓	Days 29-43 ↓
		Days 113-120 ↑	Days 57-71 ↓	Days 57-71 ↓
		Days 141-148 ↑		Days 204-211 ↑

#### Statistically significant differences in mean food consumption

Sex	Group 2 (SOM230 B, 3 mg/animal/month)	Group 3 (SOM230 B, 6 mg/animal/month)	Group 4 (SOM230 A, 6 mg/animal/month)
Male	Days 15-211 ↓	Days 15-50 ↓	Days 15-162 ↓
	Days 218-231 ↓	Days 50-211 ↓	
		Days 218-225 ↓	
Female	Days 22-134 ↓	Days 1-8 ↓ Days 15-141 ↓	Days 43-141 ↓

- There were changes in hematological parameters (i.e. decreases in platelets and fibrinogen and APTT prolongation) in treated animals at termination (Days 85/86). Changes were greater in Formulation B treated animals and recovery was evident on Day 232.

#### Test article-related differences in hematology and coagulation parameters

Sex	Day	Parameter	Group	Statistically significant value	Concurrent control value	Normalized historical control range
Males	85/86	Platelets	Group 2 ↓	752	893	428.0 – 1202.0
			Group 4 ↓	768		
		Activated PTT	Group 2 ↑	28.1	18.0	12.60 – 24.20
			Group 3 ↑	31.3		
			Group 4 ↑	27.6		
		Prothrombin time	Group 3 ↓	14.4	15.2	14.60 – 15.90
			Group 4 ↓	14.2		
		Fibrinogen	Group 2 ↓	170	258	N/A
			Group 3 ↓	172		
			Group 4 ↓	176		
Females	85/86	Platelets	Group 2 ↓	794	959	808.0 – 1361.0
			Group 3 ↓	687		
			Group 4 ↓	820		
		Activated PTT	Group 2 ↑	23.7	15.6	11.70 – 20.00
			Group 3 ↑	23.4		
			Group 4 ↑	22.5		
		Prothrombin time	Group 3 ↓	14.4	15.5	14.40 – 16.50
		Fibrinogen	Group 4 ↓	145	175	N/A
Group 2 (SOM230 B, 3 mg/animal/month)			Group 3 (SOM230 B, 6 mg/animal/month)			
Group 4 (SOM230 A, 6 mg/animal/month)						

- There were changes in clinical chemistry parameter (i.e. differences in mean total bilirubin, mean total protein, albumin, globulin, A/G ratio, calcium, and phosphorus) in treated animals at termination. Changes were greater in Formulation B treated animals and partial to full recovery was seen on Day 232.

**Test article-related differences in mean clinical chemistry data - males**

Sex	Day	Parameter	Group	Statistically significant value	Concurrent control value	Normalized historical control range
Males	85/86	Total bilirubin	Group 3 ↑	0.70	0.48	0.415 – 0.716
			Group 4 ↑	0.66		
		Total protein	Group 2 ↓	5.20	5.82	5.778 – 6.643
			Group 3 ↓	5.25		
		Globulin	Group 4 ↓	5.20	2.70	2.566 – 3.454
			Group 2 ↓	2.17		
			Group 3 ↓	2.18		
		A/G ratio	Group 4 ↓	2.14	1.16	0.892 – 1.331
			Group 2 ↑	1.40		
			Group 3 ↑	1.42		
		Calcium	Group 4 ↑	1.43	10.16	9.834 – 11.012
			Group 2 ↓	9.63		
	Group 3 ↓		9.90			
	Phosphorus	Group 4 ↓	9.79	5.8	5.44 – 8.03	
		Group 3 ↑	6.4			
	232	Total protein	Group 4 ↑	6.6	5.63	5.778 – 66.43
			Group 2 ↑	6.07		
			Group 3 ↑	5.96		
		Albumin	Group 4 ↑	5.96	2.93	2.897 – 3.540
			Group 2 ↑	3.26		
			Group 3 ↑	3.25		
		A/G ratio	Group 4 ↑	3.22	1.09	0.892 – 1.311
		A/G ratio	Group 3 ↑	1.20		
		Calcium	Group 4 ↑	1.18	10.09	9.834 – 11.012
Group 3 ↑			10.63			
Phosphorus		Group 4 ↑	10.52	4.6	5.44 – 8.03	
		Group 2 ↑	6.0			
	Group 3 ↑	7.4				
		Group 4 ↑	7.3			
Group 2 (SOM230 B, 3 mg/animal/month)			Group 3 (SOM230 B, 6 mg/animal/month)			
Group 4 (SOM230 A, 6 mg/animal/month)						

**Test article-related differences in mean clinical chemistry data - females**

Sex	Day	Parameter	Group	Statistically significant value	Concurrent control value	Normalized historical control range
Females	85/86	Total bilirubin	Group 2 ↑	0.81	0.53	0.432 – 0.771
			Group 3 ↑	0.75		
			Group 4 ↑	0.68		
		Total protein	Group 2 ↓	5.22	6.09	5.681 – 6.944
			Group 3 ↓	5.00		
			Group 4 ↓	5.11		
		Albumin	Group 2 ↓	3.01	3.35	2.862 – 3.564
			Group 3 ↓	2.95		
			Group 4 ↓	2.99		
		Globulin	Group 2 ↓	2.22	2.74	2.407 – 3.515
			Group 3 ↓	2.09		
			Group 4 ↓	2.12		
	A/G ratio	Group 2 ↑	1.37	1.22	0.904 – 1.434	
		Group 3 ↑	1.42			
		Group 4 ↑	1.43			
	Calcium	Group 2 ↓	9.80	10.21	9.569 – 10.813	
		Group 3 ↓	9.66			
		Group 4 ↓	9.66			
	Phosphorus	Group 2 ↑	6.3	5.3	3.69 – 7.33	
		Group 3 ↑	7.6			
		Group 4 ↑	6.6			
	232	Globulin	Group 2 ↑	3.00	2.75	2.407 – 3.515
		Calcium	Group 2 ↑	10.65	9.90	9.569 – 10.813
			Group 3 ↑	10.80		
Group 4 ↑			10.76			
Phosphorus		Group 2 ↑	6.4	3.8	3.69 – 7.33	
		Group 3 ↑	6.7			
	Group 4 ↑	6.5				
Group 2 (SOM230 B, 3 mg/animal/month)			Group 3 (SOM230 B, 6 mg/animal/month)			
Group 4 (SOM230 A, 6 mg/animal/month)						

- There were also changes in urine parameters (i.e. decreases in urine volume) at termination. No change was noted at recovery termination.
- Decreased organ weights were observed in adrenal gland, pituitary gland, and thyroid gland at termination. Effects were greater in formulation B treated animals.

#### Statistically significant differences in organ weights

Sex	Day	Organ	Absolute weight	Relative to body weight	Relative to brain weight	
Males	85/86	Adrenals	Group 2, 3, 4 ↓	Group 2, 3, 4 ↑	Group 3, 4 ↓	
		Pituitary	Group 2, 3, 4 ↓	Group 2, 3 ↓	Group 2, 3 ↓	
		Thyroid glands	Group 2, 3, 4 ↓	--	Group 2, 3 ↓	
	232	Adrenals	Group 2, 3, 4 ↓	--	Group 2 ↓	
		Pituitary	Group 2, 3 ↓	--	Group 2, 3 ↓	
		Thyroid glands	Group 3 ↓	--	--	
Females	85/86	Adrenals	Group 2, 3, 4 ↓	Group 2, 3, 4 ↓	Group 2, 3, 4 ↓	
		Pituitary	Group 2, 3, 4 ↓	--	Group 2, 3, 4 ↓	
		Thyroid glands	Group 3 ↓	--	--	
	232	Thyroid glands	Group 3, 4 ↓	--	Group 3, 4 ↓	
		Group 2 (SOM230 B, 3 mg/animal/month)		Group 3 (SOM230 B, 6 mg/animal/month)		
		Group 4 (SOM230 A, 6 mg/animal/month)				

- Microscopic findings consisted of SOM230-related histopathology findings in injection sites (i.e. inflammation and accumulation), pituitary (i.e. atrophy), and thyroid glands (i.e. atrophy), bones (i.e. atrophy of the humerus and sternum) and adrenal gland (i.e. atrophy, vacuolation). These findings were consistent with a primary inhibitory effect on the pituitary gland, which lead to a secondary disruption of endocrinological stimulation n the adrenal gland, bone, and thyroid gland. Injection findings were due to injection procedures. All findings were resolved following the 21 week recovery period except at the injection site.

#### Necropsy findings - Day 85/86

Sex	Finding	Group 1	Group 2	Group 3	Group 4
Males	Injection site – discoloration	--	6/10	8/10	9/10
Females	Injection site – discoloration	--	7/10	10/10	10/10
Group 2 (SOM230 B, 3 mg/animal/month)		Group 3 (SOM230 B, 6 mg/animal/month)			
Group 4 (SOM230 A, 6 mg/animal/month)					

- TK data showed that all treated animals were exposed to SOM230.

Table 14 Study No r0770082: 3 month rat tox study with LAR formulation – TK data

#### Mean toxicokinetic parameters of SOM230 in rat plasma

	Group 2		Group 3		Group 4	
	Males	Females	Males	Females	Males	Females
<b>1<sup>st</sup> dose</b>						
$t_{max}$	21.0	27.0	27.0	27.0	27.0	21.0
$C_{max}$	143	166	253	1170	46.5	227
$C_{max}/dose$	47.7	55.3	42.2	195	7.75	37.8
$AUC_{(0.083-27d)}$	1230	1100	2070	5300	408	1750
$AUC_{(0.083-27d)}/Dose$	411	368	345	884	68.0	291
<b>2<sup>nd</sup> dose</b>						
$t_{max}$	21.0	21.0	21.0	27.0	27.0	27.0
$C_{max}$	1120	1920	1960	4730	2020	1350
$C_{max}/dose$	373	640	327	788	337	225
$AUC_{(0.083-27d)}$	13700	18700	29700	45200	18900	17600
$AUC_{(0.083-27d)}/Dose$	4580	6220	4940	7540	3150	2930
<b>3<sup>rd</sup> dose</b>						
$t_{max}$	21.0	27.0	27.0	21.0	14.0	27.0
$C_{max}$	3910	2550	4000	3680	2090	3980
$C_{max}/dose$	1300	850	667	613	348	663
$AUC_{(0.083-27d)}$	49400	36200	58200	59500	34000	46900
$AUC_{(0.083-27d)}/Dose$	16500	12100	9710	9910	5670	7810
$AUC_{(0.083-175d)}$	256000	232000	294000	282000	148000	225000
$AUC_{(0.083-175d)}/Dose$	85200	77300	49000	47000	24700	37500
$T_{1/2}$ (21-175d)	23.3	20.6	30.1	23.6	31.0	22.1
R-squared	0.960	0.994	0.986	0.999	0.993	0.992
Units: $t_{max}$ (days). $C_{max}$ (ng/mL). $C_{max}/dose$ ([ng/mL]/mg). AUC (days*ng/mL). AUC/dose ([days*ng/mL]/mg). $t_{1/2}$ (days).						

- The immune response inhibited by SOM230 was seen in 21 animals of Group 2, 30 animals of Group 3, and 28 animals of Group 4. Immunogenicity interfered with the TK assay. Anti-SOM230 antibodies capturing the biotinylated SOM230 would lead to an artificially high SOM230 level.
- NOAEL was not determined in this study.

## 7 Genetic Toxicology

Genotoxicity studies (reviewed under NDA 200677) showed that SOM230 was not mutagenic (Ames assay) or clastogenic (in vitro chromosome aberration assay and bone marrow micronuclei rat study).

### **pcs-r412410-01: micronucleus assays**

The sponsor submitted the amendment 01 for this study which has been reviewed under NDA 200677 (approved for Signifo®). The sponsor amended this missing information on the vehicle. This did not affect the integrity of this study report.

## 8 Carcinogenicity

Carcinogenicity studies were reviewed under NDA 200677. These studies were done in transgenic mice and rats and showed that SOM230 was not carcinogenic.

- In 26 week tg-mouse study, SOM230 was given sc at daily doses of 0, 0.5, 1, and 2.5 mg/kg to tg-mice or 0, 2.5 mg/kg to wt-mice. MNU by a single ip injection was used as a positive control. There was no neoplastic finding. However, non-neoplastic findings were noted in pancreas (increased zymogene granules) and at injection site. Decreased body weight and organ weights (heart, kidney, and liver) were noted.
- In 2 yr rat study, SOM230 was given sc at daily doses of 0, 0.01, 0.05, and 0.3 mg/kg/day to rats. MNU by a single ip injection was used as a positive control. There was no neoplastic finding. However, non-neoplastic findings were noted at injection site (panniculus muscle degeneration). Decreased body weights were noted.

### **pcr0670694-802088-02: 2-year carci rat study**

The sponsor submitted amendement 02 for this study which has been reviewed under NDA200677 (approved for Signifor). The sponsor included the summary of hematology and clinical chemistry data tables for health screen animals. However, this change did not alter the interpretation or conclusion as individual hematology and clinical chemistry results for health screen animals were included and discussed in the original report. Such omission was not considered to have an effect on the integrity of the study,

## 9 Reproductive and Developmental Toxicology

All reproductive/developmental toxicity studies (reviewed under NDA 200677) were conducted in rats and/or rabbits. Most findings were attributed to an exaggerated effect of pasireotide (decreased maternal fertility and fetal adverse effects as a consequence of maternal toxicity). These studies showed that SOM230 was not teratogenic. In addition, as a part of PK studies, approx. 28% of SOM230 can be transferred from plasma into milk in rats (milk to plasma AUC ratio - 0.28).

In **Seg I** rat study (0, 0.1, 1, 10 mg/kg/day, 2 week before mating till GD 20), reproductive effects were seen in females only (prolonged estrus cycles, decreased numbers of corpora lutea, implantation sites, and/or viable fetuses).

In **Seg II** rat study (0, 1, 5, 10 mg/kg/day, GDs 6-17), maternal toxicity (i.e. decreased body weight, swollen paws, purple-colored tails) was seen at ~ 1 mg/kg/day. Mortality was noted in one dam at 10 mg/kg/day (HD exceeds MTD). Effects of F1 generation were noted (increased early/total resportions, decreased fetal weights at 10 mg/kg/day,

increased pre- and post-implantation loss, increased incidence of malrotated limbs, supernumerary ribs, etc), attributable to pronounced maternal toxicity.

- The maternal NOAEL was *not* determined due to decreased body weight/food consumption and swollen paws seen at all doses, decreased/soft stool observed at  $\geq 5$  mg/kg/day, and increased early resorptions seen at 10 mg/kg/day as well as mortality in addition to increased preimplantation loss observed at 1 mg/kg/day. One dam given 1 mg/kg/day had a complete litter resorption at c-sectioning.
- The fetal NOAEL was determined at 5 mg/kg/day based on malformations noted at 10 mg/kg/day.

In **Seg II** rabbit study (0, 0.05, 1, 5 mg/kg/day, GDs 7-20), maternal toxicity (i.e. decreased stool at 1 mg/kg/day and decreased body weight at 5 mg/kg/day) was observed. Mortality was seen in 2 pregnant dams and 16 deaths were seen at 5 mg/kg/day (HD exceeds MTD). Effects of F1 generation were noted (increased resorptions and post-implantation losses, decreases in the numbers of viable fetuses at  $\geq 1.0$  mg/kg/day), attributable to pronounced maternal toxicity. There was also increased incidence of skeletal malformation (fused, misaligned, absent, misshapened ribs and etc at  $\geq 0.05$  mg/kg/day).

- The maternal NOAEL was determined at 0.05 mg/kg/day based on decreased body weight/food consumption, decreased/soft stool, and increased early resorptions at  $\geq 1.0$  mg/kg/day.
- The fetal NOAEL was determined at  $< 0.05$  mg/kg/day based on various skeletal malformations noted at the 0.05 mg/kg/day and visceral malformations noted at  $\geq 1.0$  mg/kg/day.

In **Seg III** rat study (0, 2, 5, 10 mg/kg/day, GDs 15 – LDs 21), maternal toxicity was seen (decreased body weights) and lower F1 body weight was seen at all doses. There was a slight retardation in development (increased mean day of pinna unfolding), attributed to lower pup weights.

## 10 Special Toxicology Studies

### **Memo-27523: cell counts for rat MLN**

The sponsor submitted an memo with regards to manual and automatic viability cell count for rat mesenteric lymph node (MLN) cell suspensions. For each cell count, the results were reported as the viable cell concentration (cells/ml), total cell concentration (cells/ml) and viability percentage (%). The manual cell counts were done by using an hemacytometer as per SOP CAC-033 (Trypan blue dye exclusion method) whereas the automatic cell counts were done by using the Guava PCA cytometer.

The sponsor showed that the automatic cell count method using the Guava PCA cytometer was determined as suitable for use with rat MLN cell suspension.

**Table 15 Immunotox memo-27523: cell counts for rat MLN cell suspensions**

Summary of manual cell counts (using an hemacytometer) and automatic cell counts (using the Guava® PCA™ cytometer) for rat mesenteric lymph node (MLN) cell suspension.

	Results		Assay precision CV%		Difference percentage with manual cell count method results
	Manual cell count	Automatic cell count	Manual cell count	Automatic cell count	
<b>Intra assay</b>					
Mean viable cell concentration	1.83 x 10 <sup>7</sup> cells/mL	1.42 x 10 <sup>7</sup> cells/mL	13.2 %	3.0 %	22.4 %
Mean total cell concentration	1.91 x 10 <sup>7</sup> cell/mL	1.58 x 10 <sup>7</sup> cells/mL	14.6 %	4.0 %	17.3 %
Mean viability percentage	95.2 %	90.2 %	2.3 %	1.1 %	5.3 %
<b>Inter assay</b>					
Mean viable cell concentration	1.55 x 10 <sup>7</sup> cell/mL	1.49 x 10 <sup>7</sup> cells/mL	10.0 %	4.2 %	3.9 %
Mean total cell concentration	1.63 x 10 <sup>7</sup> cell/mL	1.66 x 10 <sup>7</sup> cells/mL	10.6 %	3.8 %	-1.8 %
Mean viability percentage	95.3 %	89.8 %	1.2 %	0.5 %	5.8 %

***r0320064: local tolerance rabbit IM study (reviewed under NDA 200677)***

Study title: Intramuscular Toxicokinetic and Local Tolerance Study in Rabbits (by Inveresk study no. 506331)

Study design: A single dose of SOM230 (batch no Y160 0703; free base; 28, 34, or 40 mg in 2 either 1.0 ml or 0.7 ml) was given to rabbits via IM administration (right and left hind limbs). One animal treated with placebo and the other treated with SOM230 were each sacrificed on Days 2, 5, 10, 22, 33, 46, 60, 75, or 92. The endpoints included clinical and injection site observations, body weight, gross pathology, histopathology (injection stie), and TK analysis.

Group	Treatment	Dose (mg freebase/animal)	Dose Volume (mL)	Dose Concentration (mg/mL)	Animal
1	SOM230 Placebo	0	2 x 1.0	0	1-9
2	SOM230	40	2 x 1.0	20	10-18

Group	Treatment	Animal	Dose Volume Received (mL)		Total Dose Received (mg freebase/animal)
			Right Hind Limb (Injection Site 1)	Left Hind Limb (Injection Site 2)	
1	SOM230 Placebo	1,3,4,6-8	1.0	1.0	0
		2	0.7	0.7	0
		5	1.0	0.7	0
		9	0.7	1.0	0
2	SOM230	10,12-17	1.0	1.0	40
		11	0.7	0.7	28
		18	0.7	1.0	34

**Findings:**

- No adverse clinical signs were noted during the study. No erythema or oedema was seen at the injection site.
- Body weight loss was observed in all SOM230-treated animals between Days 22-36.
- Plasma exposure to SOM230 was detected at least 60 days with the highest concentration seen on Day 33 (17.36 ng/ml).
- Gross pathology findings included pale or dark foci at the injection sites of most animals.
- Test article deposition was evident at one or both injection sites in 7 out of 9 animals given SOM230 placebo and in all 9 animals given SOM230. This was accompanied by subacute, chronic, or chronic active inflammation. By Days 75 and 92, no histological findings were associated with SOM230 placebo administration. However, minimal inflammation was still observed at the injection sites given SOM230 at Day 92.

**Summary of Histology Findings at Injection Sites**

SOM230 Placebo

Finding	Day of Study/Animal								
	2	5	10	22	33	46	60	75	92
<i>Injection Site 1</i>									
No abnormality detected							7	8	9
Test material deposition with inflammation (intramuscular) Minimal Mild			3	4	5	6			
Test material deposition with inflammation (subcutaneous) Minimal Mild	1	2							
Test material deposition (subcutaneous)									
<i>Injection Site 2</i>									
No abnormality detected			3		5	6		8	9
Test material deposition with inflammation (intramuscular) Minimal Mild	1	2		4			7		
Test material deposition with inflammation (subcutaneous) Minimal Mild									
Test material deposition (subcutaneous) Inflammation (subcutaneous) Minimal	1								
Haemorrhage Minimal Mild									

SOM230

Finding	Day of Study/Animal								
	2	5	10	22	33	46	60	75	92
<i>Injection Site 1</i>									
No abnormality detected		11							
Test material deposition with inflammation (intramuscular)									
Minimal									
Mild	10			13	14	15			
Test material deposition with inflammation (subcutaneous)							16	17	18
Minimal									
Mild									
Test material deposition (subcutaneous)	10		12			15			
<i>Injection Site 2</i>									
No abnormality detected			12			15		17	
Test material deposition with inflammation (intramuscular)									
Minimal									18
Mild	10	11		13	14		16		
Test material deposition with inflammation (subcutaneous)									
Minimal				13					
Mild									
Test material deposition (subcutaneous)		11							
Inflammation (subcutaneous)									
Minimal									
Haemorrhage									
Minimal									
Mild	10								

- This study indicated that single IM administration of SOM230 (in 2 different sites) to rabbits was associated with a minimal or mild reaction surrounding the test item or its placebo, suggesting it was locally tolerable.

**r0320065: local tolerance rat IM study (reviewed under NDA 200677)**

Study title: Intramuscular Toxicokinetic and Local Tolerance Study in Rats (by (b) (4) study no. 506352)

Study design: A single dose of SOM230 (batch no Y160 0703; free base; 5mg in 0.5 ml) was given to rats via IM administration (right hind limbs). One animal treated with placebo and 2 treated with SOM230 were each sacrificed on Days 2, 5, 10, 22, 33, 46, 60, 75, or 92. The endpoints included clinical and injection site observations, body weight, gross pathology, histopathology (injection site), and TK analysis.

Group	Dose (mg freebase/animal)	Dose Volume (mL)	Dose Concentration (mg/mL)	Animal
1	0	0.5	0	1-9
2	5	0.5	10	10-27

Findings:

- No adverse clinical signs were noted during the study. No erythema or oedema was seen at the injection site.
- Body weight loss was observed in 14 of the 18 SOM230-treated animals up to Days 5.
- Plasma exposure to SOM230 was detected at least 92 days with the highest concentration seen on Day 46 (30.28 and 51.52 ng/ml).
- Gross pathology findings included pale or dark foci at the injection sites of most animals.
- At the injection site there were vacuolated foreign materials in 3 out of 9 SOM230-placebo treated animals and pigmented foreign materials in 16 out of 18 SOM230 treated animals. Test item deposition associated with minimal inflammation was still observed at the injection sites given SOM230 at Day 92.

### Summary of Histology Findings at Injection Sites in Muscle

#### SOM230 Placebo

Finding	Day of Study/Animal								
	2	5	10	22	33	46	60	75	92
No abnormality detected							7	8	9
Vacuolated foreign material									
Minimal				4					
Mild			3		5				
Pigmented foreign material									
Minimal									
Mild									
Moderate									
Inflammatory cell infiltration									
Minimal		2							
Mild	1		3			6			
Foreign body reaction									
Minimal				4					
Mild					5				
Moderate									

#### SOM230

Finding	Day of Study/Animal								
	2	5	10	22	33	46	60	75	92
No abnormality detected								25	
Vacuolated foreign material									
Minimal									
Mild									
Pigmented foreign material									
Minimal	10, 11	13	15	16			22		27
Mild			14	17	18	20, 21	23	24	26
Moderate					19				
Inflammatory cell infiltration									
Minimal		12, 13	15	16			22		
Mild	10, 11								
Foreign body reaction									
Minimal			14	17			22		27
Mild					18	20	23	24	26
Moderate					19	21			

- This study indicated that single IM administration of SOM230 to rats was associated was locally tolerable.

**r0470162: local tolerance rat IM study (reviewed under NDA 200677)**

**Study title:** A single dose intramuscular (IM) toxicokinetic and local tolerance study in male rats with recovery using a new LAR formulation

**Study design:** This study evaluated the local IM tolerability and TK profile of SOM230 (batch no Y024 0204) up to 13 weeks after a single IM injection in male rats at 6 mg/animal in 0.5 ml. Animal were sacrificed on Days 2, 33, 60, 75, and 92. The endpoints included clinical and injection site observations, body weight, gross pathology, histopathology (injection site), and TK analysis.

<b>Study design. animal allocation and test article doses</b>				
Group	Animal Numbers (males)	Dose (mg free base/animal)*	Concentration mg/mL*	Necropsy Day/Recovery Day
1	1001-3	6	12	2/1
2	2001-3	6	12	33/32
3	3001-3	6	12	60/59
4	4001-3	6	12	75/74
5	5001-3	6	12	92/91

**Findings:**

- No adverse clinical signs were noted during the study. Clinical signs were limited to the injection site (swelling mostly 1 hr postdose, bruising or redness; recoverable). Very slight erythema or edema was observed at the injection site, with highest incidence of occurrence at the 1 and 24 hr postdose and no finding by 72 hr postdose).

<b>Summary incidence of erythema and edema</b>		
Hours Postdose from Day 1	Erythema (Grade)	Edema (Grade)
1	0/15 (0)	11/15 (1-2)
24	2/15 (1)	9/15 (1-2)
48	0/12 (0)	5/12 (1)
72	0/12 (0)	1/12 (1)
96	0/12 (0)	0/12 (0)
120	0/12 (0)	0/12 (0)

0 = none; 1 = very slight; 2 = slight

- Plasma exposure to SOM230 was detected in all treated animals. The overall mean value for tmax was 33 days, Cmax was 156.7 ng/ml, and AUC0-92d was 8020 ng/ml.

**Individual and mean results and toxicokinetic parameters of SOM230 in rat plasma after i.m. administration of 6 mg/animal LAR**

Time / Rat No.	1001	1002	1003	2001	2002	2003	3001	3002	3003	4001	4002	4003	5001	5002	5003	Mean	SD	CV
Plasma concentration of SOM230 [ng/mL]																		
2	28.0	45.6	30.3	*	*	*	*	*	*	*	*	*	*	*	*	34.6	9.6	27.7
33	*	*	*	79.2	85.9	305.0	*	*	*	*	*	*	*	*	*	156.7	128.5	82.0
60	*	*	*	*	*	*	223.0	60.5	18.6	*	*	*	*	*	*	100.7	108.0	107.2
75	*	*	*	*	*	*	*	*	*	5.7	4.7	134.6	*	*	*	48.3	74.7	154.7
92	*	*	*	*	*	*	*	*	*	*	*	*	1.7	1.1	3.1	2.0	1.0	50.0
t <sub>max</sub>																33	*	*
C <sub>max</sub>																156.7	*	*
AUC(0-92d)																8020	*	*

Mean: n=3

AUC is calculated by linear trapezoidal integration.

Units: t [days]. C [ng/mL]. AUC(0-92days) [days-ng/mL].

Missing C(0) has been replaced for AUC(0-92days) calculation by 0.

SD and CV [%]

\*: not available or applicable.

- The initial inflammation was seen following the injection which elicited granulomatous inflammation over time. Such response was still present at the end of the 13 week post-treatment period.

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: R1

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO. ANIMALS:	3	-	-	-	-	
INJECTION SITE :	3	-	-	-	-	
- Hemorrhage :	2	-	-	-	-	
Grade 1:	2	-	-	-	-	
- Edema :	1	-	-	-	-	
Grade 2:	1	-	-	-	-	
- Inflamm Mixed Cell :	3	-	-	-	-	
Grade 2:	2	-	-	-	-	
Grade 3:	1	-	-	-	-	
- FOREIGN BODY (DEPOT):	3	-	-	-	-	

Group 1, RECOVERY DAY 1, males: SOM230 (5 ML)  
 Group 2, RECOVERY DAY 32, males: SOM230 (5 ML)  
 Group 3, RECOVERY DAY 59, males: SOM230 (5 ML)  
 Group 4, RECOVERY DAY 74, males: SOM230 (5 ML)  
 Group 5, RECOVERY DAY 91, males: SOM230 (5 ML)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: R2

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO. ANIMALS:	-	3	-	-	-	
INJECTION SITE :	-	3	-	-	-	
- Inflamm Granulomatous:	-	3	-	-	-	
Grade 3:	-	2	-	-	-	
Grade 4:	-	1	-	-	-	
- FOREIGN BODY (DEPOT):	-	3	-	-	-	

---

 NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
 STATUS AT NECROPSY: R3
 

---

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO.ANIMALS:	-	-	3	-	-	
<hr/>						
INJECTION SITE :	-	-	3	-	-	
- Inflamm Granulomatous:	-	-	3	-	-	
Grade 2:	-	-	1	-	-	
Grade 3:	-	-	2	-	-	
- Necrosis, Myofiber :	-	-	2	-	-	
Grade 1:	-	-	1	-	-	
Grade 2:	-	-	1	-	-	
- FOREIGN BODY (DEPOT):	-	-	3	-	-	

---

 NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
 STATUS AT NECROPSY: R4
 

---

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO.ANIMALS:	-	-	-	3	-	
<hr/>						
INJECTION SITE :	-	-	-	3	-	
- Inflamm Granulomatous:	-	-	-	3	-	
Grade 2:	-	-	-	1	-	
Grade 3:	-	-	-	2	-	
- FOREIGN BODY (DEPOT):	-	-	-	3	-	

---

 NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
 STATUS AT NECROPSY: R5
 

---

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO.ANIMALS:	-	-	-	-	3	
<hr/>						
INJECTION SITE :	-	-	-	-	3	
- Inflamm Granulomatous:	-	-	-	-	3	
Grade 2:	-	-	-	-	1	
Grade 3:	-	-	-	-	2	
- FOREIGN BODY (DEPOT):	-	-	-	-	3	

---

M = Male animal  
 R1...R9 = Recovery / post-treatment group 1...9

 CODES AND SYMBOLS USED AT FINDING LEVEL:
 

---

GRADE 1 = Minimal / very few / very small  
 GRADE 2 = Slight / few / small  
 GRADE 3 = Moderate / moderate number / moderate size  
 GRADE 4 = Marked / many / large  
 P = Finding present, severity not scored

- This study indicated that single IM administration of SOM230 (6 mg free base/animal) to rats resulted in slight injection site changes including slight to very slight erythema/edema which were no longer apparent after recovery day 3. Histopathological changes were still evident by the end of the recovery and included

inflammation due to injection procedure and a local foreign body reaction which over time became a granulomatous response.

#### Other studies (reviewed under NDA 200677)

Immunogenicity study in rats (0, 0.08, 0.24, 0.8 mg/kg/day for 28 days) demonstrated that SOM230 had effects on body weight and lymphocyte cell populations and on bone marrow (hematopoietic hypocellularity, increased adipose tissue) and lymphoid tissues (hypocellularity in spleen, thymus, lymph nodes). There was no SOM230 related effect on TDAR response (anti-KLH IgM, anti-KLH IgG responses) but there were decreases in the T/B/NK lymphocytes at 0.24 mg/kg/day, suggesting immunosuppression.

Local toxicity studies in rabbits showed that SOM230 was non-irritating to rabbit skin and eyes. In vitro phototoxicity study (0.008-25 mg/ml, UV exposure for 45 min) indicated that SOM230 was not phototoxic.

Impurities studies were also conducted. Eleven impurities were identified and there were within acceptable limits. Several product-related substances were further qualified. A series of impurity genotoxicity studies (tested three lots in 6 in vitro assays and 2 in vivo studies) showed that SOM230 (with impurities including (b) (4) ) was not genotoxic. In vitro studies, Ames assays and chromosome aberration assay in human peripheral lymphocytes were used. In vivo studies, rats were given SOM230 (b) (4) for 4 weeks. These studies showed that there was no difference in exposure or toxicity from those of SOM230 seen in the absence of these impurities.

## 11 Integrated Summary and Safety Evaluation

### SOM230

Pasireotide (SOM230) is a somatostatin analogue. The applicant plans to market in three dose strengths – 20, 40, or 60 mg solutions for once monthly intramuscular injection to treat patients with acromegaly (i.e. excessively secreted growth hormone). Like natural somatostatin and other analogues, it exerts its pharmacological activity via binding to somatostatin receptors (sst). There are 5 known receptors (sst1, sst2, sst3, sst4, and sst5). Currently approved somatostatin analogues (i.e. octreotide) have a high affinity to sst2 but not to remaining sst subtypes. On the other hand, SOM230 has high affinity to 4 of these 5 receptors (sst1, sst2, sst3, and sst5). While octreotide is effective to treat patients with acromegaly, Based on its sst binding profile, pasireotide maybe a better therapeutic intervention than octreotide for acromegaly patients.

The sponsor first submitted NDA 200677 for SOM230 (Signifor®) and it was later approved for Cushing disease in 2012. The sponsor now submitted NDA 203255 for SOM230 LAR formulation to treat acromegaly.

### PD profile of SOM230

One PD study (**Study No rd-2011-00248**) was conducted to evaluate the effect of a single sc injection of SOM230 LAR on the plasma levels of GH, IGF-1, glucose, insulin, and glucagon over a 1 month period in male Lewis rats. Due to different PK profiles of octreotide and pasireotide (octreotide has lag phase of 5-7 days in rats compared to pasireotide), they were also applied by osmotic minipumps to allow comparison of the long-term effects of both compounds on GH secretion.

One single sc injection of pasireotide LAR (8 mg/kg) resulted in pharmacologically active plasma level without 24 hr in rats and reached peak exposure after 28 days. At 8 mg/kg, a strong (40% of control) and long term (49 days) inhibition of plasma IGF-1 was observed which was not enhanced with increasing doses. However, the inhibition of GH and glucose was transient. The small hyperglycemia was seen in Day 1 only, indicating rapid tachyphylaxis. When compared to octreotide, pasireotide caused a stronger inhibition of GH and IGF-1 than octreotide and showed less tachyphylaxis.

Based on these data, by different effects seen with pasireotide and octreotide, one can speculated that the non-desensitizing effects of pasireotide on GH, insulin, and IGF-1 might be mediated primarily via sstr5 whereas the desensitizing effect of pasireotide on glucagon is mediated primarily via sstr2.

### **Safety Pharm profile of SOM230**

Two in vitro studies were conducted. In **Study No pcs-r1270349-01**, SOM230 inhibited hERG trafficking at concentrations in the range of 100 µM or greater. In **Study No pcs-r1270473**, except hNCX1, SOM230 did not inhibit more than 50% in all other channels.

### **PK profile of SOM230**

Few PK drug interaction in vitro studies were conducted. The plasma protein binding was moderate across species including human.

- In **Study No dmpk-r12002480-01**, SOM230 was shown to be an inhibitor of P-gp and BCRP in vitro. The IC<sub>50</sub> were 0.851±0.41 µM (P-gp) and ~ 10 µM (BCRP) with maximal inhibition of 91% (P-gp) and 48% (BCRP). The in vivo inhibition will depend on dose and the actual concentrations achieved at the active site of either transporter.
- In **Study No dmpk-r1200761**, SOM230 was shown not to be an inhibitor of human OCT1 or OCT in vitro.
- In **Study No dmep-r1200835**, SOM230 was shown to be an inhibitor of human OAT1 or OAT3 in vitro.
- Overall, there were some potentials of Pgp mediated and/or transporter mediated drug-drug interaction between pasireotide and co-medications in vivo.

### **TOX Profile of SOM230**

All studies (general tox, genotox, carci, repro/dev tox, local tolerance, immunotox, impurities) were performed in mice, rats, rabbits, and monkeys following sc

administration of pasireotide, and its administration by the oral and iv routes. These studies were all reviewed under NDA 200677.

Repeated dose toxicity studies showed that most of toxicities seen in these studies were due to exaggerated effects of pasireotide. In rats up to 26 weeks of dosing and mice up to 4 weeks of dosing, there were changes in clinical chemistry (i.e. increased ALT)/hematological (i.e. RBCs)/coagulation (i.e. increased PT and APTT) parameters and microscopic findings in pituitary, spleen, bone marrow, bone, ovary, uterine, and injection site. In monkeys up to 39 weeks of dosing, there were microscopic findings in thyroid, pituitary, GI, and injection site. In dogs up to 2 weeks of dosing, there was GI intolerance (i.e. severe vomiting and diarrhea). These target organs identified with SOM230 were also seen in other somatostatin analogs (i.e. octreotide), indicating that there were no significant differences or unexpected toxicities with SOM230 compared to other somatostatin analogs.

Genotoxicity and carcinogenicity studies showed that SOM230 did not have mutagenic or carcinogenic potential. Reproductive/development toxicity studies also indicated that SOM230 was not teratogenic. SOM230 was also not a local irritant and not phototoxicant.

**Under NDA 200677, there were 5 bridging studies to a LAR formulation** - 3 local tolerance studies (in rats: single dose at 5/6 mg/kg and in rabbits: 28, 34, 40 mg/kg) and 2 repeat dose toxicity studies (in rats: 3 monthly at 0, 10, 12.5 mg/kg and 6 monthly at 0, 3.125, 6.25 mg/kg). These studies showed the LAR formulation was tolerable. The findings of LAR pasireotide were similar to those observed after sc administration (i.e. decreased body weight, increased PTT, target organs including adrenals/pituitary/thyroid glands). However, injection site findings (erythema and granulomas) were noted in microparticle placebo- and SOM230-treated animals, attributed to microparticles contained in the LAR formulation.

Table 16 Studies with SOM230 LAR formulation

**Studies with LAR pasireotide formulations**

Species/ strain	Method of administration /design	Duration of dosing	Doses (free base)	Gender and no. per group	Noteworthy findings	GLP compliance	Study number
Rat	Intramuscular/ local tolerance	Single dose	6 mg/kg	15M	Slight injection site changes including slight to very slight erythema/edema which were no longer apparent after recovery day 3.  Histopathological changes were still evident by the end of the recovery and included inflammation due to mechanical trauma and a local foreign body reaction which over time became a granulomatous response.	Yes	[0470162]
Rat	Intramuscular/ local tolerance	Single dose	5 mg/kg	18M SOM230 9M SOM230 placebo	A single intramuscular administration to rats of SOM230 or SOM230 placebo resulted in minimal to moderate inflammatory or foreign body reactions at injection sites. 5 mg/kg well tolerated locally.	Yes	[0320065]
Rat	Intramuscular/ toxicity and local tolerance	3 months (3 monthly doses)	3mg or 6mg /animal	20M/20F	No test article mortality was observed. Target organ effects were observed in all dose groups and consisted of microscopic changes in the adrenal gland, bone (humerus, sternum), injection site, pituitary gland, and thyroid gland. No NOAEL.	Yes	[0770082]

Species/ strain	Method of administration /design	Duration of dosing	Doses (free base)	Gender and no. per group	Noteworthy findings	GLP compliance	Study number
Rat	Intramuscular/ toxicity and local tolerance	6 months (6 monthly doses)	3.125 mg or 6.25 mg/ animal	10M	Excluding the granulomas seen in placebo-control as well as SOM230-treated animals, the NOAEL was 3.125 mg/injection, based on an increase in AST and ALP at 6.25 mg/injection. Slight increases in injection site erythema and injection site granulomas were attributed to the microparticle formulation. In addition, granulomas at injection sites of SOM230-treated animals contained eosinophilic granular materials.  SOM230 was tolerated when administered as monthly injections using a long acting release formulation at doses of 3.125 and 6.25 mg/injection.	Yes	[0470138]
Rabbit	Intramuscular/ local tolerance	Single dose	28 to 40 mg/ animal	9M	Test item deposition was evident at one or both injection sites in 7 out of 9 animals given SOM230 placebo, and in all 9 animals given SOM230. In the animals given SOM230 the deposition was pigmented. In all cases, SOM230 and SOM230 Placebo, test item deposition was accompanied by subacute, chronic or chronic active inflammation, with the chronic inflammation noted around the deposition becoming increasingly predominant over time. By Days 75 and 92 there were no histological findings associated with administration of SOM230 placebo. Test item deposition associated with minimal inflammation was still evident at the injection sites given SOM230 at Day 92.  SOM230 was well tolerated locally.	Yes	[0320064]

NA: not applicable

When compared to other analogues (i.e. octreotide), SOM230 exerts similar exaggerated pharmacological effects of somatostatin. Pasireotide inhibits the secretion of multiple hormones such as GH, IGF-1, ACTH, corticosterone, insulin, and glucagon. Its lack of binding affinity to sst2 makes pasireotide perhaps a better choice in treating acromegaly when compared to octreotide which has a high binding affinity to sst2.

With octreotide, there are injection site tumors (sarcomas or squamous cell carcinoma at 10x human exposure; attributed to irritation/inflammation at the injection site which were not rotated) and uterine adenocarcinomas. Lanreotide also shows a similar profile of injection site fibrous connective tissue tumors in rats and mice. In addition, octreotide LAR Depot does not impair fertility in rats (at 7x human exposure) nor cause harm to fetus in rats and rabbits (at 16x the highest recommended human dose). On the contrary, pasireotide has an effect in female fertility but has no carcinogenic potential in animals. Despite some minor differences, pasireotide has similar toxicological profile with other somatostatin analogues.

All in all, as established under NDA 200677, the vast majority of the findings (reduced cellularity in hematopoietic organs, prolongation of the estrus cycle, decreased eosinophilia of the somatotrophs in pituitary, minimal or slight small follicles in thyroid, proteinaceous material present in the crypts of the mucosa in the cecum and colon of large intestine, and inflammation at injection sites in rats and/or monkeys) were attributed to the pharmacological effect of pasireotide. There were no unexpected findings identified with pasireotide. With additional studies added under NDA 203255, no new concerns were identified with regards to SOM230 LAR formulation for treating acromegaly.

### **Safety Margin**

Based on NOAELs established in the 6 month rat study at 6.25 mg SOM230 LAR via IM administration led to C<sub>max</sub> of 133 ng/ml and AUC<sub>0-284d</sub> of 1062.5 ng.d/ml after the first cycle, leading to exposure multiples of 5.2 and 2.3x fold for C<sub>max</sub> and AUC<sub>0-284d</sub> over the systemic exposure at human dose at 60 mg.

Table 17 Safety Margin for Signifor LAR formulation

**The systemic exposure of pasireotide LAR in rats following i.m. injection and in healthy volunteers following multiple i.m. injection of 60 mg of pasireotide LAR**

	C <sub>max,ss</sub> (ng/mL)	AUC <sub>0-t,ss</sub> (ng*d/mL)	Exposure ratio (animal/human) by C <sub>max</sub>	Exposure ratio (animal/human) by AUC <sub>0-t,ss</sub>
Rats (LAR 2, 3.125 mg) <sup>a</sup>	68.8 <sup>b</sup>	620.8 <sup>b</sup>	2.7	1.3
Rats (LAR 2, 6.25 mg)	133 <sup>b</sup>	1062.5 <sup>b</sup>	5.2	2.3
Human (LAR 2b, 60 mg)	25.8 <sup>c</sup>	463 <sup>c</sup>		

<sup>a</sup>: NOAEL of the study.

<sup>b</sup>: Since the exposure estimate at steady-state may have been compromised by immunogenicity, the systemic exposure after first injection, which would have less impact from anti-drug antibody, was used for safety margin calculation.

<sup>c</sup>: C<sub>max,ss</sub> and AUC<sub>0-t,ss</sub> were simulated from multiple monthly (every 28 days) dosing of pasireotide LAR in healthy volunteers, based on plasma concentration data from a single dose of pasireotide LAR 60 mg formulation 2b.

Source: [Study 0470138], [Summary of Clinical Pharmacology-Table 1-2]

## 12 Appendix/Attachments

n/a

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

/s/  
-----

MIYUN M TSAI-TURTON  
08/01/2014

KAREN L DAVIS BRUNO  
08/01/2014

## Pharmacology/Toxicology Mid-Cycle Deliverables

### Drug Information

This NDA 203255 is for Signifor® LAR (long-acting release) submitted by (b) (4) for acromegaly. Pasireotide (SOM230) is a somatostatin analogue which has high affinity to four of the five receptors (SSTR1, 2, 3, and 5). This long acting release somatostatin comes with three strengths: 20, 40, and 60 mg for injection. This drug product is intended for once a month IM administration.

Pasireotide depot formulation consists of:

- Pasireotide microparticles (i.e. 20, 40, and 60 mg powder) filled in 6 ml vials containing the drug substance pasireotide pamoate
- Solvent (i.e. 2 ml vehicle solution) filled in prefilled syringes in which the microparticles are suspended prior to im injection

#### Declared content of one vial of SOM230 20mg, 40mg and 60mg Powder for suspension for injection

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>					
Poly(D,L-lactide-co-glycolide) (50-60:40-50) <sup>2</sup>	26.290	52.580	78.870	(b) (4)	Novartis
Poly(D,L-lactide-co-glycolide) (50:50) <sup>3</sup>	26.290	52.580	78.870	(b) (4)	Novartis

#### Declared content of the syringe of vehicle, 2ml solution<sup>1</sup>

Ingredient	Composition in mg/ml	Composition in mg/syringe	Function	Reference to standards
Mannitol	45.0	90.0	(b) (4)	Ph. Eur., USP
(b) (4)	7.0	14.0	(b) (4)	Ph. Eur., USP
Carboxymethylcellulose sodium				
(b) (4)	q.s.	q.s.	(b) (4)	Ph. Eur., USP
Poloxamer 188	2.0	4.0	(b) (4)	Ph. Eur., NF
Water for injections / (b) (4)	ad 1.0ml	ad 2.0ml	(b) (4)	Ph. Eur., USP

<sup>1</sup> The (b) (4) ml overfill which permits the delivery of the labeled volume of the vehicle from the syringe is not included in this table.

Signifor® LAR is not approved in any country. However, Signifor® (the pasireotide sc formulation) was approved under NDA 200677 in the US in Dec 2012 for treatment of Cushing's disease. The maximum recommended clinical dose of pasireotide for Cushing's disease is 900 µg/b.i.d. via sc administration.

In this NDA 203255, there are two pivotal Phase III trials.

- Study CSOM230C2305 - Blinded study comparing pasireotide intramuscular use with octreotide intramuscular use in patients with active acromegaly
- Study CSOM230C2402 - Parallel-group study comparing the efficacy and safety of double-blind pasireotide intramuscular use 50 mg and pasireotide intramuscular use 60 mg vs. open-label octreotide intramuscular use of lanreotide ATG in patients with inadequately controlled acromegaly.

Most nonclinical studies were submitted previously for the NDA 200677. New nonclinical data includes hERG trafficking, cardiac ion channels, and combination toxicity study of SOM230 and LCI699 in rats. The majority of the findings (i.e. pituitary gland, reduced cellularity in the hematopoietic organs, prolongation of the estrus cycle in rats, pituitary, thyroid, large intestine, and injection sites in the monkeys) were considered related to the pharmacological effects of pasireotide. In addition, the studies with pasireotide LAR formulation in rats (at doses up to 6 mg/animal) had an estimated systemic exposure ( $AUC_{0-28\text{day}}$ ) at 2.3x of the estimated human exposure for pasireotide LAR at 60 mg/28 days.

**MCR Checklist**

Mid-Cycle Deliverable	Goal Date	Status
<p><b>Filing Review Meeting</b></p> <ul style="list-style-type: none"> <li>Deliverable: Regulatory history, summary of pharmacology and toxicology findings from preliminary review of existing data, adequacy of NDA submission</li> </ul>	45- day of NDA submission	Completed
<p><b>Genetox Study Review (impurities and drug substance)</b></p> <ul style="list-style-type: none"> <li>Deliverable: Draft review, label recommendation/interact with genetox committee</li> </ul>	2-3 months of NDA submission	n/a Relies on studies conducted under NDA 200677
<p><b>Carcinogenicity Study Review</b></p> <ul style="list-style-type: none"> <li>Deliverable: Identify statistical reviewer</li> </ul>	1-month of NDA submission	n/a Relies on studies conducted under ND A200677
<ul style="list-style-type: none"> <li>Deliverable: Schedule ECAC meeting</li> </ul>	1-month of NDA submission	n/a
<ul style="list-style-type: none"> <li>Deliverable: Draft review of Carcinogenicity study with statistical input, <i>Interact with statistician</i></li> </ul>	6-months of NDA submission	n/a
<ul style="list-style-type: none"> <li>Deliverable: ECAC review of carcinogenicity study, incorporation of eCAC comments in the review, Identification of issues from Carcinogenicity study &amp; related post marketing commitments, labeling recommendation</li> </ul>	7- month of NDA submission	n/a
<p><b>ReproTox Study Review</b></p> <ul style="list-style-type: none"> <li>Deliverable: Draft review, Identify issue/s (special studies for post marketing commitments), labeling recommendation, <i>Interact with Reprotox committee</i></li> </ul>	5- month of NDA submission	n/a Relies on studies conducted under NDA 200677 Sponsor is seeking Category C labeling.
<p><b>Impurity/Extractable Qualification</b></p> <ul style="list-style-type: none"> <li>Deliverable: Begin review; <i>interact with CMC</i></li> </ul>	3-month of NDA submission-will depend on CMC also	(b) (4)
<ul style="list-style-type: none"> <li>Deliverable: Identify whether the impurities are qualified, Identify approvability/post marketing commitment issues</li> </ul>	5-6 month of NDA submission-if sponsor has final formulation	The sponsor submitted 6 in vitro studies and 2 in vivo studies re: impurities.
<p><b>Toxicokinetic Study Review</b></p> <ul style="list-style-type: none"> <li>Deliverable: Draft review; <i>Interact with Clinical Pharmacology</i> for dose and ADME, <i>Interact with Medical Reviewer</i></li> </ul>	6- months of NDA submission	n/a

for adverse event comparison and dose multiples		
<p><b>Chronic Toxicity Study Review</b></p> <ul style="list-style-type: none"> <li>• Deliverable: Draft review</li> </ul>	6- months of NDA submission	<p>In progress</p> <p>Relies on studies conducted under NDA 200677.</p> <ul style="list-style-type: none"> <li>▪ Study 0770082 (3 month LAR at 3 and 6 mg)</li> <li>▪ Study 0470138 (6 month LAR at 3.125 and 6 mg)</li> <li>▪ Vehicle used in these 2 studies seemed to be the same as the one proposed to use in the clinic</li> </ul>
<p><b>Pharmacology Study Review</b></p> <ul style="list-style-type: none"> <li>• Deliverable: Draft review, identify PD issues</li> </ul>	6- months of NDA submission	<p>In progress.</p> <p>Few in vitro primary PD, safety pharm, and PK studies are submitted under this NDA 203255.</p>
<p><b>Tox findings compared in animal chronic studies and human phase 3 studies</b></p> <ul style="list-style-type: none"> <li>• Deliverable: Input in ODS database</li> </ul>	8- months of NDA submission	<p>The final recommendation is pending completion of comprehensive review.</p>

## Appendix

### Proposed labeling by the sponsor

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

###### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits (b) (4) showed evidence of (b) (4) harm to the fetus due to pasireotide. (b) (4) SIGNIFOR LAR should be used during pregnancy only if (b) (4)

##### 8.2 Labor and Delivery

No data in humans are available. Studies in rats with pasireotide via subcutaneous route have shown no effects on labor and delivery [see *Nonclinical Toxicology (13)*]. (b) (4)

##### 8.3 Nursing Mothers

It is not known whether pasireotide is excreted in human milk. (b) (4) As a risk to the breast-fed child cannot be excluded, SIGNIFOR LAR should not be used by the nursing mother. (b) (4)

##### 8.4 Pediatric Use

Safety and effectiveness of SIGNIFOR LAR have not been established in pediatric patients. (b) (4)

#### 13 NONCLINICAL TOXICOLOGY

##### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

###### *Carcinogenesis*

A life-time carcinogenicity study was conducted in rats and transgenic mice. Rats were given daily subcutaneous doses of pasireotide at 0.01, 0.05, and 0.3 mg/kg/day for 104 weeks. There were no drug-related tumors in rats at exposures up to (b) (4) higher than the maximum recommended clinical exposure of the pasireotide LAR 60mg dose. Mice were given subcutaneous doses of pasireotide at 0.5, 1.0, and 2.5 mg/kg/day for 26 weeks and did not identify any carcinogenic potential. (b) (4)

###### *Mutagenesis*

Pasireotide was not genotoxic in a battery of in vitro assays (Ames mutation test in *Salmonella* and *E coli*. and mutation test in human peripheral lymphocytes). Pasireotide was not genotoxic in an in vivo rat bone marrow nucleus test. (b) (4)

###### *Impairment of Fertility*

Subcutaneous dosing at 0.1 mg/kg/day before mating and continuing into gestation in rats at exposures less than the human clinical exposure based on body surface area comparisons across species resulted in statistically significant increased implantation loss and decreased viable fetuses, corpora lutea, and implantation sites. Abnormal cycles or acyclicity were observed at 1 mg/kg/day (4) (b) (4) fold higher than the maximum therapeutic exposure of pasireotide LAR based on surface area, comparisons across species). (b) (4)

##### **Key nonclinical studies re: LAR formulation (submitted under NDA 200677)**

Under NDA 200677, most studies were performed in mice, rats, rabbits, and monkeys following sc administration of pasireotide, and its administration by the oral and iv routes. Five bridging studies to a LAR formulation were also conducted.

### Studies with LAR pasireotide formulations

Species/ strain	Method of administration /design	Duration of dosing	Doses (free base)	Gender and no. per group	Noteworthy findings	GLP compliance	Study number
Rat	Intramuscular/ local tolerance	Single dose	6 mg/kg	15M	Slight injection site changes including slight to very slight erythema/edema which were no longer apparent after recovery day 3.  Histopathological changes were still evident by the end of the recovery and included inflammation due to mechanical trauma and a local foreign body reaction which over time became a granulomatous response.	Yes	[0470162]
Rat	Intramuscular/ local tolerance	Single dose	5 mg/kg	18M SOM230 9M SOM230 placebo	A single intramuscular administration to rats of SOM230 or SOM230 placebo resulted in minimal to moderate inflammatory or foreign body reactions at injection sites. 5 mg/kg well tolerated locally.	Yes	[0320065]
Rat	Intramuscular/ toxicity and local tolerance	3 months (3 monthly doses)	3mg or 6mg /animal	20M/20F	No test article mortality was observed. Target organ effects were observed in all dose groups and consisted of microscopic changes in the adrenal gland, bone (humerus, sternum), injection site, pituitary gland, and thyroid gland. No NOAEL.	Yes	[0770082]
Rat	Intramuscular/ local tolerance	6 months (6 monthly doses)	3.125 mg or 6.25 mg/ animal	10M	Excluding the granulomas seen in placebo-control as well as SOM230-treated animals, the NOAEL was 3.125 mg/injection, based on an increase in AST and ALP at 6.25 mg/injection.  Slight increases in injection site erythema and injection site granulomas were attributed to the microparticle formulation. In addition, granulomas at injection sites of SOM230-treated animals contained eosinophilic granular materials.  SOM230 was tolerated when administered as monthly injections using a long acting release formulation at doses of 3.125 and 6.25 mg/injection.	Yes	[0470138]
Rabbit	Intramuscular/ local tolerance	Single dose	28 to 40 mg/ animal	9M	Test item deposition was evident at one or both injection sites in 7 out of 9 animals given SOM230 placebo, and in all 9 animals given SOM230. In the animals given SOM230 the deposition was pigmented. In all cases, SOM230 and SOM230 Placebo, test item deposition was accompanied by subacute, chronic or chronic active inflammation, with the chronic inflammation noted around the deposition becoming increasingly predominant over time. By Days 75 and 92 there were no histological findings associated with administration of SOM230 placebo. Test item deposition associated with minimal inflammation was still evident at the injection sites given SOM230 at Day 92.  SOM230 was well tolerated locally.	Yes	[0320064]

NA: not applicable

### Key clinical studies re: LAR formulation

### Overview of key clinical studies in acromegaly and their status

Study	Number of patients	Details	Status
<b>LAR formulation</b>			
C2305 Phase 3	Core: 358 176 pasireotide LAR 182 octreotide LAR Extension: 74 continued pasireotide LAR 46 continued octreotide LAR Crossover: 81 to pasireotide LAR 38 to octreotide LAR	Phase 3, randomized, blinded, active control, study of pasireotide LAR 40 mg vs. octreotide LAR 20 mg every 28 days in patients with acromegaly who have not been treated medically Core : 12 injections (blinded) Extension *: responders could continue the same blinded treatment (i.e. pasireotide LAR or octreotide LAR), non-responders crossed over to the other treatment. Blind was broken at Month 26; thereafter patients on pasireotide LAR could continue open-label treatment, patients on octreotide LAR were no longer followed.	Core and extension up to Month 26 completed. Extension ongoing for patients on pasireotide LAR
C2402 Phase 3	65 pasireotide LAR 40 mg 65 pasireotide LAR 60 mg 68 active control	Phase 3, randomized, active control study of 2 doses of pasireotide LAR (40 mg and 60 mg, double blind) vs. open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly	Core completed, extension ongoing
C2110 Phase 1 PoC study	Acromegaly: 35	Phase 1, randomized, open-label study of pasireotide LAR (20 mg, 40 mg or 60 mg) im every 28 days for 3 months (3 injections) in patients with acromegaly or carcinoid disease**	Completed
C2110E	Acromegaly :29	Extension to C2110: Long-term safety and tolerability	Ongoing
<b>Subcutaneous formulation</b>			
B2201 Phase 2 PoC study	60	Phase 2, open-label, randomized, crossover study in patients with acromegaly. Patients treated with octreotide 100 µg tid for 28 days, followed by pasireotide 200, 400, or 600 µg bid for 28 days each.	Completed
B2201E	30	Extension to B2201: Long-term safety, efficacy and PK	Ongoing
B2103 Phase 1	12	Phase 1, randomized, double-blind, cross-over study in patients with acromegaly Treatment sequence with a single injection of pasireotide 100 µg, pasireotide 250 µg or octreotide 100 µg	Completed
PoC: Proof of Concept; Responders: Month 12 GH <2.5 µg/L and normal IGF-1 (sex and age adjusted)			
*Describes extension treatment after Protocol Amendment 4 was implemented. Prior to Amendment 4, octreotide was not a treatment option in the extension. For further details see Section 4.			
** data for patients with carcinoid disease are not discussed in this document			
Source: [SCE-Table 1-1], [Tabular Listing of Studies]			

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

/s/  
-----

MIYUN M TSAI-TURTON  
04/04/2014

KAREN L DAVIS BRUNO  
04/04/2014  
comments for sponsor

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:** 203255    **Applicant:** Novartis

**Stamp Date:** 10/15/2013

**Drug Name:** Signifor® LAR    **NDA/BLA Type:** 505b1  
(SOM230)

Pasireotide (SOM230) is a somatostatin analogue which has high affinity to four of the five receptors (SSTR1, 2, 3, and 5). This NDA submission was for the LAR (long-acting release) formulation of pasireotide for the treatment of patients with acromegaly.

Signifor® LAR is not approved in any country. However, the pasireotide sc formulation (Signifor®) was approved in the US in Dec 2012 for treatment of Cushing's disease. In this NDA submission, there are two pivotal Phase III trials – Study CSOM230C2305 (blinded study comparing pasireotide intramuscular use with octreotide intramuscular use in patients with active acromegaly) and CSOM230C2402 (parallel-group study comparing the efficacy and safety of double-blind pasireotide intramuscular use 50 mg and pasireotide intramuscular use 60 mg vs. open-label octreotide intramuscular use of lanreotide ATG in patients with inadequately controlled acromegaly). The maximum recommended clinical dose of pasireotide for Cushing's disease is 900 µg/b.i.d. sc and the clinical dose of pasireotide LAR for acromegaly is up to 60 mg/28 days im.

Most nonclinical studies were submitted previously for the NDA 200677 – pasireotide sc formulation for Cushing's disease. New nonclinical data includes hERG trafficking, cardiac ion channels, and combination toxicity study of SOM230 and LCI699 in rats. The majority of the findings (i.e. pituitary gland, reduced cellularity in the hematopoietic organs, prolongation of the estrus cycle in rats, pituitary, thyroid, large intestine, and injection sites in the monkeys) were considered related to the pharmacological effects of pasireotide.

Exposure margins are based on 26 week rat study (NOAEL = 0.024 mg/kg/day) and 39 week monkey study (NOAEL = 1.6 mg/kg/day). At high doses of 0.24 mg/kg/day in rats and 3.2 mg/kg/day in monkeys, the AUC in rats and monkeys was 2.3x and 100x fold of that human exposure at 900 µg b.i.d. In addition, the studies with pasireotide LAR formulation in rats (at doses up to 6 mg/animal) had an estimated systemic exposure (AUC<sub>0-28day</sub>) at 2.3x of the estimated human exposure for pasireotide LAR at 60 mg/28 days.

### The systemic exposure of pasireotide in animals following multiple s.c. injections and exposure ratios to healthy volunteers following s.c. injections of 900 µg bid of pasireotide

Study	Dose* (mg/kg/day)	Sampling	Exposure		Exposure ratio (animal/human) <sup>a</sup>	
			C <sub>max</sub> ng/mL	AUC <sub>0-24h</sub> ng·h/mL	C <sub>max</sub>	AUC <sub>0-24h</sub>
26-week rat (Study 0210056)	0.24 (o.d.)	Week 22	M: 143 F: 144	M: 748 F: 560	M: 4.9 F: 5.0	M: 2.6 F: 1.9
39-week monkey (Study 0270130)	3.2 (o.d.)	Week 35	M: 4850 F: 5443	M: 27984 F: 29881	M: 167 F: 188	M: 96 F: 103

Abbreviations: \* = expressed as free base; M = male; F = female; o.d. = once daily; b.i.d. = twice daily; s.c. = subcutaneous; <sup>a</sup>: Exposure ratio = animal exposure / human exposure at 900 µg s.c. b.i.d., where the human steady-state exposure (AUC<sub>0-24h</sub>) was calculated to be 291.2 ng·h/mL based on the AUC<sub>12h,25</sub> 145.6 ng·h/mL (mean value from [SOM230 Clinical Study B2113]) multiplied by a factor 2; the C<sub>max,25</sub> at 900 µg b.i.d. was 29.0 ng/mL.

### The systemic exposure of pasireotide LAR in rats following i.m. injection and in healthy volunteers following multiple i.m. injection of 60 mg of pasireotide LAR

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	$C_{max,ss}$ (ng/mL)	$AUC_{0-24, ss}$ (ng*d/mL)	Exposure ratio (animal/human) by $C_{max}$	Exposure ratio (animal/human) by $AUC_{0-24, ss}$
Rats (LAR 2, 3.125 mg) <sup>a</sup>	68.8 <sup>b</sup>	620.8 <sup>b</sup>	2.7	1.3
Rats (LAR 2, 6.25 mg)	133 <sup>b</sup>	1062.5 <sup>b</sup>	5.2	2.3
Human (LAR 2b, 60 mg)	25.8 <sup>c</sup>	463 <sup>c</sup>		

<sup>a</sup>: NOAEL of the study.

<sup>b</sup>: Since the exposure estimate at steady-state may have been compromised by immunogenicity, the systemic exposure after first injection, which would have less impact from anti-drug antibody, was used for safety margin calculation.

<sup>c</sup>:  $C_{max,ss}$  and  $AUC_{0-24,ss}$  were simulated from multiple monthly (every 28 days) dosing of pasireotide LAR in healthy volunteers, based on plasma concentration data from a single dose of pasireotide LAR 60 mg formulation 2b. Source: [Study 0470138], [Summary of Clinical Pharmacology-Table 1-2]

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Under its 505b1 submission, the sponsor submitted: <ul style="list-style-type: none"> <li>▪ Primary (1) – <b>rd-2011-00248</b> (hormone secretion in rats)</li> <li>▪ Safety Pharmacology (2) – <b>pcs-r1270349-01</b> (hERG channels) and <b>pcs-r1270473</b> (ion channels)</li> <li>▪ PK (3) – <b>dmpk-r1200248-01</b> (p-gp and BCRP), <b>dmpk-r1200761</b> (OCT1 and OCT2), and <b>dmpk-r1200835</b> (anion transporters 1 and 3)</li> <li>▪ Tox (3) - genotox (<b>pcs-r0412410</b> – micronucleus test amendment 01), carci (<b>pcs-r0670694</b> – 2 year carci amendment 02), immunotox (<b>memo-27523</b> re: guava cell counts for rat MLN cell suspension)</li> </ul>
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		Intended route: IM injection

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Sections related to pharm/tox were appropriately addressed in the Section 8.1 Pregnancy (category C) and Section 13.1
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Impurities/degradants in drug substance and drug product are quantified and are below specifications.  <div style="background-color: #cccccc; height: 200px; width: 100%;"></div> <span style="float: right;">(b) (4)</span>
11	Has the applicant addressed any abuse potential issues in the submission?			n/a
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			n/a

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?     YES**

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

n/a

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no nonclinical comments for the 74-day letter.

---

Reviewing Pharmacologist

Date

---

Team Leader/Supervisor

Date

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

/s/  
-----

MIYUN M TSAI-TURTON  
01/06/2014

KAREN L DAVIS BRUNO  
01/06/2014