CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200677Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	200677
Submission Date(s)	February 17, 2012
Brand Name	Signifor®
Generic Name	pasireotide
Reviewer	Sang M. Chung, Ph.D.
Pharmacometric Reviewer	Jingyu (Jerry) Yu, Ph.D.
Team Leader	Immo Zadezensky, Ph.D.
Pharmacometric Team Leader	Nitin Mehrotra, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Novartis
Submission Type	Standard
Formulation Strength(s)	0.3, 0.6, and 0.9 mg/1mL
Indication	Cushing's disease who require medical therapeutics intervention
Dosage & Administration	(sponsor's proposal) • (b) (4) • (b) (4) • 0.3 mg twice a day and a maximum of 0.6 mg twice a day for patients with moderate hepatic impairment (Clinical Pharmacology Recommendation) • 0.6 mg by subcutaneous injection twice a day as an initial dose with option of 0.9 mg twice a day • 0.3 mg twice a day and a maximum of 0.6 mg twice a day for patients with moderate hepatic impairment

Table of Contents

1. Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 200677 and finds it acceptable.

The Office of Clinical Pharmacology / Division of Pharmacometrics (OCP/DPM) has reviewed NDA 200677 and recommended a lower starting dose of 0. 6 mg BID with option of 0.9 m BID, sponsor has agreed with this proposed dose by agency.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Background

Pasireotide (SIGNIFOR®, SOM230) is a cyclohexa-peptide somatostatin analog. Somatostatin is known as somatropin release-inhibiting factor. There are 5 known somatostatin receptors (SSRs) and pasireotide binds to four among those, namely sst1, sst2, sst3, and sst5. Through binding to SSTRs, pasireotide inhibits hormone secretion such as adrenocorticotropic hormone (ACTH) and growth hormone. Cushing's disease is caused by an ACTH-secreting pituitary adenoma.Pasireotide is indicated for Cushing's disease patients who require medical therapeutics intervention. Pasireotide was granted for orphan-drug designation. (b) (4) acromegaly and Cusing's disease (IND 68635) with subcutaneous (s.c.) injection and with the LAR intramuscular formulation (b) (4) (b) (4) The sponsor proposed 3 strengths: 0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL for SIGNIFOR as an immediate-release dosage form.

The sponsor submitted the original application in June, 2011, and withdrew it in August, 2011 because of stability problems with pre-filled syringes of the to-be-marketed supply. The sponsor resubmitted the application with ampoule for the to-be-marketed product and the ampoule was used in the pivotal clinical trials.

The primary endpoint for efficacy was cortisol reduction and it was assessed by 24-hour urinary-free cortisol. Pasireotide worsened patient's glucose control and it is one of the safety issues to be considered for dose selection. An Endocrinologic and Metabolic Drugs Advisory Committee for new drug application (NDA) 200677 Signifor (pasireotide) will be held on November 8, 2012 and exposure – response will be one of topics to be discussed at the meeting.

Clinical Pharmacology Data
The following clinical pharmacology data of pasireotide were obtained from 15 trials results; 11 trials in healthy subjects, 1 trial in patients with hepatic impairment and 3 trials in patients with Cushing's disease. Refer Section 2.2.1 of the review for lists of studies.

Absorption
Absolute bioavailability of pasireotide was not evaluated in humans and it was predicted to be low (<5%) from *in vitro* studies with low permeability. Maximum concentrations (Cmax) were reached between 0.25 and 0.5 hour following s.c. injection. Pasireotide exposure measured using the maximum concentration and area under the concentration-time curve (AUC) showed apparent proportionality to doses up to 1.5 mg.

Distribution
Pasireotide plasma protein binding was 88%. Volume of distribution (Vd/F) varied significantly among studies and was generally greater than 100 L. Pasireotide seemed to be a substrate of P-glycoprotein (P-gp) because there was polarized permeability and P-gp inhibitors (i.e., cyclosporine and verapamil) resulted in directional permeability in Caco-2 model. Meanwhile, pasireotide was not a substrate or inhibitor for breast cancer resistance protein (BCRP), organic cation transporter 1 (OCP1), organic-transporting polypeptide (OATP) 1B1, 1B3, or 2B1 according to *in vitro* study results.

Metabolism
Its metabolism was insignificant according to mass balance study results. In addition, *in vitro* study results indicate that pasireotide is not a substrate, inhibitor, or inducer for metabolic isozymes including UGT1A1 particularly at the proposed dosing range.

Elimination
Fecal excretion was the major route of elimination with 48 % total radioactivity recovered in feces compared to 7.6 % in urine over 10 days post dosing. Hepatic impairment increased pasireotide exposure and it indicates that biliary excretion may significantly contribute to pasireotide hepatic clearance. The population analysis indicates that pasireotide clearance (CL/F) in patients with Cushing's disease is lower (3.8 L/h) compared to that of healthy volunteers (6.7 L/h). Accumulation was more than expected according to cross study comparison. Terminal half-life was increased with increasing dose, especially with 600 and 1200 mg. The effective half-life was about 12 hours. Meanwhile, accumulation seems to be less than 2 based on AUC and steady-sate is reached within 3 days following QD dosing.

Intrinsic factors
Upon correction for covariate effect (age, BMI and albumin), AUCinf was increased by 60% and 79%, and Cmax increased by 67% and 69%, respectively, in the moderate and severe hepatic impairment groups relative to the control group with normal hepatic function. We recommend dose adjustment to 0.3 mg BID starting dose and maximum 0.6 mg BID for patients with moderate hepatic impairment. Population analysis was

conducted to assess the impact of other intrinsic factors because there was no devoted clinical pharmacology study for those and the analysis indicates that there is no significant intrinsic factor to suggest a dosing adjustment.

Extrinsic factors
There was no drug interaction potential to or from pasireotide. Meanwhile, *in vivo* drug interaction between pasireotide and a few anti-diabetics (i.e., metformin, nateglinide, vildagliptin and liraglutide) was evaluated and there was no significant interaction between them.

Thorough QT study
Pasireotide increased the double-corrected QTcI by 13.19 ms (90%CI: 11.38; 15.01) and 16.12 ms (90%CI: 14.30; 17.95 ms) following 0.6 mg BID and 1.95 mg BID, respectively.

Exposure-Response
The proposed initial dose of 900 ug BID is not supported by exposure-response (E-R) relationship for efficacy. There is no clear relationship between exposure (i.e., average trough concentration) and probability of response, suggesting no significant additional benefit of 900 µg BID over 600 µg BID In addition, exposure-response analysis was also conducted using mUFC as a continuous variable for efficacy and conclusions regarding the exposure-response relationship for efficacy remain the same. The proposed initial dose of 900 ug BID for patients with normal baseline HbA1C is not supported by exposure-response (E-R) relationship for safety. In patients with normal baseline HbA1C, there is a clear trend toward increasing probability of experiencing ≥1% post-baseline increase of HbA1C with the increasing exposure in the pivotal trial, suggesting that 900 µg BID will result in a higher probability of post-baseline hyperglycemia than 600 µg BID. Therefore, for patients with normal baseline HbA1c, we recommend a lower starting dose of 600 µg BID. Similar exposure-response relationship was identified for patients with pre-diabetic or diabetic status at baseline. Therefore, for such patients, we agree with sponsor's proposed dose of 600 µg BID.

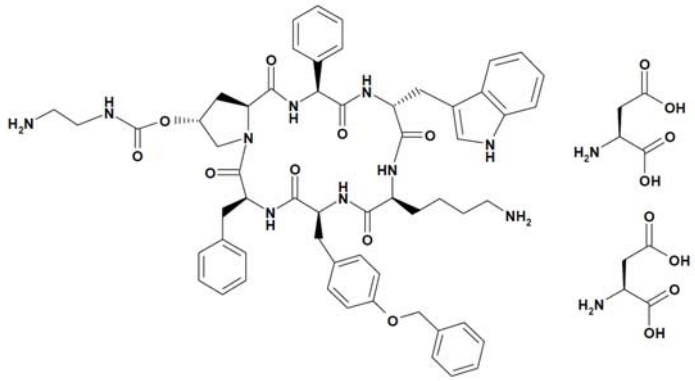
2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Pasireotide (SOM230) is a somatostatin analog. It is a novel cyclohexapeptide containing [redacted] (b) (4) The aqueous ionization constants (pKa) of pasireotide are : pKa1 = 10.2, pKa2 = 9.1. It is freely soluble in water with greater than 100 mg/ml aqueous solubility. The partition coefficient of pasireotide diaspartate can not be measured due to the very low solubility in octanol (< 0.01 mg/ml).

Pasireotide solution for injection contains pasireotide diaspartate as the active drug substance (Figure 1). Pasireotide diaspartate has been formulated as 0.3 mg/1 ml, 0.6 mg/1 ml and 0.9 mg/1 ml solution for injection in ampoules. It is an immediate-release dosage form for subcutaneous administration. The composition of pasireotide solution for injection is summarized in Table 1. The to-be-marketed formulation was used in the pivotal clinical trials.



$C_{58}H_{66}N_{10}O_9.2C_4H_7NO_4$
MW: 1047.206+266.205=1313.41

Figure 1 **Structural formula and relative molecular mass of pasireotide diaspartate**

Table 1 **Components and composition of one ampoule of Pasireotide 0.3 mg, 0.6 mg and 0.9 mg solution for injection**

Ingredient	Amount per ampoule (mg)			Function	Reference to standards
	0.3 mg	0.6 mg	0.9 mg		
Pasireotide diaspartate (SOM230 diaspartate)	0.3762 1	0.7524 2	1.1286 3	Active ingredient	Novartis
				(b) (4)	
Mannitol	49.50	49.50	49.50		Ph. Eur. / USP
Tartaric acid	1.501	1.501	1.501		Ph. Eur. / NF
Sodium hydroxide	ad pH 4.2	ad pH 4.2	ad pH 4.2		Ph. Eur. / NF
Water for injections / Water for injection	ad 1 ml	ad 1 ml	ad 1 ml		Ph. Eur. / USP
					(b) (4)

Note: Each ampoule contains an overfill of 0.1 ml to allow accurate administration of 1 ml from the ampoule.

1 corresponds to 0.3 mg Pasireotide free base (salt/base ratio: 1.254)

2 corresponds to 0.6 mg Pasireotide free base (salt/base ratio: 1.254)

3 corresponds to 0.9 mg Pasireotide free base (salt/base ratio: 1.254)

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Pasireotdie binds to four of the five known SSTs, namely sst1, sst2, sst3, and sst5 (Table 2). Activation of somatostatin receptors results in inhibition of hormone secretion such ACTH and growth hormone. The proposed indication is for the treatment of patients with Cushing's disease who require medical therapeutics intervention.

Cushing's disease is caused by an ACTH-secreting pituitary adenoma most commonly affecting adult females. The elevated ACTH in turn stimulates the adrenal gland to produce cortisol and the development of the clinical signs and symptoms of hypercortisolism. According to the epidemiologic study, about 17,000 patients with Cushing's disease are living in United States.

There are two somatostatin analogs approved for different indications as follows:

- Octreotide acetate, a cyclic octapeptide, for acromegaly, carcinoid tumors, vasoactive intestinal peptide tumors
- Lanreotide acetate, a cyclic octapeptide, for acromegaly

Table 2 Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide and somatuline to the five human sst receptor subtypes (hsst1-5)

Compound	hsst1	hsst2	hsst3	hsst4	hsst5
Somatostatin (SRIF-14)	0.93+0.12	0.15+0.02	0.56+0.17	1.5+0.4	0.29+0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	> 1000	0.16±0.01
Octreotide	280±80	0.38+0.08	7.1±1.4	> 1000	6.3±1.0
Lanreotide	180±80	0.54+0.08	14+9	230±40	17+5

Results are the mean+SEM of IC_{50} values expressed as nmol/l

2.1.3 What are the proposed dosages and routes of administration?

The recommended initial dose is 0.9 mg by subcutaneous (s.c.) injection twice a day. An initial dose of 0.6 mg twice a day may be considered for patients with pre-diabetes or diabetes mellitus. The recommended initial dose for patients with moderate hepatic impairment (Child Pugh B) is 0.3 mg twice a day. A maximum dose of 0.6 mg twice a day is recommended for patients with moderate hepatic impairment. It should not be used in patients with severe hepatic impairment (Child Pugh C).

2.1.4 What is available pharmacology management for Cushing's disease?

There is no pharmacologic therapy approved for the treatment of Cushing's disease. Although ketoconazole (anti-fungal), metyrapone, mitotane (insecticide DDT) and cabergoline (prolactinomas/Parkinson's disease) have been used in patients with Cushing's disease, those have not been prospectively evaluated in multicenter, randomized trials. Mifepristone (Korlym™; 300 mg once daily) was approved for the Cushing's syndrome on February 17, 2012.

2.2 General Clinical Pharmacology

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

Lists of clinical pharmacology trials with PK/PD data are summarized in Table 3.

Table 3 Clinical pharmacology trials

Study	Objectives	Dose	No. of subjects
Healthy volunteers			
[B2101]	Safety, tolerability, PK, PD	1, 2.5, 10, 30, 100, 200, 300, 600, 1200 µg single dose	72
[B2102]	Safety, tolerability, PK, PD	50, 200, 600 µg qd x 14 days	33
[B2106]	Safety, tolerability, PK	900, 1200, 1500 µg single dose 450, 600, 750 µg twice a day x 1 day	17
[B2107]	Safety, tolerability	150, 300, 600, 900, 1200, 1500 µg q.d. x 8 days 150, 300, 450, 600, 750 µg b.i.d, x 8 days	66
[B2108]	Safety, tolerability, PK	450, 900, 1350, 1800, 2025, 2250 µg/day continuous infusion x 7 days	44
[B2112]	ADME, PK, safety	600 µg single dose	4
[B2113]	Cardiac safety (QT/QTc), PK, PD	Part I: 900, 1200, 1500, 1800, 1950, 2100 µg x 5 days Part II: 1950 µg x 5 days	128
[B2124]	Blood glucose metabolism, safety, PK	600 µg x 7 days	90
[B2125]	Cardiac safety (QT/QTc), safety, PK	600 µg x 5 days 1950 µg x 5 days	112
[B2216]	Blood glucose, PD, safety	600, 900, 1200 µg , x 8 days	45*
[C2101]	Safety, tolerability, PK	300 µg single dose	78
Subjects with varying degrees of hepatic impairment			
[B2114]	Hepatic impairment, PK, safety	600 µg single dose	34
Cushing's disease patients			
[B2208] (proof-of-concept)	Efficacy, safety, PK, PD	600 µg x 15 days	39
[B2208E1]	Efficacy, safety, PK, PD	300-900 µg ; dose titration allowed	19
[B2305] (pivotal study)	Efficacy, safety, PK, PD	300, 600, 900, 1200 µg ; dose titration allowed	162

q.d.: once daily; : twice a day; QTc: corrected QT interval
* Study B2216: Although 45 subjects had safety evaluations in all three dose groups, only 38 subjects in the 600µg and 900µg dose groups were included in the blood glucose and PD analyses.
Source: [SCP Table 2-1], [SCP Table 2-2].

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

Hypercortisolism is linked to clinical signs of Cushing's disease and cortisol level change is the primary response endpoint. The primary efficacy endpoint was the proportion of patients who achieved levels of mean urinary-free cortisol (mUFC) ≤ upper limit of normal (ULN) after 6 months of treatment with pasireotide and no dose increase (relative to the randomized dose) prior to Month 6. The evaluations were based on the 24-hour urinary-free cortisol test (24h-UFC).

2.3 Exposure-Response

2.3.1 What are the characteristics of the exposure-response relationship for effectiveness?

The proposed initial dose of 900 ug BID is not supported by exposure-response (E-R) relationship for efficacy. There is no clear relationship between exposure (i.e., average trough concentration) and probability of response, suggesting no significant additional benefit of 900 μg b.i.d. over 600 μg BID In addition, exposure-response analysis was also conducted using mUFC as a continuous variable for efficacy and conclusions regarding the exposure-response relationship for efficacy remain the same. Please refer the detailed pharmacometric review by Dr. Jingyu (Jerry) Yu in the attachment.

2.3.2 What are the characteristics of the exposure-response relationships for safety?

The proposed initial dose of 900 ug BID for patients with normal baseline HbA1cis not supported by exposure-response (E-R) relationship for safety. In patients with normal baseline HbA1C, there is a clear trend toward increasing probability of experiencing ≥1% post-baseline increase of HbA1C with the increasing exposure in the pivotal trial, suggesting that 900 μg BID will result in a higher probability of post-baseline hyperglycemia than 600 μg BID. Therefore, for patients with normal baseline HbA1c, we recommend a lower starting dose of 600 μg BID. Similar exposure-response relationship was identified for patients with pre-diabetic or diabetic status at baseline. Therefore, for such patients, we agree with sponsor's proposed dose of 600 μg BID. Please refer the detailed pharmacometric review by Dr. Jingyu (Jerry) Yu in the attachment.

2.3.3 Does this drug prolong QT/QTc Interval?

QTcI interval was evaluated in a randomized, blinded, crossover study in healthy subjects investigating pasireotide doses of 600 μg BID and 1950 μg BID The maximum mean (95% upper confidence bound) placebo-subtracted QTcI change from baseline was 12.7 (14.7) ms and 16.6 (18.6) ms, respectively. Both pasireotide doses decreased heart rate,

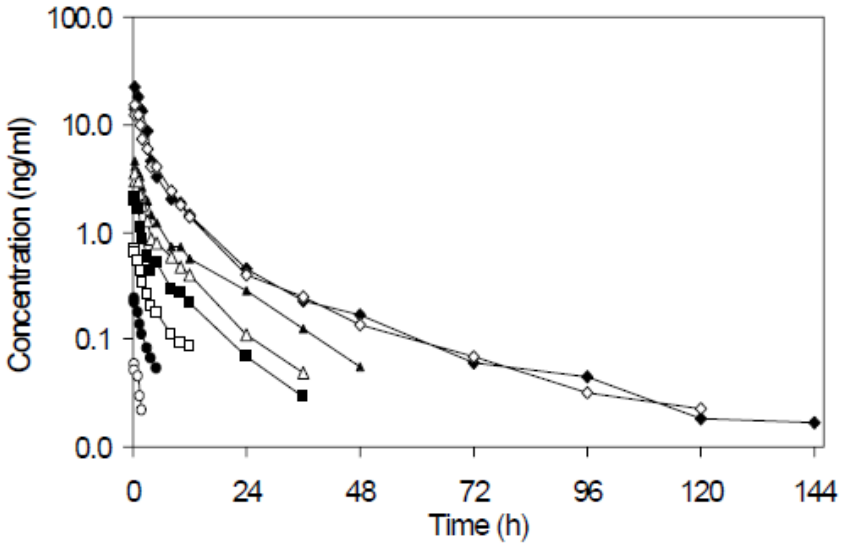
with a maximum mean (95% lower confidence bound) placebo-subtracted change from baseline of -10.9 (-11.9) bpm observed at 1.5 hours for pasireotide 600 µg , and -15.2 (-16.5) bpm at 0.5 hours for pasireotide 1950 µg BID. The supratherapeutic dose (1950 µg b.i.d) produced mean steady-state Cmax values 3.3-fold the mean Cmax for the 600 µg b.i.d dose in the study (Dr. Anshu Marathe's proposed labeling in the QT-IRT consult memo dated on August 29, 2012. Please see the detailed QT-IRT review DARRTS).

2.4 What are the PK characteristics of the drug?

2.4.1 What are the single and multiple dose PK parameters in healthy adults?

- Single dose pharmacokinetics

Single dose pharmacokinetic data of healthy subjects resulted mainly from Study B2101, a single ascending dose study, and B2106, a comparison between one dose and two doses in a day. Mean concentration-time profiles by treatments are shown in Figure 2 and the PK data are summarized in Table 4 (B2101) and 5 (B2106). The data indicate that there is apparent linearity between exposure and dose considering data from both studies (Figure 3). Pasireotide concentration-time profiles showed tri-exponential disposition around the proposed dosing range. Values of tmax were reached within 0.25 and 0.5 hours. Terminal half-life was increased with increasing dose from 2.43 to 65.9 hours following 2.5 and 1200 µg, respectively.



Mean concentration-time profiles of SOM230 at dose levels of 2.5 (○), 10 (●), 30 (□), 100 (■), 200 (Δ), 300 (▲), 600 (◊), and 1200 (♦) µg.

Figure 2 Mean concentration-time profiles

Table 4 Summary of PK parameters (B2101)

Dose (µg)	N	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{inf} (ng.h/mL)	CL/F (L/h)	$t_{1/2}$ (h)
2.5	6	0.25 (0.25-0.50)	0.06 ± 0.01	0.11 ± 0.09	NA*	NA*	2.43 ± 1.29
10	6	0.25 (0.25-0.25)	0.24 ± 0.06	0.66 ± 0.25	NA*	NA*	5.99 ± 3.23
30	6	0.25 (0.25-0.50)	0.72 ± 0.17	2.78 ± 1.02	NA*	NA*	8.62 ± 3.66
100	8	0.50 (0.25-0.50)	2.23 ± 0.45	9.10 ± 2.37	9.59 ± 2.44	11.00 ± 2.67	8.32 ± 1.70
200	4	0.38 (0.25-1.00)	3.73 ± 0.90	16.78 ± 3.65	17.35 ± 3.82	11.90 ± 2.56	9.91 ± 3.75
300	6	0.38 (0.25-1.50)	4.71 ± 1.79	25.95 ± 6.87	27.07 ± 6.98	11.92 ± 3.88	10.74 ± 1.20
600	6	0.50 (0.25-1.00)	15.55 ± 3.25	75.63 ± 11.24	78.60 ± 12.28	7.82 ± 1.39	44.08 ± 46.18
1200	6	0.50 (0.50-1.00)	22.18 ± 5.53	90.35 ± 13.21	93.55 ± 13.60	13.07 ± 2.09	65.92 ± 87.80

* This value was not determined because the number of subjects with available parameters was less than 50% of the total enrolled subjects in this cohort.

Data are median (range) for T_{max} and mean ± standard deviation for all others.

PK parameters for dose level (1 µg) were not calculated due to zero values of concentration profile.

Source: Appendix 4, PT-Tables 2.1 and 2.2

Table 5 Summary of PK parameters (B2106)

Dose (µg)	N	AUC_{inf} (h.ng/mL)	AUC_{last} (h.ng/mL)	$AUC_{(0-24)}$ (h.ng/mL)	C_{max} (ng/mL)	T_{max} (h)	CL/F (L/h)	$T_{1/2}$ (h)
900	9	109.80±28.57	107.49±27.32	89.74±19.13	22.36±4.49	0.50(0.25-1.50)	8.72±2.39	30.21±29.43
1200	8	148.69±41.87	146.14±41.30	121.49±28.15	29.75±6.00	0.50(0.25-1.50)	8.68±2.63	27.65±18.24
1500	8	187.63±51.83	183.13±50.91	152.26±36.86	36.89±5.71	0.50(0.50-1.00)	8.57±2.47	32.44±19.67

Sources: Appendix 4, PT-Table 3.1 and PT-Table 3.2

Values are median (range) for T_{max} and mean ± SD for all other parameters.

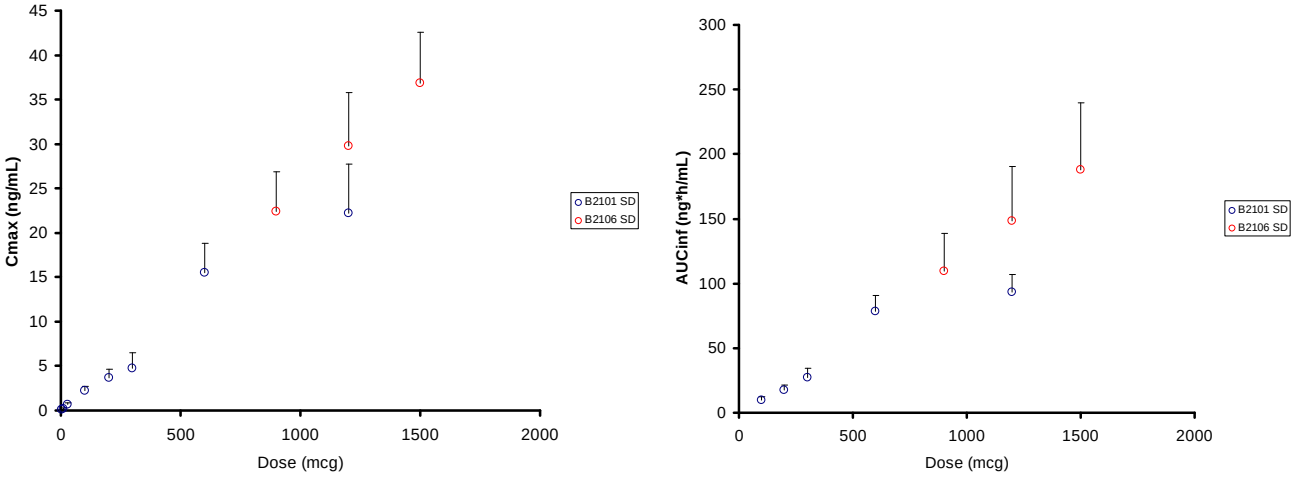


Figure 3 Mean concentration-time profiles: Cmax (left) and AUC (right)

Reviewer's Comments

Injection volumes were significantly different among treatments for B2101: 1) doses of 1 and 2.5 µg were administered as 0.1 and 0.25 mL of the five-fold diluted solution, 2) doses of 10 and 30 µg were administered as 0.2 mL and 0.6 mL of the 0.15 mg per 3 mL dose strength respectively, and 3) doses of 100, 200, 300, 600, and 1200 µg were administered as 0.1 mL, 0.2 mL, 0.3 mL, 0.6 mL, and 1.2 mL of the 3 mg per 3 mL dose

strength, respectively. Injection volumes sometimes affect PK following s.c. injection mainly through altered absorption and variability. The above data indicate injection volumes differ by up to 12 times (0.1 vs. 1.2 mL) among treatments and higher volume was used for a higher dose within each treatment arm in Study B2101. However, there is no further evidence to assess the injection volume effect on pasireotide PK.

The terminal half-lives were significantly different by doses and also for the same dose across studies (65.9 hours vs. 27.7 hours; Table 4 and 5). Sampling design was comparable between the studies and a reason for the difference is not well understood.

Blood sampling scheme was comparable between the studies as up to 144 hours post dose sampling. Comparison between AUC_{0-24} and AUC_{0-last} indicates that the terminal phase with a long half-life contribution to the total AUC may not be significant since AUC_{0-24} is about 83% of $AUC_{0-144hr}$.

- Multiple dose

Multiple dose PK resulted mainly from studies B2102 and B2108. Dosing regimen was once daily for 14 days in B2102 and twice daily dosing for 5 days in B2108. Pharmacokinetic assessment was part of the thorough QT evaluation in B2108.

Multiple dose PK data following 50, 200 and 600 μg QD for 14 days are summarized in Table 6 and 7. Steady-state was reached in a few days with accumulation in the range of 20 to 36% estimated by AUC ratio. PK linearity with dose was assessed using a power model (Log (Cmax or AUC) = a*Log (dose) + b) for both Day 1 and Day 14 data. Although the results did not meet the prespecified statistical goal post for linearity, there was apparent linearity between exposure (Cmax or AUC) and dose (Table 8).

Multiple dose PK data following 600 and 1950 μg for 5 days were comparable to those of QD dosing. The accumulation was 61 and 70 % for 600 and 1950 μg, respectively. Higher accumulation was expected following BID compared to that of QD. (Table 9 and 10).

Reviewer's Comments

It was apparent that AUC_{0-tau} following multiple dose was comparable to AUC_{0-inf} following single dose (Figure 4). Therefore, it seems that there is no non-linearity with time.

The terminal half-life of 600 μg (13.1 hours) estimated following multiple dose on Day 14 was shorter than that of 600 μg single dose (44 hours, Table 4). In general, blood sampling following multiple dose is often limited within the dosing interval and it may impact on pasireotide half-life estimation.

Values of AUC_{0-12} following BID was greater than AUC_{0-24} following QD or AUC_{0-inf} following single dose (Figure 5). With those, CL/F became 7.6 and 5.2 L/h following

single dose and BID dosing, respectively. It indicates that accumulation is more than expected following BID with the time dependent CL/F change.

Table 6 Summary of PK parameters on day 1

Dose (µg)	N	T_{max} (h)	C_{max} (ng/ml)	AUC_{0-24hr} (h.ng/mL)	CL/F (L/h)	V/F (L)	$t_{1/2}$ (h)
50	11	0.30 (0.25 -0.83)	1.3 ± 0.4	5.2 ± 1.0	9.4 ± 1.9	96 ± 19	8.0 ± 3.0
200	9	0.30 (0.25 -1.47)	5.3 ± 1.8	19.8 ± 4.3	9.2 ± 1.8	124 ± 36	9.4 ± 2.1
600	11	0.25 (0.23 -2.00)	13.1 ± 4.5	54.1 ± 7.0	10.4 ± 1.4	114 ± 21	7.2 ± 1.8

Sources: Appendix 4, PT-Table 2.1 and PT-Table 2.2
Data are median (range) for T_{max} and arithmetic mean ± SD for all others.

Table 7 Summary of PK parameters on day 14

Dose (µg)	N	$T_{max,,ss}$ (h)	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	AUC_{tau} (h.ng/mL)	$C_{avg,ss}$ (ng/mL)	CL/F (L/h)	V/F (L)	$t_{1/2}$ (h)	Accumulation Ratio	Fluctuation (%)
50	10	0.35 (0.23, 0.53)	1.39 ± 0.28	0.08 ± 0.06	6.6 ± 1.8	0.27 ± 0.08	8.10 ± 2.14	251 ± 274	10.4 ± 3.4	1.26 ± 0.17	498 ± 129
200	8	0.25 (0.25, 0.50)	5.53 ± 1.22	0.25 ± 0.10	22.6 ± 3.5	0.94 ± 0.15	9.03 ± 1.37	1051 ± 774	9.7 ± 3.4	1.20 ± 0.17	573 ± 158
600	10	0.50 (0.25, 1.05)	16.76 ± 4.96	0.74 ± 0.33	72.9 ± 14.7	3.04 ± 0.61	8.54 ± 1.76	1091 ± 656	13.1 ± 3.7	1.36 ± 0.22	525 ± 119

Sources: Appendix 4, PT-Table 3.1 and PT-Table 3.2
Data are median (range) for $T_{max,ss}$, and arithmetic mean ± SD for all others.

Table 8 Estimate of the slope for the linear regression between log-PK parameter and log-dose

Day	PK parameter (unit)	Slope estimate	Lower 90% confidence limit	Upper 90% confidence limit	Dose proportionality across the whole dose range?
Day 1	AUC_{0-24hr} (hr.ng/mL)	0.95	0.90	1.00	No
	C_{max} (ng/mL)	0.92	0.82	1.02	No
ss	AUC_{tau} (hr*ng/mL)	0.97	0.90	1.04	No
	$C_{max,ss}$ (ng/mL)	0.99	0.91	1.07	Yes

Source: Appendix 6, PT-Table 1

The 90% CI for the slope was to be within the critical region (0.91, 1.09) in order to conclude dose-proportionality for a dose range of 50 µg to 600 µg .

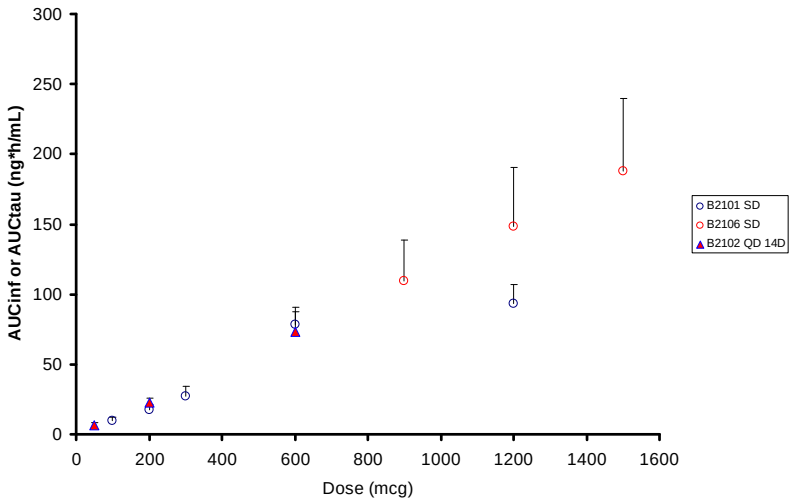


Figure 4 **AUC (SD) vs. dose by treatments: AUCinf after single dose and AUC0-24 after multiple dose**

Table 9 **Summary of pasireotide PK parameters for Day 1**

Treatment	Statistics	$C_{max,d1}$ (ng/mL)	$T_{max,d1}$ (h)	$AUC_{tau,d1}$ (h*ng/mL)
Pasireotide 600 µg bid* (N=105)	n	28	28	27
	Mean (SD)	20.3 (6.11)		77.6 (19.58)
	CV% mean	30.1		25.2
	Geo-mean	19.4		75.4
	CV% geo-mean	30.9		25.3
	Median	19.2	0.52	70.9
	Min; Max	8.9; 37.7	0.5; 1.5	46.4; 120.1
Pasireotide 1950 µg bid* (N=104)	n	27	27	27
	Mean (SD)	55.1 (17.80)		226.2 (58.23)
	CV% mean	32.3		25.7
	Geo-mean	52.5		219.1
	CV% geo-mean	32.4		26.3
	Median	54.6	0.52	217.7
	Min; Max	29.9; 98.4	0.5; 2.0	134.1; 343.9

*On Day 1, PK samples were obtained pre-dose and up to 12 hours after subjects were administered a single dose of pasireotide.

Source: Table 14.2-1.1

Table 10 **Summary of pasireotide PK parameters for Day 5**

Treatment	Statistics	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$ (h)	$AUC_{tau,ss}$ (h*ng/mL)	CL/F_{ss} (L/h)	Vz/F_{ss} (L)	$t_{1/2,ss}$ (h)	AR_{Cmax} (%)	AR_{AUCtau} (%)
Pasireotide 600 µg bid* (N=105)	n	105	105	105	105	105	105	103	28	27
	Mean (SD)	4.0 (1.61)	24.3 (7.20)		115.7 (35.84)	5.6 (1.51)	101.3 (43.75)	12.8 (4.99)	34.2 (25.45)	61.3 (30.10)
	CV% mean	40.4	29.7		31.0	26.9	43.2	38.9	74.3	49.1
	Geo-mean	3.7	23.3		110.9	5.4	93.4	12.0	34.0	52.8
	CV% geo-mean	48.0	29.5		29.1	29.1	42.2	36.4	59.8	67.8
	Median	3.8	23.4	0.52	107.3	5.6	90.2	11.9	34.3	54.6
	Min; Max	0.3; 8.6	12.4; 49.1	0.0; 2.0	59.8; 244.4	2.5; 10.0	25.7; 310.7	6.1; 38.9	-11.3; 109.3	7.7; 112.9
Pasireotide 1950 µg bid* (N=104)	n	103	103	103	103	103	103	101	27	27
	Mean (SD)	14.5 (6.40)	80.6 (25.25)		424.6 (139.77)	5.1 (1.54)	76.7 (29.88)	10.7 (3.34)	35.9 (23.37)	69.9 (28.90)
	CV% mean	44.1	31.3		32.9	30.4	38.9	31.3	65.1	41.3
	Geo-mean	13.2	77.1		404.2	4.8	71.0	10.2	30.6	64.1
	CV% geo-mean	45.2	30.6		32.0	32.0	42.1	30.8	84.5	46.0
	Median	13.4	77.8	0.60	402.4	4.9	70.0	10.2	31.6	65.0
	Min; Max	5.6; 33.6	34.1; 173.0	0.2; 1.5	194.0; 857.8	2.3; 10.1	23.0; 168.6	5.3; 21.7	-2.5; 114.1	25.1; 125.4

*On Day 5, PK samples were obtained pre-dose and up to 24 hours after subjects were administered a single dose of pasireotide.

Source: Table 14.2-1.2

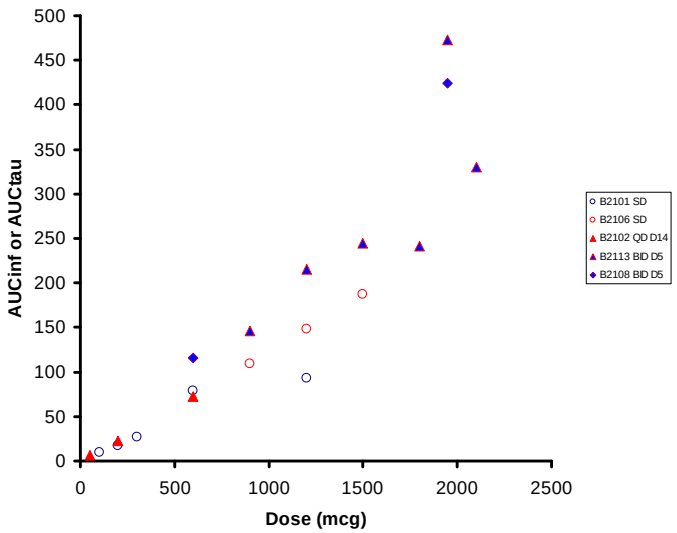


Figure 5 **AUC vs. dose by treatments: AUCinf after single dose, AUC0-24 after QD and AUC0-12 after BID**

Table 11 **PK/PD parameters obtained by nonlinear regression analysis of GH AUC data and the average pasireotide plasma concentration on Day 2 and at steady state (Day 13)**

	Day 2		Day 13		Day 2 and Day 13	
Parameter	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
E_{max} (ng*hr/ml)	12.92	(9.07, 18.40)	9.95	(6.84, 14.47)	11.14	(8.24, 15.07)
EC_{50} (ng/mL)	0.28	(0.18, 0.44)	0.46	(0.15, 1.47)	0.41	(0.27, 0.61)

Source: Appendix 6, PT-Table 2

2.4.2 Was PK comparable between healthy subjects and patients?

Patients' PK was characterized as part of Phase 2 study (B2208). Pasireotide plasma concentration-time profiles are shown in Figure 6 and its PK parameters are summarized in Table 12. Values of tmax and AUC were estimated in a different sampling scheme and thus it may be not appropriate to compare those to data of healthy subjects.

Reviewer's Comment

Cross study comparison indicates that patients' accumulation based on AUC (93% as Day 15/Day 1 following BID) is higher than those of healthy subject (i.e., 61% following 600 μg BID and 36% following 600 μg QD) (Table 12, Table 10 and Table 7).

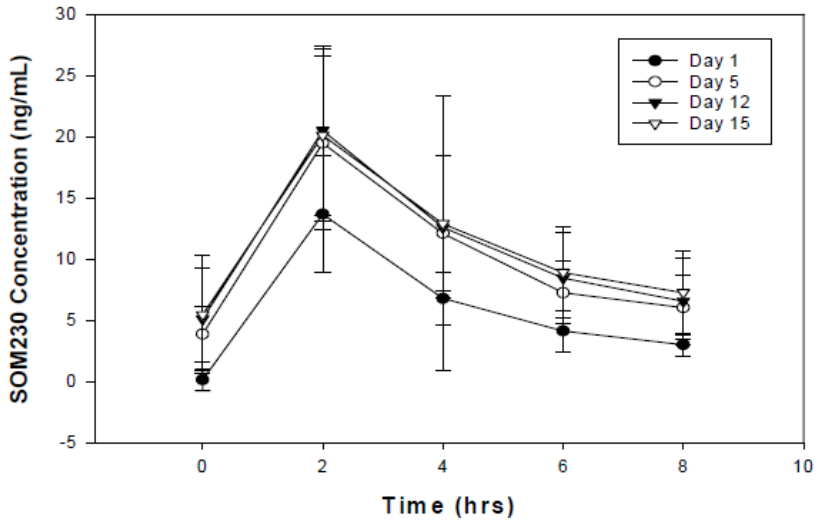


Figure 6 **Mean (SD) pasireotide plasma concentration versus time profiles**

Table 12 **Summary of Patients' PK parameters**

Pasireotide 600 µg s.c. b.i.d.	Day 1 (N=36)	Day 5 (N=38)	Day 12 (N=36)	Day 15 (N=34)
C_{min} (ng/mL)	0	3.87 ± 2.24	4.81 ± 3.43	4.93 ± 2.56
C_{max} (ng/mL)	13.8 ± 4.5	20.8 ± 11.7	20.8± 6.9	21.3 ± 6.9
T_{max} (hr)	2 (2-4)	2 (2-4)	2 (2-2)	2 (02-2)
AUC_{0-8hr} (hr*ng/mL)	51.7 ± 16.0	87.0 ± 34.2	96.4 ± 37.3	99.7 ± 33.8

C_{min}, C_{max} and AUC_{0-8hr} data are represented as mean ± SD. T_{max} data are expressed as median (range); data is presented for all patients having completed 15 days of treatment (N=38)

Source: PT-Table 14.2-1.6

2.4.3 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The majority of dose (48.3%) was recovered in the feces as pasireotide (37.2 ±7.89% of dose) following s.c. injection of [^{14}C]pasireotide (600 µg) in the mass balance study (Table 13, Study B2112). In urine, 7.63% of dose was found as total radioactivity and about 6% of dose was pasireotide. The ratio of plasma pasireotide to plasma radioactivity was close to 1 based on AUC (Table 14). In plasma, the only contributor to the exposure was pasireotide and metabolites were not detected. The metabolites of pasireotide in urine and feces were not structurally identified because poor detection limits. The above data indicate that its metabolism is insignificant.

Table 13 **Excretion of radioactivity in urine and feces for 10 days[a] (% of dose)**

	Subject USA/0501/ 00002	Subject USA/0501/ 00003	Subject USA/0501/ 00005	Subject USA/0501/ 00014	Mean ± SD
Urine (0-240 hours)	9.88	6.92	5.18	8.53	7.63 ± 2.03
Feces (0-240 hours)	38.1	46.2	57.2	51.8	48.3 ± 8.16
Dose recovery (%)	48.0	53.1	62.4	60.3	55.9 ± 6.63

Source: Appendix 16.2.5-3

[a] Subject 00003 withdrew from the study at 216 hours postdose

Table 14 **Ratio of plasma pasireotide to plasma radioactivity**

Parameter	Subject USA/0501/ 00002	Subject USA/0501/ 00003	Subject USA/0501/ 00005	Subject USA/0501/ 00014	Mean
Plasma pasireotide AUC_{24h} (ng•h/mL)	78.7	50.9	51.9	90.6	68.0
Plasma radioactivity AUC_{24h} (ngEq•h/mL)	73.4	46.4	49.3	82.5	62.9
AUC ratio (pasireotide /radioactivity)	1.07	1.10	1.05	1.10	1.08

Sources: Table 11-3 (AUC_{24h} was recalculated) and Table 11-5

Reviewer's Comments

The recovery of total radioactivity was about 57% in 10 days and it is considered incomplete. Therefore, it should be cautious at the interpretation of the study results. Meanwhile, relative comparison within the study results such as urine vs. feces or plasma vs. blood seems acceptable.

Although the recovery of total radioactivity was incomplete, its terminal half-life (211 hours, Table 15) was significantly longer compared to those of other studies, but factor(s) for the difference are not well understood.

Table 15 Pharmacokinetic parameters for total radioactivity in plasma (upper panel) and blood (lower panel) following a single s.c. dose of 600 micrograms [14C]pasireotide

Subject	C_{max} ngEq/mL	t_{max} h	$t_{1/2}$ H	AUC_{240h} ngEq•h/mL	AUC_{inf} ngEq•h/mL
USA/0501/00002	23.5	0.25	NC d	105	NC d
USA/0501/00003	12.6	0.5	310	65.4a	90.8
USA/0501/00005	12.3	0.5	146	65.8	74.0
USA/0501/00014	17.8	0.5	176	104	115
Mean (median)[b]	16.6	0.5	211	85.1	93.3
SD (range)[c]	5.28	0.25-0.5	87.3	22.5	20.6
CV%	32	NA	41	26	22

Source: PT-Table 14.2-1.1

[a] The last time point included in the calculation of AUC was 216 hours for Subject USA/0501/00003, since the 240-hour sample was not collected due to withdrawal.

[b] Values are median for t_{max} and mean for $t_{1/2}$, C_{max} and AUCs

[c] Values are range for t_{max} and SD for $t_{1/2}$, C_{max} and AUCs

[d] NC = not calculable (the slope could not be estimated due to higher concentrations at later time points

Subject	C_{max} ngEq/mL	t_{max} h	$t_{1/2}$ h	AUC_{240h} ngEq•h/mL	AUC_{inf} ngEq•h/mL
USA/0501/00002	13.6	0.5	NC	73.5	NC
USA/0501/00003	6.93	0.5	73.2	46.0[a]	51.3
USA/0501/00005	7.93	1	119	46.3	52.2
USA/0501/00014	11.1	0.5	674	65.1	119
Mean (median)[b]	9.89	0.5	289	57.7	74.2
SD (range)[c]	3.05	0.5-1.0	334	13.8	38.8
CV%	31	NA	116	24	52

Source: PT-Table 14.2-1.2

[a] The last time point included in the calculation of AUC was 216 hours for Subject USA/0501/00003 since the 240 hour sample was not collected.

[b] Values are median for t_{max} and mean for $t_{1/2}$, C_{max} and AUCs

[c] Values are range for t_{max} and SD for $t_{1/2}$, C_{max} and AUCs

NA = not applicable; NC = not calculable (the slope could not be estimated due to higher concentrations at later time points

2.5 Intrinsic Factors

2.5.1 Hepatic Impairment

The hepatic function impact on pasireotide exposure was evaluated in an open-label, multi-center, single dose study following 600 µg subcutaneous pasireotide in subjects with varying degrees of hepatic function.

Pasireotide plasma concentration-time profiles are shown in Figure 7 and PK parameters are summarized in Table 16. Pasireotide AUC and Cmax were increased by 12 and 3%

for mild, 56 and 46% for moderate, 42 and 33% for severe hepatic impairment sub-groups, respectively, compared to those of healthy subjects (Table 17). Meanwhile, AUCinf was increased by 60% and 79%, and Cmax increased by 67% and 69%, respectively, in the moderate and severe hepatic impairment groups relative to the control group upon correction for covariate effect (age, BMI and albumin).

Reviewer's Comments

The sponsor proposed the adjustment to 0.3 mg BID and maximum 0.6 mg BID for patients with moderate hepatic impairment and contraindication with sever hepatic impairment because of mild but acute elevations in liver chemistry enzymes were observed across development program. According to sponsor's summary, those changes appear to be transient and required no additional therapy. Therefore, the sponsor (b) (4)

The sponsor indicates that 1) elevations in liver chemistry tests have been described for somatostatin analogues (SSAs), 2)cholelithiasis is a known complication of somatostatin analogues, and 3) drug induced liver injury cases have been reported with the treatment of lanreotide and octreotide. Meanwhile, Agency considers recommendation of 0.6 mg as initial dose at this time (refer the pharmacometric review for the details). The sponsor's proposed adjustment (i.e., 0.3 mg BID and limit to maximum 0.6 mg BID) seems working for the Agency's recommendation of new initial dose based on exposure increase.

The sponsor did not assess the impact of renal impairment on pasireotide exposure. The effect of renal impairment on pasireotide may not be significant because of minor renal elimination. Meanwhile, labeling of two somatostatin analogs (i.e., octreotide and lanreotide) indicates that exposure of those compounds was significantly increased by severe renal impairment. However, renal elimination of both analogs was significantly greater (e.g., >30% for lanreotide) compared to that of pasireotide and thus there was no information to bridge among those analogs related to the effect of renal impairment on pasireotide exposure.

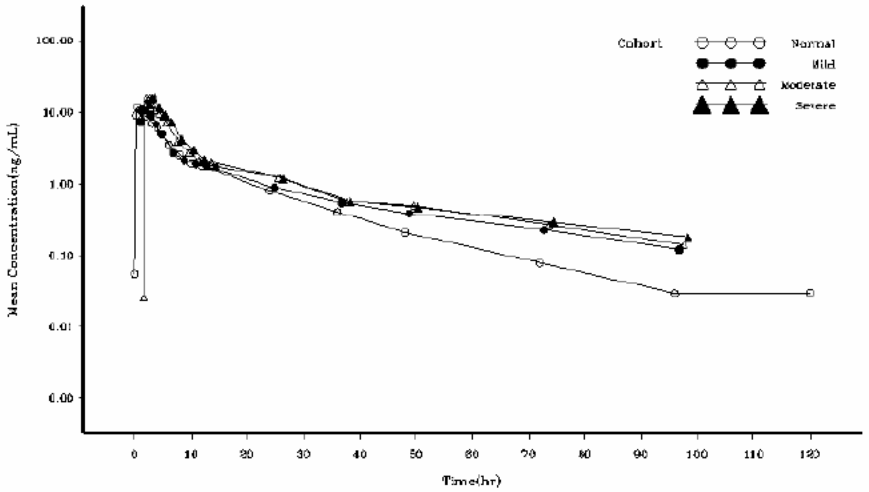


Figure 7 **Arithmetic mean concentration-time profiles for single dose of pasireotide with varying degrees of hepatic function**

Table 16 Summary of pasireotide PK parameters by cohort

PK Parameter (unit)	Normal (N = 12)	Mild (N = 6)	Moderate (N = 7)	Severe (N = 6)
AUC_{inf} (ng.hr/mL)	88.9 (33.8)	100.0 (24.8)	138.9 (31.3)	125.9 (41.5)
AUC_{last} (ng.hr/mL)	83.2 (33.4)	91.9 (28.9)	120.2 (32.1)	116.3 (40.0)
C_{max} (ng/mL)	11.4 (48.4)	11.8 (29.2)	16.6 (42.4)	15.2 (46.1)
T_{max} (hr)	0.76 (0.25 - 2.00)	1.00 (0.50 - 2.00)	0.67 (0.47 - 2.00)	1.00 (0.50 - 1.00)
$T_{1/2}$ (hr)	15.4 (71.7)	22.1 (42.8)	36.4 (73.4)	29.1 (74.3)
CL/F (L/hr)	6.7 (33.7)	6.0 (24.8)	4.3 (31.4)	4.8 (41.4)
V_z/F (L)	149.6 (54.8)	191.3 (24.7)	226.3 (49.0)	199.8 (42.5)
λ_z (1/hr)	0.045 (71.7)	0.031 (42.6)	0.019 (73.6)	0.024 (74.4)

Values are median (range) for T_{max}, and geometric mean (CV%) for all other PK parameters.
Source: PT-Tables 14.2-2.1 and 14.2-2.2

Table 17 Summary of statistical analysis of key PK parameters for pasireotide

					Comparison		
						90% CI	
PK Parameter (unit)	Cohort	n *	Non age- and BMI-adjusted Geo-mean	Comparison (s)	Geo-mean Ratio	Lower	Upper
AUC_{inf} (ng.hr/mL)	Control	12	88.9				
	Mild	6	100.0	Mild : Control	1.12	0.85	1.48
	Moderate	6	138.9	Moderate : Control	1.56	1.18	2.06
	Severe	6	125.9	Severe : Control	1.42	1.07	1.87
AUC_{last} (ng.hr/mL)	Control	12	83.2				
	Mild	6	91.9	Mild : Control	1.10	0.84	1.46
	Moderate	7	120.2	Moderate : Control	1.44	1.11	1.88
	Severe	6	116.3	Severe : Control	1.40	1.06	1.85
C_{max} (ng/mL)	Control	12	11.4				
	Mild	6	11.8	Mild : Control	1.03	0.72	1.47
	Moderate	7	16.6	Moderate : Control	1.46	1.04	2.04
	Severe	6	15.2	Severe : Control	1.33	0.94	1.90
CL/F (L/hr)	Control	12	6.7				
	Mild	6	6.0	Mild : Control	0.89	0.67	1.17
	Moderate	6	4.3	Moderate : Control	0.64	0.49	0.85
	Severe	6	4.8	Severe : Control	0.71	0.54	0.93
T_{max} (hr)	Control	12	0.76				
	Mild	6	1.00	Mild : Control	0.26	0.00	1.00
	Moderate	7	0.67	Moderate : Control	0.00	-0.33	0.48
	Severe	6	1.00	Severe : Control	0.00	-0.02	0.50

n* = number of subjects with non-missing values
Control is the hepatic function normal cohort
PK parameters were analyzed separately on the log scale by means of an ANOVA model including cohort as a fixed effect
For T_{max}, median is presented under 'Adjusted Geo-mean', Hodges Lehmann estimate for the difference between the hepatic impairment cohort and the control cohort under "Geo-mean ratio", and the corresponding 90% distribution free CI under "Lower" and "Upper".
Source: PT-Table 14.2-1.1a

2.6 Extrinsic Factors

2.6.1 Were there data to suspect *in vivo* metabolic drug-drug interactions?

Mass balance study results indicate metabolism is not significant. *In vitro* microsomal and hepatocyte study results indicate pasireotid is metabolically stable.

Pasireotide metabolic inhibition potential was assessed using standard in vitro studies and results of those studies are summarized in Table 18. Values of IC50 against major CYP isozymes were in the range of μM. It indicates that pasireotide is unlikely to inhibit those CYP isozymes considering nM range (e.g., Cmax of 15.5 ng/mL or ca. 15 nM) of anticipated therapeutic pasireotide plasma concentrations 600 μg subcutaneous dose to healthy subjects.

Table 18 Summary of in vitro study results for the metabolic inhibition potential

Inhibitory effect of SOM230 on CYP enzyme-selective metabolic reactions		
CYP Enzyme	Probe reaction	SOM230 IC_{50} value[a] (μM)
CYP1A2	phenacetin *O*-deethylation	~ 10
CYP2C8	paclitaxel 6α-hydroxylation	~ 50
CYP2C9	diclofenac 4′-hydroxylation	~ 5
CYP2C19	*S*-mephenytoin 4′-hydroxylation	~ 25
CYP2D6	bufuralol 1′-hydroxylation	~ 5
CYP2E1	chlorzoxazone 6-hydroxylation	> 100
CYP3A4/5	midazolam 1′-hydroxylation	~ 15
CYP3A4/5	testosterone 6β-hydroxylation	~ 10

[a]SOM230 concentration producing 50% inhibition of probe substrate metabolism.

Test compound	Enzyme	Probe reaction	IC_{50} value (μM)
SOM230	CYP2B6	bupropion hydroxylation	~ 80

[a] Test compound concentration estimated to inhibit probe substrate reaction by 50%. Values are not corrected for microsomal protein binding.

Pasireotide did not show metabolic induction potential according to in vitro study results.

2.6.2 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

Pasireotide appears to be substrate of P-glycoprotein because there was polarized

permeability in Caco-2 cell model study results (Table 19). However, the sponsor concluded that role of P-gp might not be significant in pasireotide disposition because its permeability remained much lower than that of mannitol when P-gp was inhibited by transporter inhibitors such as cyclosporine (CsA) and verpamil. The sponsor's assessment seems reasonable.

Pasireotide was not a substrate or inhibitor to other important export and import transporters including BCRP, OATP1B1, OATP1B3, OATP 2B1 and OCT1 according to *in vitro* study results. Assessment of hepatic accumulation and influence of known hepatic transporter inhibitors on it using human hepatocytes and HEK 292 cells are shown in Figure 8-10. There was no significant effect of those inhibitors on hepatic accumulation of pasireotide (Figure 7-9).

Table 19 Summary of Caco-2 cell study results

Compound	Conc. [µM]	Caco-2 permeability					
		$P_{app(AP-BL)}$ [10^{-5} cm/min]	SD		$P_{app(BL-AP)}$ [10^{-5} cm/min]	SD	
SOM230	0.2	0.00	0.00	(100)	5.89	2.6	(57)
SOM230	10	0.00	0.00	(99)	1.82	1.3	(98)
SOM230	50	0.12	0.02	(103)	0.14	0.03	(101)
SOM230+ CsA	0.2/10	0.09	0.03	(101)			
SOM230+ Verapamil	0.2/100	0.13	0.01	(109)			
Mannitol	0.01	1.9	0.3	(103)			
Propranolol	0.01	22.0	2	(55)			

() = recovery values in %

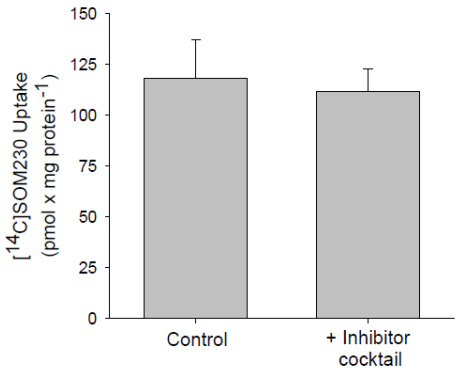


Figure 8 Uptake of [14C]SOM230 into human hepatocytes in suspension

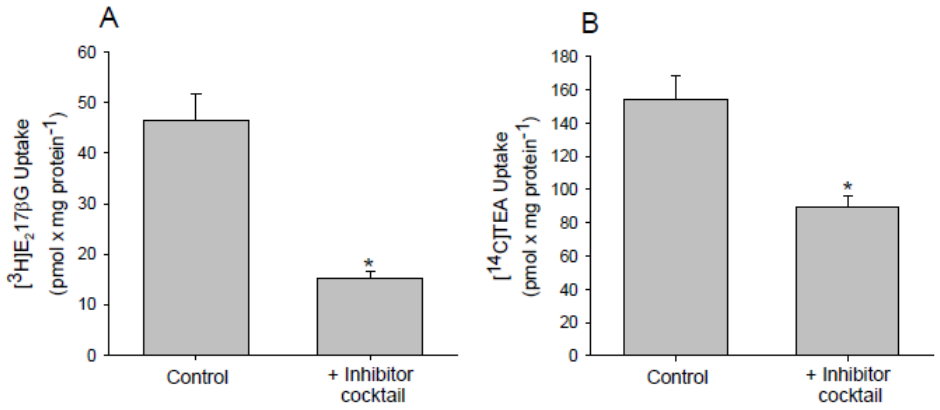


Figure 9 **Uptake of probe substrates of OATPs ($E_2$17βG) and OCT1 (TEA) into human hepatocytes in suspension**

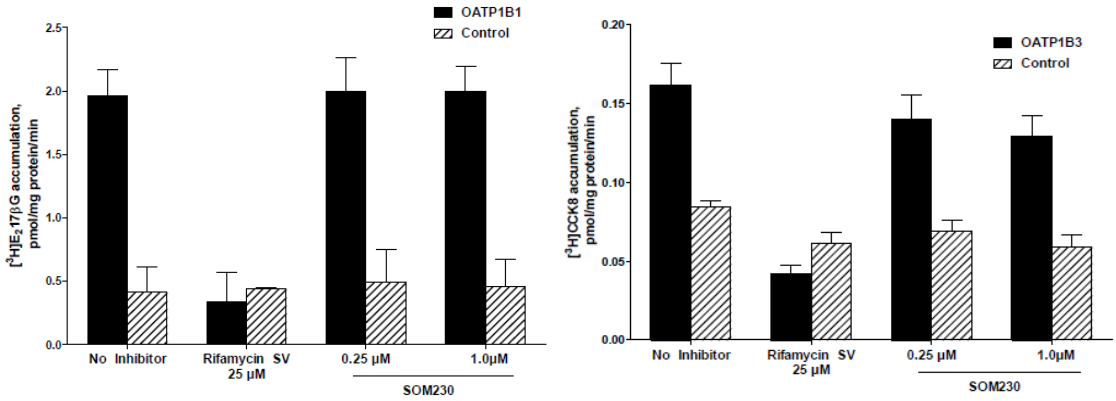


Figure 10 **Assessment of SOM230 as an inhibitor of OATP1B1 (left) and OATP1B3 (right) using HEK292 cells**

2.6.3 What are known *in vivo* the drug-drug interactions?

Drug interaction between pasireotide and anti-hyperglycemic drugs (i.e., metformin, nateglinide, vildagliptin and liraglutide) was evaluated in a randomized, open-label, single center study (B2124). Study design is summarized in Figure 11. Statistical analyses on the study results are summarized in Table 20. There is no clinically significant drug interaction between pasireotide and anti-diabetic medications.

Pasireotide effect on glucose is one of safety concerns and PD interaction was assessed in this study. After 7 days of treatment, pasireotide increased the mean percent from baseline in plasma glucose $AUC_{0–4hr}$ and anti-diabetics reduced pasireotide effect in sequence of liraglutide (by 29% compared to that of pasireotide) > vildagliption (15%) > nateglinide (10%) > metformin (2%) (Table 20). There was no empirical correlation between insulin change and glucose change among treatments (Table 21).

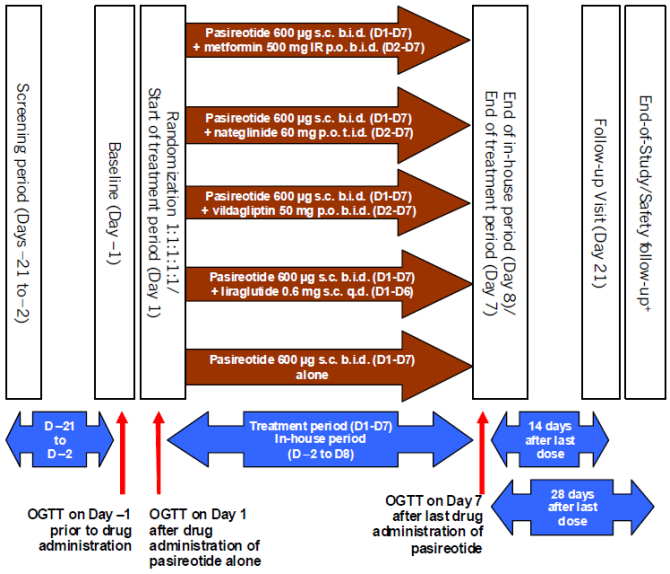


Figure 11 **Schematic summary of study design of B2124**

Table 20 **Summary of statistical analysis of Day -7 PK parameters**

PK Parameter (unit)	Arm	n*	Adjusted geo-mean	Comparison	Arm comparison		
					Geo-mean ratio	90% CI	
						Lower	Upper
$C_{trough,d7}$	1	17	4.51	Arm 1/arm 5	1.04	0.80	1.34
(ng/mL)	2	18	3.42	Arm 2/arm 5	0.79	0.61	1.01
	3	18	5.09	Arm 3/arm 5	1.17	0.91	1.51
	4	16	3.86	Arm 4/arm 5	0.89	0.69	1.15
	5	17	4.35				
$C_{max,d7}$	1	17	21.86	Arm 1/arm 5	1.04	0.88	1.23
(ng/mL)	2	18	17.80	Arm 2/arm 5	0.85	0.72	1.00
	3	18	19.91	Arm 3/arm 5	0.95	0.80	1.12
	4	16	18.23	Arm 4/arm 5	0.87	0.73	1.03
	5	17	20.99				
$AUC_{0-4hr,d7}$	1	17	58.89	Arm 1/arm 5	1.03	0.87	1.22
(hr·ng/mL)	2	18	49.46	Arm 2/arm 5	0.87	0.73	1.02
	3	18	57.03	Arm 3/arm 5	1.00	0.85	1.18
	4	16	47.69	Arm 4/arm 5	0.84	0.71	0.99
	5	17	57.08				
$AUC_{0-10h,d7}$	1	17	102.58	Arm 1/arm 5	1.03	0.86	1.24
(hr·ng/mL)	2	18	84.41	Arm 2/arm 5	0.85	0.71	1.02
	3	18	104.19	Arm 3/arm 5	1.05	0.88	1.26
	4	16	86.10	Arm 4/arm 5	0.87	0.72	1.04
	5	17	99.21				

Arm 1 = Pasireotide 600 µg s.c. b.i.d. + metformin 500 mg IR p.o. b.i.d.
Arm 2 = Pasireotide 600 µg s.c. b.i.d. + nateglinide 60 mg p.o. t.i.d.
Arm 3 = Pasireotide 600 µg s.c. b.i.d. + vildagliptin 50 mg p.o. b.i.d.
Arm 4 = Pasireotide 600 µg s.c. b.i.d. + liraglutide 0.6 mg s.c. q.d.
Arm 5 = Pasireotide 600 µg s.c. b.i.d.

- n* = number of subjects with non-missing values; $C_{trough,d7}$ = the trough plasma concentration at 0 hours pre-morning dose on Day 7, $C_{max,d7}$ = the maximum plasma concentration post-morning dose on Day 7, $AUC_{0-4hr,d7}$ = the partial AUC from 0 to 4 hours post-morning dose on Day 7, $AUC_{0-10h,d7}$ = the partial AUC from 0 to 10 hours post-morning dose on Day 7.
- Geo-mean, Geo-mean ratio and 90% CI were all determined from an ANOVA and back-transformed from log scale.
- The model for log-transformed PK parameters included treatment arm as fixed effect.

Table 21 **Summary of statistical analysis for AUC0–4hr of plasma glucose on Day 7 (hr·mg/dL)**

PD Parameter (unit)	Arm	n*	Adjusted geo-mean	Arm comparison: Comparison	Arm comparison: Geo-mean ratio	Arm comparison: 90% CI Lower	Arm comparison: 90% CI Upper
AUC_{0-4hr}	1	18	659.71	Arm 1/arm 5	0.98	0.91	1.05
(hr·mg/dL)	2	18	602.06	Arm 2/arm 5	0.90	0.83	0.96
	3	18	571.58	Arm 3/arm 5	0.85	0.79	0.91
	4	18	474.93	Arm 4/arm 5	0.71	0.66	0.76
	5	18	672.14				

Arm 1 = Pasireotide 600 µg s.c. b.i.d. + metformin 500 mg IR p.o. b.i.d.
Arm 2 = Pasireotide 600 µg s.c. b.i.d. + nateglinide 60 mg p.o. t.i.d.
Arm 3 = Pasireotide 600 µg s.c. b.i.d. + vildagliptin 50 mg p.o. b.i.d.
Arm 4 = Pasireotide 600 µg s.c. b.i.d. + liraglutide 0.6 mg s.c. q.d.
Arm 5 = Pasireotide 600 µg s.c. b.i.d.

- n* = number of subjects with non-missing values

- Geo-mean, Geo-mean ratio and 90% CI were all determined from a mixed effect model and back-transformed from log scale.
- The model for log-transformed parameter included treatment arm, day and the interaction between treatment arm and day as fixed effects as well as a random effect for subject and log-transformed baseline value of AUC_{0-4hr} as covariate.

Table 22 **Summary of statistical analysis for AUC_{0-4hr} of serum insulin on Day 7 (hr·mU/L) (PD set)**

PD Parameter (unit)	Arm	n*	Adjusted geo-mean	Arm comparison: Comparison	Arm comparison: Geo-mean ratio	Arm comparison: 90% CI Lower	Arm comparison: 90% CI Upper
AUC_{0-4hr}	1	18	42.03	Arm 1/arm 5	1.06	0.82	1.36
(hr·mU/L)	2	18	40.88	Arm 2/arm 5	1.03	0.80	1.32
	3	18	67.82	Arm 3/arm 5	1.71	1.33	2.19
	4	18	53.17	Arm 4/arm 5	1.34	1.03	1.73
	5	18	39.75				

Arm 1 = Pasireotide 600 µg s.c. b.i.d. + metformin 500 mg IR p.o. b.i.d.
Arm 2 = Pasireotide 600 µg s.c. b.i.d. + nateglinide 60 mg p.o. t.i.d.
Arm 3 = Pasireotide 600 µg s.c. b.i.d. + vildagliptin 50 mg p.o. b.i.d.
Arm 4 = Pasireotide 600 µg s.c. b.i.d. + liraglutide 0.6 mg s.c. q.d.
Arm 5 = Pasireotide 600 µg s.c. b.i.d.

- n* = number of subjects with non-missing values

- Geo-mean, Geo-mean ratio and 90% CI were all determined from a mixed effect model and back-transformed from log scale.
- The model for log-transformed parameter included treatment arm, day and the interaction between treatment arm and day as fixed effects as well as a random effect for subject and log-transformed baseline value of AUC_{0-4hr} as covariate.
- Values below the limit of quantification were set to zero.

2.7 Analytical Section

Radioimmunoassay was used for plasma pasireotide concentration measurement and the limit of quantification was 30 pg/mL using 50 µL of plasma. The QC data indicate that the bioanalytical methods are acceptable (Table 23).

Table 23 Summary on representative QC data

Date of analysis	Nominal concentrations					
	156.3 pg/mL		312.5 pg/mL		625 pg/mL	
	ng/mL	Accuracy	ng/mL	Accuracy	ng/mL	Accuracy
21.03.02	169.3	108.3%	309.3	99.0%	610.8	97.7%
26.03.02	146.5	93.8%	345.0	110.4%	694.3	111.1%
N	15		15		15	
Mean (ng/mL)	155.9		329.0		631.8	
SD (ng/mL)	6.6		9.7		44.8	
CV (%)	4.2		3.0		7.1	
Bias (%)	-0.3		5.3		1.1	

Mean C standard values are reported.

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

4. Attachment

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

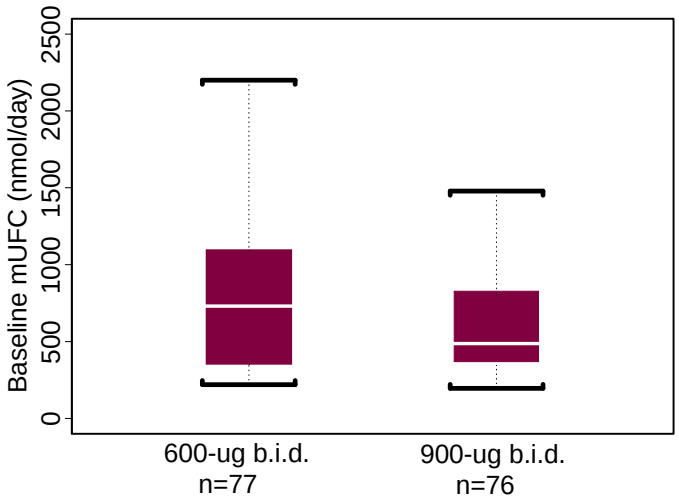
The purpose of this review is to address the following key questions.

1.1.1 Does the exposure-response relationship for efficacy support the proposed initial dose of 900 µg b.i.d.?

No. The proposed initial dose of 900 µg b.i.d. is not supported by exposure-response (E-R) relationship for efficacy.

In the 900 µg b.i.d. group, 21 out of 82 patients (26.3%) were responders at Month 6 with 95% CI (16.6, 35.9). In the 600 µg b.i.d. group, 12 out of 83 patients (14.6%) were responders at Month 6 with 95% CI (7.0, 22.3). The pre-specified criterion for the lower bound of the 95% confidence interval (CI) of the response rate was 15%. Therefore, 900 µg b.i.d. dose group met the pre-specified primary efficacy endpoint while 600 µg b.i.d. dose group did not.

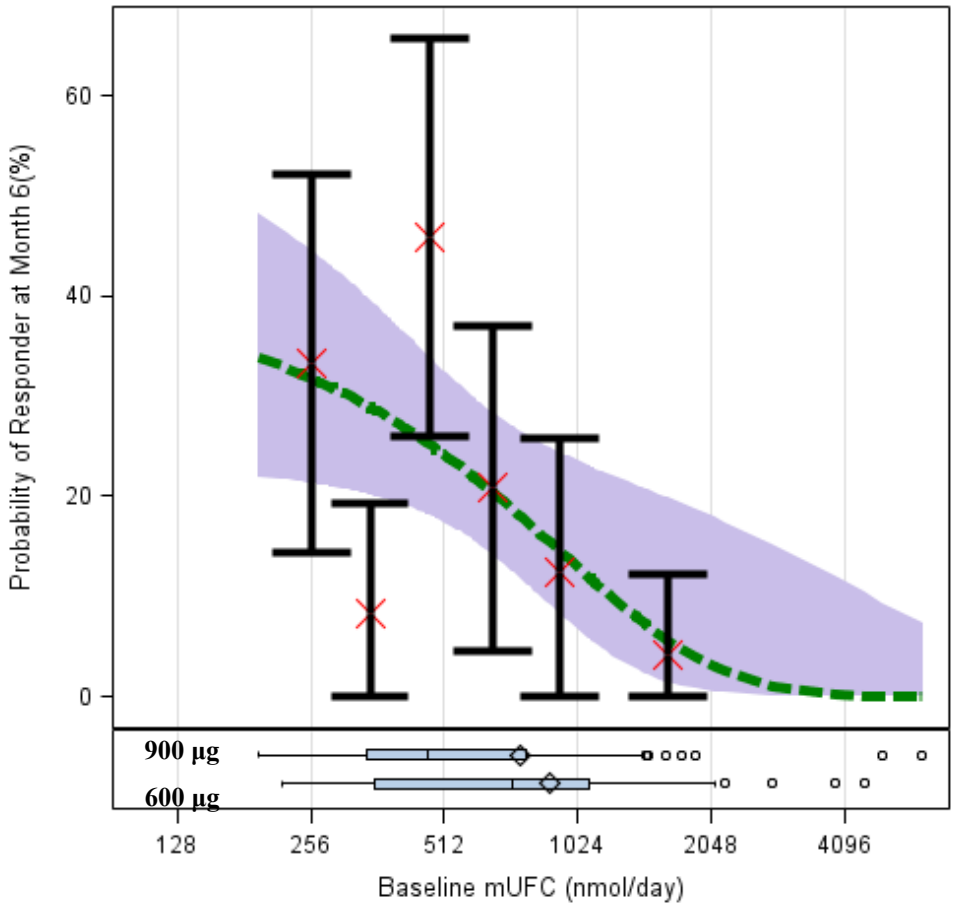
Figure 1: Imbalance in baseline mUFC between 600 µg b.i.d. and 900 µg b.i.d. (Geometric Mean Ratio of 600 µg vs 900 µg: 1.50). The box plots depict the distribution of baseline mUFC in the two dose groups.



It is important to note that although the pivotal trial (Study B2305) was randomized, the baseline mUFC of patients in 600 µg b.i.d. dose group was 50% higher than in the 900 µg b.i.d. dose group (Figure 1). Furthermore, it was observed that the probability of responding to pasireotide decreases with the increase in baseline mUFC (Figure 2). In

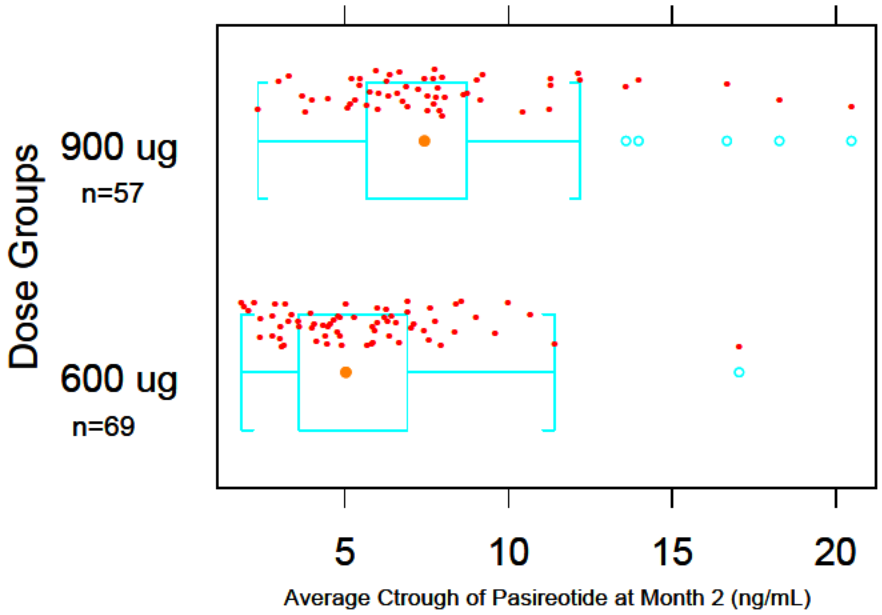
other words, patients with higher baseline had lower probability of response as they have to undergo larger reduction in mUFC to go below the ULN in order to be defined as a responder. Therefore, direct comparison of primary efficacy endpoint (i.e., response rate) between two dose groups may not be appropriate.

Figure 2: Responder Status is associated with baseline mUFC. Logistic regression model includes the probability of responder at month 6 as a function of baseline mUFC. The mean and 95% CI of the observed response rate versus the mean observed baseline mUFC is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of response rate (P value=0.04). The box plots at the bottom represent the distribution of baseline mUFC in each dose group.



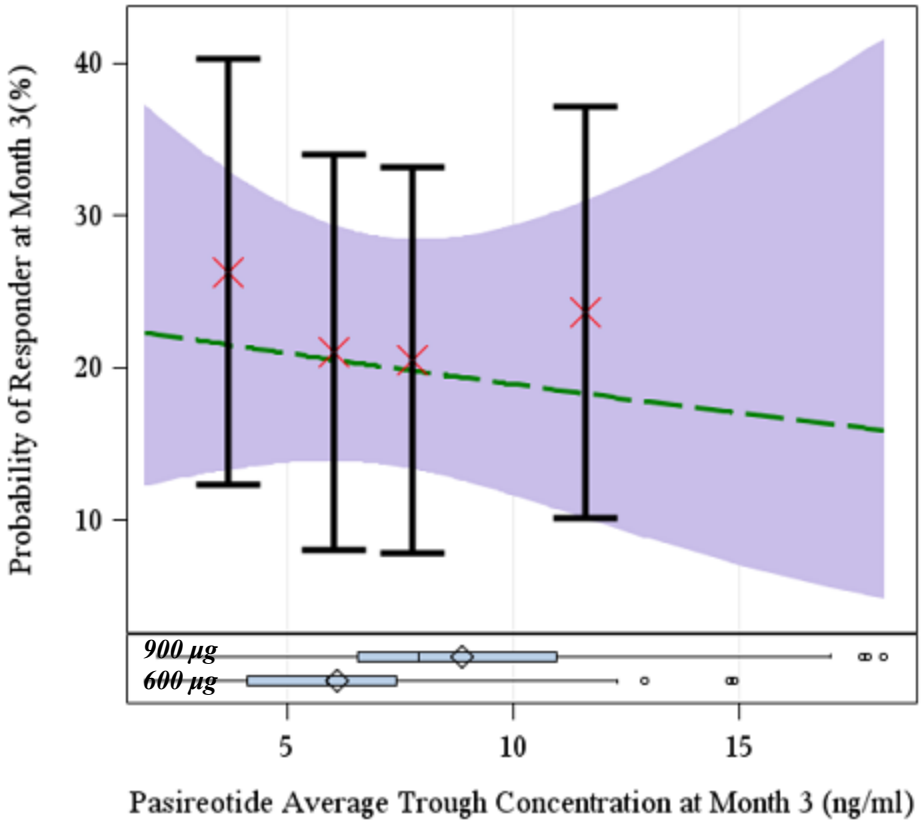
Furthermore, despite the fact that the median trough concentration is 50% higher in 900 µg b.i.d. dose group compared to 600 µg b.i.d. dose group, there is a substantial overlap in exposures between these two dose groups due to the high inter-subject variability in pharmacokinetics (Figure 3).Thus, exposure-response analysis using individual level exposure and response was conducted.

Figure 3: Two dose groups have substantial overlap in exposure. The box plots depict the distribution of average trough concentration at month 2 in the two dose groups. Red dots are observed data for individual patients.



Exposure-response analysis was conducted with average trough concentration at month 3 as the exposure variable and normalization of mUFC as the response variable. A patient who had mUFC below the ULN was defined as the responder. As some patients underwent dose escalation based on pre-specified criteria after Month 3, and response as measured by mUFC already reached steady state at month 2 or 3, exposure-response was explored at Month 3 instead of Month 6. As evident from Figure 4, there is no clear relationship between exposure (i.e., average trough concentration) and probability of response, suggesting no significant additional benefit of 900 µg b.i.d. over 600 µg b.i.d. It should be noted that the results are consistent if response at Month 6 is used as the response variable and average steady state concentration over 6 months as the exposure variable. In addition, exposure-response analysis was also conducted using mUFC as a continuous variable for efficacy and conclusions regarding the exposure-response relationship for efficacy remain the same.

Figure 4: No evident relationship between exposure and response rate after adjusting for baseline mUFC. Logistic regression model includes the probability of responder at month 3 as a function of average pasireotide concentration at month 3 after controlling for baseline mUFC (Ctrough P value=0.65; Baseline mUFC P value=0.046). The mean and 95% CI of the observed response rate versus the mean observed baseline mUFC is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of response rate. The box plots at the bottom represent the distribution of trough concentration in each dose group.



1.1.2 Does the exposure-response relationship for safety support the proposed initial dose of 900 µg b.i.d. for patients with normal baseline HbA1C and 600 µg b.i.d. for patients with pre-diabetic or diabetics?

The proposed initial dose of 900 µg b.i.d. for patients with normal baseline HbA1C is not supported by E-R relationship for safety. Dose of 600 µg b.i.d. for patients with pre-diabetic or diabetics is supported by E-R relationship for safety.

One of the main safety concerns for pasireotide is hyperglycemia. As hyperglycemia effect caused by pasireotide reached plateau at month 2, exposure-response analysis was conducted at month 2. In patients with normal baseline HbA1C, there is a clear trend toward increasing probability of experiencing ≥1% post-baseline increase of HbA1C with the increasing exposure in the pivotal trial (Figure 5), suggesting that 900 µg b.i.d. will result in a higher probability of post-baseline hyperglycemia than 600 µg b.i.d.. Therefore, for patients with normal baseline HbA1c, we recommend a lower starting dose of 600 µg b.i.d.

The analysis was repeated for patients who were pre-diabetic or diabetic at baseline. It was observed that there is a clear trend toward increasing probability of experiencing ≥1% post-baseline increase of HbA1c with the increasing exposure in the pivotal trial (Figure 6), suggesting 900 µg b.i.d. will result in a higher probability of post-baseline hyperglycemia than 600 µg b.i.d. Therefore, for patients with pre-diabetic or diabetic status at baseline, we agree with sponsor's proposed dose of 600 µg b.i.d.

It should also be noted that exposure-response relationship for trough concentration is more pronounced in patients with pre-diabetic or diabetic (odds ratio: 1.55 for 1 ng/ml increase of trough concentration) than that in patients with normal HbA1c baseline (odds ratio: 1.31 for 1 ng/ml increase of trough concentration).

Figure 5: Increase in probability of developing post-baseline hyperglycemia (>1% HbA1c increase from baseline) at month 2 with the increase of exposure in patients with normal baseline HbA1c. Logistic regression model includes the probability of post-baseline hyperglycemia at month 2 as a function of average pasireotide concentration at month 2 (Ctrough P value=0.011). The mean and 95% CI of the observed response rate versus the mean observed baseline mUFC is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of probability of post-baseline hyperglycemia. The box plots at the bottom represent the distribution of trough concentration in each dose group.

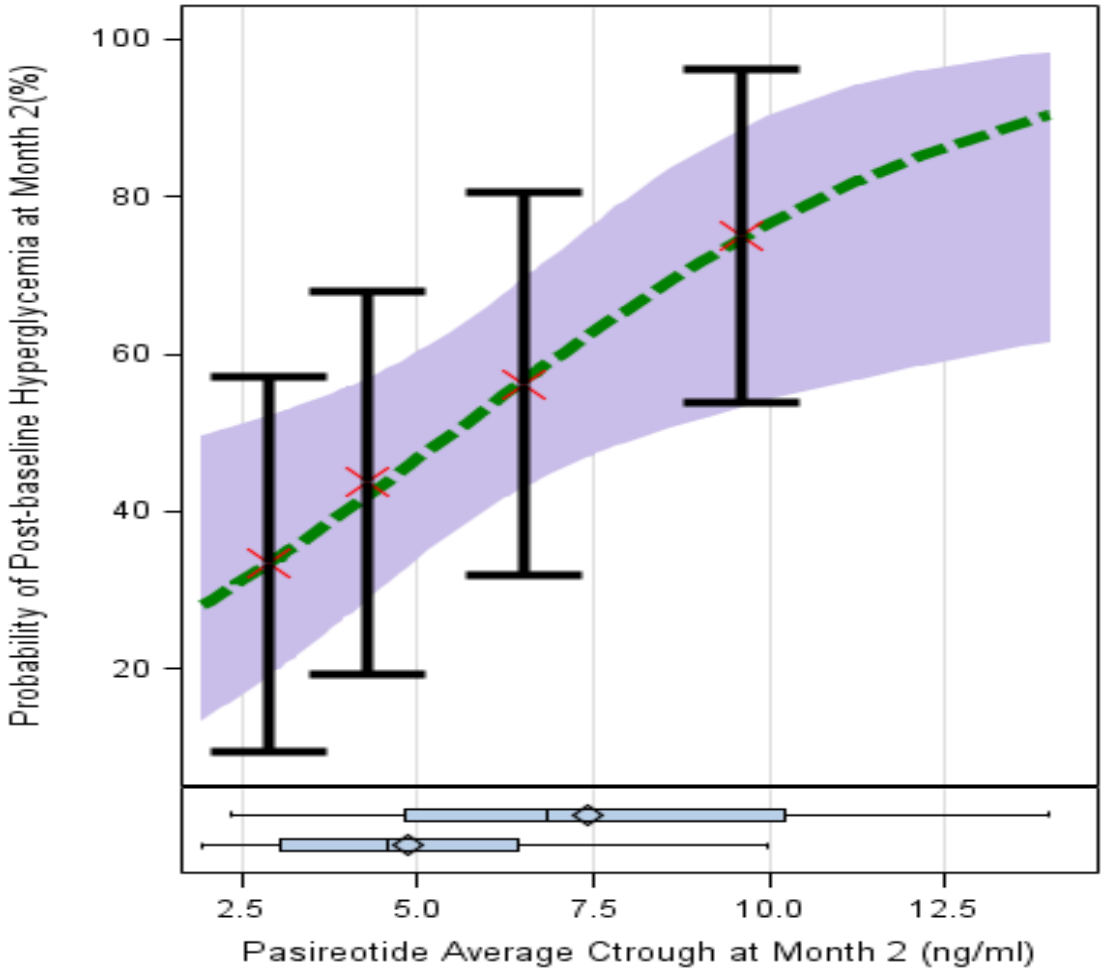
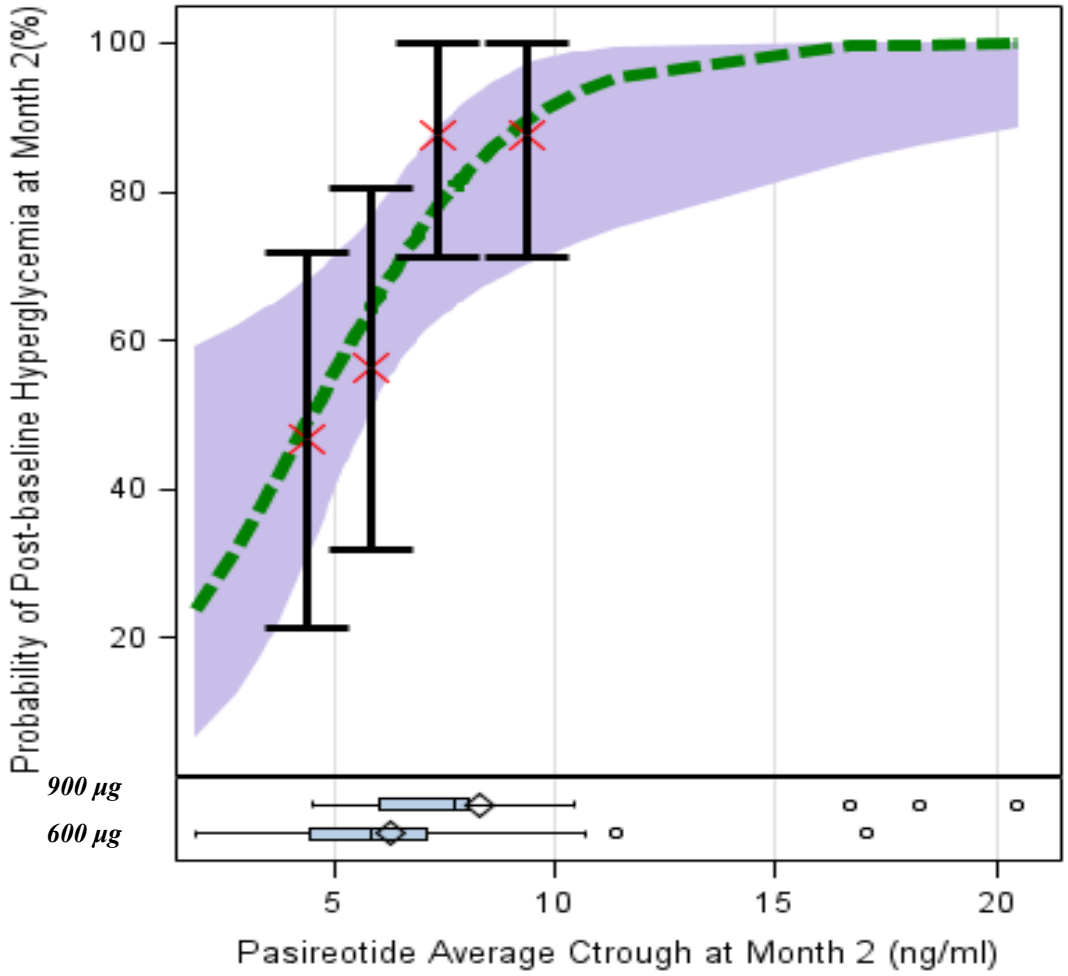
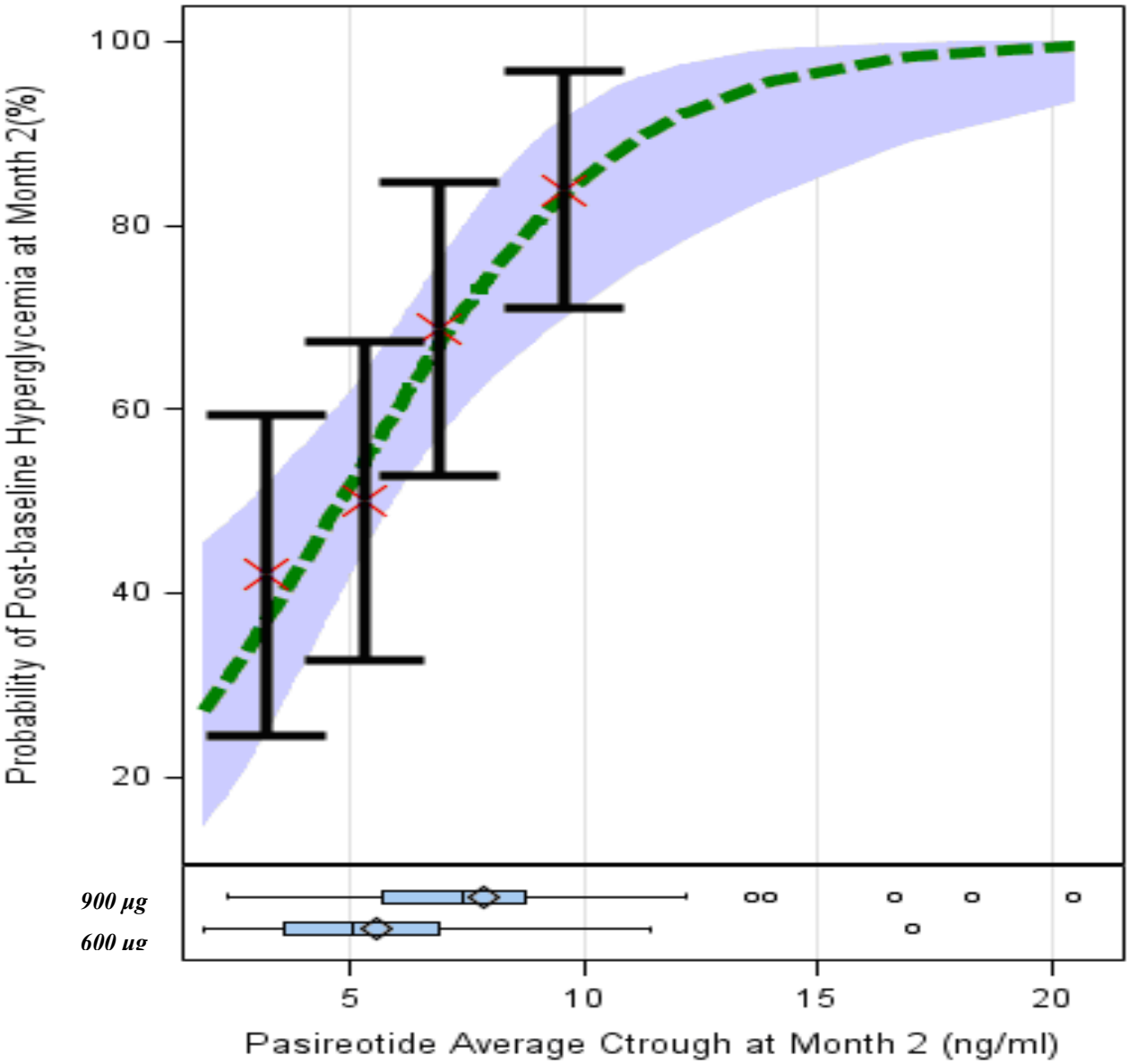


Figure 6: Increase in Probability of Developing Post-baseline Hyperglycemia (>1% HbA1c increase from baseline) at Month 2 with the Increase of Exposure in Patients who are pre-diabetic or diabetic at baseline. Logistic regression model includes the probability of post-baseline hyperglycemia at month 2 as a function of average pasireotide concentration at month 2 (Ctrough P value=0.011). The mean and 95% CI of the observed response rate versus the mean observed baseline mUFC is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of probability of post-baseline hyperglycemia. The box plots at the bottom represent the distribution of trough concentration in each dose group.



Furthermore, the possibility of developing post-baseline hyperglycemia was found to be positively correlated with baseline HbA1c (p value = 0.045). After adjusting for baseline HbA1c, exposure-response relationship is also evident in the overall population (Figure 7). In summary, there is a significant exposure-response relationship for hyperglycemia.

Figure 7: Increase in Probability of Developing Post-baseline Hyperglycemia (>1% HbA1c increase from baseline) at Month 2 with the Increase of Exposure in all Patients after adjusting for baseline HbA1c. Logistic regression model includes the probability of post-baseline hyperglycemia at month 2 as a function of average pasireotide concentration at month 2 after controlling for baseline mUFC (Ctrough P value=0.0004; Baseline HbA1c P value=0.045). The mean and 95% CI of the observed response rate versus the mean observed baseline mUFC is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of probability of post-baseline hyperglycemia. The box plots at the bottom represent the distribution of trough concentration in each dose group.



Overall, exposure-response analysis suggests that 600 µg b.i.d. may be as effective as 900 µg b.i.d., and will provide better hyperglycemia-related safety profile than 900 µg b.i.d. for all patients. Therefore, we recommend 600 µg b.i.d. instead of 900 µg b.i.d. as initial dose for patients. However, due to the high unexplained variability in response, 900 µg b.i.d. may be beneficial for some patients not responding to 600 µg b.i.d. and should be allowed as an option.

1.1.3 Dose the body weight, age, race, gender have effect on PK parameters?

Population PK analysis suggests that age, body weight, race, gender have no meaningful effect on clearance of pasireotide (see sponsor's analysis later in the review).

1.2 Recommendations

Based on the exposure-response analysis for efficacy and safety, we recommend that 600 µg b.i.d. should be approved as initial dose irrespective of the diabetes status. Option of dose escalation to 900 µg b.i.d. should be provided to patients who do not respond and can tolerate higher dose.

1.3 Label Statements

1.3.1.1 Special Populations:

Population PK analyses of SIGNIFOR indicate that body weight, age, gender do not affect pasireotide pharmacokinetics and there is no meaningful difference in pharmacokinetics between Caucasian and non-Caucasian.

(b) (4)

Geriatric patients

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

Cushing's disease is a rare endocrine disease. Currently there are about 40,000 patients living with Cushing's disease: United States (~16,848), Japan (~6,604), France, Germany, Italy, Spain and the United Kingdom (~16,120 in the EU) combined. The current first-line treatment for Cushing's disease is pituitary resection of the adenoma. For patients not cured by pituitary surgery, irradiation or bilateral adrenalectomy are the remaining non-medical treatment options. In April, 2012 EMA approved pasireotide for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. This is the first medical therapy approved for Cushing's

disease in the world. However, in US there are no medical therapies approved for the treatment of Cushing's disease. Sponsor submitted this NDA application to seek approval of the s.c. formulation of pasireotide for the treatment of patients with Cushing's disease for whom medical therapy is appropriate.

3 RESULTS OF SPONSOR'S ANALYSIS

Sponsor assessed the exposure-response relationship for UFC (efficacy endpoint) and fast plasma glucose (FPG) (safety endpoint) through population PK/PD modeling.

3.1 Sponsor's population PK/PD model for UFC

Nonlinear mixed-effect model was used to characterize the UFC as a function of pasireotide trough concentrations and patient covariates using the pooled data from one Phase 2 study (CSOM230B2208) and one phase 3 (CSOM230B2305). The parameter estimates were provided in Table 1.

$$\log(UFC/mUFC_{baseline}) = intercept + E_{max} \times trough/(C_{50} + trough) + residual\ error$$

Intercept:	zero
Emax:	$\beta_2 + \beta_4 \times \log(mUFC_{baseline}/900) + \beta_5 \times Female + \beta_6 \times (Other\ Race) + \eta_2$
C_{50}:	$\exp(\beta_3 + \beta_7 \times Female + \eta_3)$
η_2 and η_3:	normally distributed random variables with mean zero representing unexplained between-patient variability
residual error:	normally distributed random variable with mean zero representing unexplained within-patient variability

Table 1. Parameter estimates from the final model for UFC versus trough concentration

Parameter	Estimate	Standard Error
β_2	-1.61	0.44
β_3	9.12	0.68
β_4	-0.72	0.13
β_5	-0.03	0.45
β_6	0.74	0.40
β_7	-1.78	0.76
var(η_2)	0.93	0.15
var(η_3)	1.90	0.49
var(ε)	0.45	0.01

Source: ufcbdall.sas

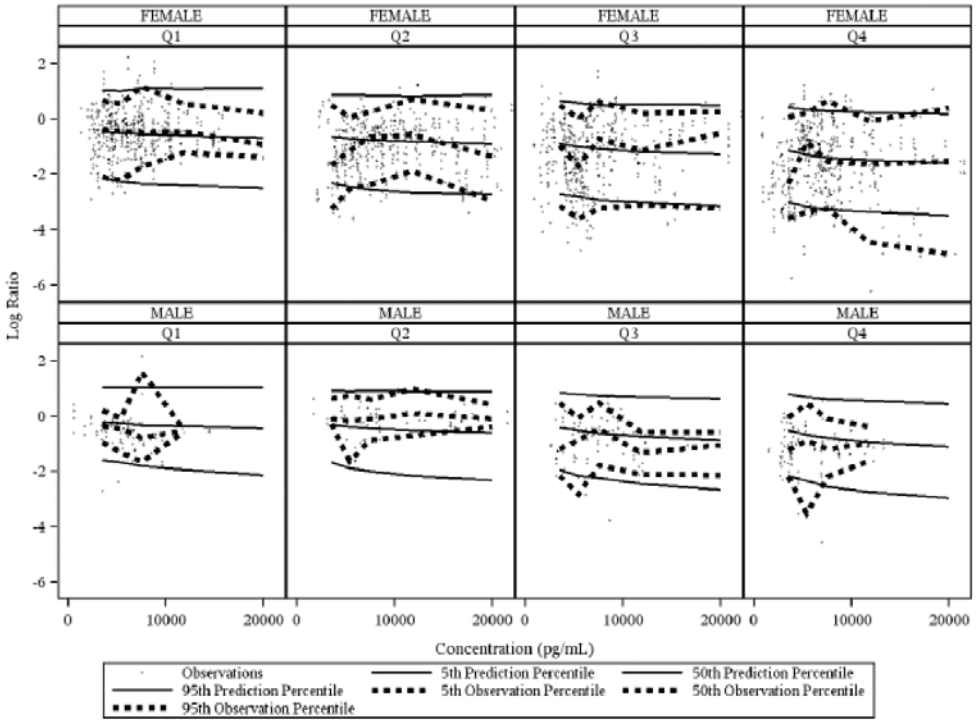
Sources: Sponsor's Population PK/PD of pasireotide: 12-month update, Page 21

Reviewer's Comments: The UFC model by sponsor can adequately describe the observed UFC data from phase 2 and phase 3 studies. The typical value of C50 for female is 1540 pg/mL. However, the median concentration for 600 ug and 900 b.i.d. is 5410 and 7570 pg/mL, respectively, and is much higher than C50. In addition, As shown in Figure 8, the

simulated log ratio of UFC to baseline UFC did not decrease substantially with increasing concentrations, and reached plateau at the observed concentration with 600 ug or 900 ug b.i d. dose. Sponsor also simulated the profiles of normalization of mUFC at concentrations corresponding to the median concentration of 300, 600, 900, 1200 ug b.i.d. dose. The difference in probability of normalization of UFC between 600 and 900 ug b.i.d. is only 2-4% in female (Table 2). These suggest that the efficacy may not be dependent on exposure within the range of observed concentrations, raising the question about the selection of Emax model.

No clear exposure-response relationship was identified by visual inspection of observed individual profiles of mUFC vs concentrations (see examples in Figure 9).Fitting data like this with Emax model may result in reasonable estimates for some parameters, especially Emax, even though no underlying association exists between concentration and response in the given data. In this particular case, successful estimation of Emax is mainly because similar responses observed at all concentrations were identified as maximal effect despite insufficient observations of lower response at lower concentration. Therefore, successful estimation of Emax does not necessarily mean there is a PK/PD relationship following Emax model. This also explains a very high inter-subject variability associated with C50 (CV%=138%), suggesting that the observed data does not allow a good estimation of C50, a critical parameter in the Emax model. To summarize, Emax model does not offer insight regarding the underlying PK/PD relationship. An independent analysis by reviewer suggested there is no evidence of exposure-response relationship for efficacy (see section 4.).

Figure 8: Visual predictive check: log ratio of UFC to baseline mUFC versus pasireotide trough concentration by sex and quartile of baseline mUFC, non-Other race only



Sources: Sponsor's ***Population PK/PD of pasireotide: 12-month update, Page 23***

Table 2. Probability of attaining normalization (UFC < ULN) versus pasireotide trough concentration, given sex and baseline UFC (non-Other race only)

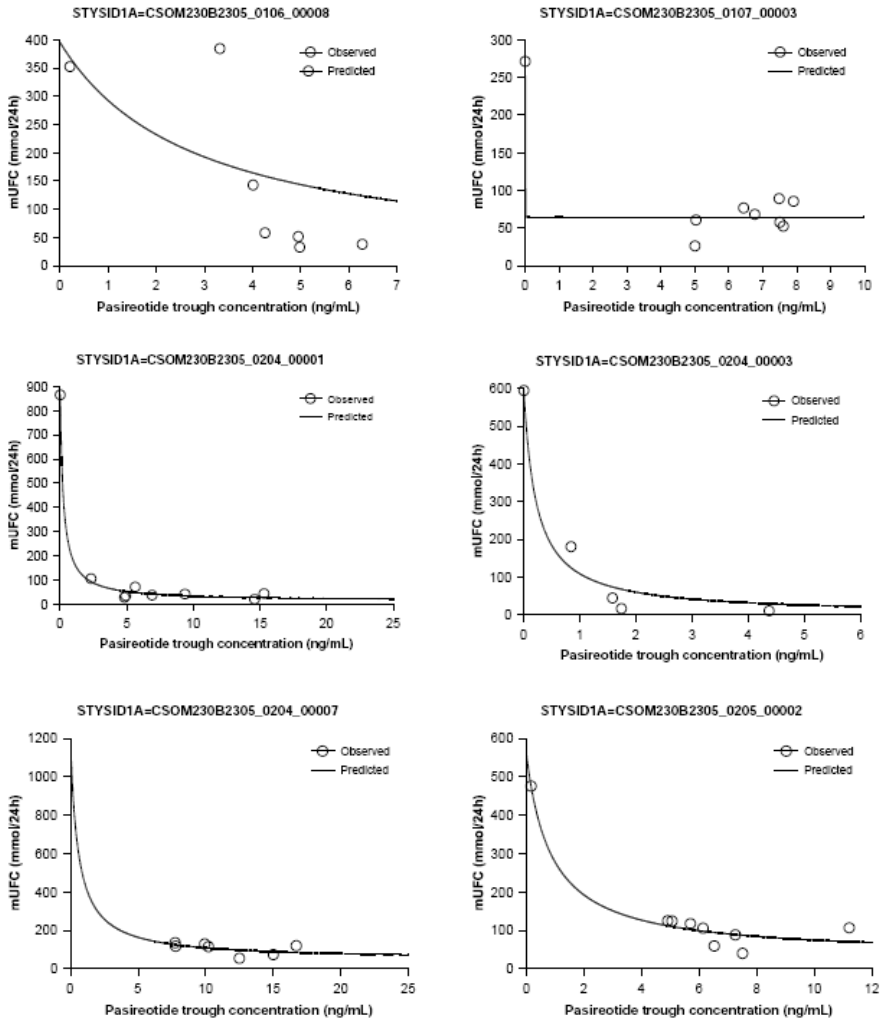
Sex	Pasireotide trough (pg/mL)	Baseline mUFC (nmol/d) 264 nmol/d	344 nmol/d	521 nmol/d	891 nmol/d	1479 nmol/d
M	3480	0.16	0.12	0.07	0.04	0.02
M	5410	0.22	0.16	0.10	0.07	0.04
M	7570	0.26	0.20	0.14	0.09	0.06
M	11800	0.32	0.25	0.18	0.12	0.09
M	Infinite	0.53	0.50	0.46	0.41	0.36
F	3480	0.39	0.33	0.25	0.18	0.13
F	5410	0.43	0.38	0.30	0.22	0.17
F	7570	0.45	0.41	0.34	0.26	0.19
F	11800	0.48	0.43	0.38	0.31	0.23
F	Infinite	0.54	0.51	0.47	0.43	0.37

Notes:

- 3480, 5410, 7570, and 11800 pg/mL are the median observed concentrations at doses of 300, 600, 900, and 1200 µg b.i.d., respectively.
- 264, 344, 521, 891, and 1479 nmol/d are the 10th, 25th, 50th, 75th, and 90th observed percentiles of baseline mUFC.
- ULN = 145 nmol/d

Sources: Sponsor's ***Population PK/PD of pasireotide: 12-month update, Page 28***

Figure 9: Examples of Individual mUFC levels vs pasireotide concentration



Sources: Full Clinical Study Report-Study No. SOM230B 2305, Page 261

3.2 Sponsor's population PK/PD model for FPG

To assess association between the hyperglcyemia risk and pasireotide exposures for Cushing's disease patients, sponsor constructed a mixed-effect model for FPG versus trough concentration, which had the form of a linear dependence of the log-transformed FPG level on the log-transformed trough concentration with baseline characteristics and other relevant factors (e.g., concomitant medication) as covariates. The results suggested that FPG increases on average with increasing pasireotide trough concentration. In addition, at a given concentration of pasireotide, FPG tends to be higher for patients with higher baseline FPG, with a baseline hyperglycemia history, and for older patients.

Reviewer's Comments: The model appears to adequately describe the data. The findings based on the modeling are physiological relevant considering the mechanism of action of

pasireotide and are comparable with the results from reviewer's independent analysis in section 4.

3.3 Sponsor's population PK model

Population PK analyses were performed to estimate PK parameters of pasireotide and identify covariates accounting for the variability in exposure.

The structural model fitted to the data was a three-compartment disposition model with first-order absorption after subcutaneous injection from the depot compartment and first order elimination from the central compartment. The data set consisted of the PK data collected from the healthy volunteers (HV) and patients. The HV PK data included 4244 observations from 216 subjects. The patients PK data included 2368 observations from 197 patients.

Based on results from previous population PK analysis conducted separately for HV and patients, only four covariates were considered in this analysis, including disease status, age, WT and lean body weight (LBW). Disease status (HV versus patients) was considered as a covariate on all parameters. The population PK models were fitted using NONMEM 6.2 with first order conditional estimation with interaction (METHOD = 1 INTERACTION) method. The final model was selected according to the criterion of minimum BIC. Sponsor concluded that no dosage adjustment of pasireotide based on age and body size is warranted.

Key PK parameter estimates were provided in Table 3. Clearance increases with body size and decreases with age in a similar way for patients and HV. But the typical values of CL/F and V2/F differ between HV and patients. The model predicts that the clearance and central volume in patients is 59.3% and 42.6% of that in HV with same age and LBW. HV and patients are similar in Ka, k23, and k32, but k24 and k42 are different between HV and patients.

Table 3: Estimates of Key population PK parameters

Parameter	Original Model 5		Reduced Model 5 for $COV	
	Parameter Estimate	Bootstrap Standard Error	Parameter Estimate	$COV Standard Error
θ_1	38.0	0.899	38.0	0.771
θ_2	7.96	0.162	7.96	0.160
θ_8	0.426	0.0335	0.427	0.0352
θ_9	0.634	0.0277	0.634	0.0374
θ_{15}	0 FIXED	-	0 FIXED	-
θ_{16}	0.746	0.0821	0.746	0.105
θ_{17}	0 FIXED	-	0 FIXED	-
θ_{18}	0 FIXED	-	0 FIXED	-
θ_{19}	0.468	0.0837	0.468	0.0759
θ_{20}	-0.229	0.0529	-0.229	0.0527
θ_{21}	0 FIXED	-	0 FIXED	-
θ_{22}	1 FIXED	-	1 FIXED	-
θ_{23}	0.935	0.0305	0.935	0.0266
θ_{24}	0 FIXED	-	0 FIXED	-
θ_{25}	0 FIXED	-	0 FIXED	-
θ_{26}	0 FIXED	-	0 FIXED	-
ω_{11}	0.0325	0.00634	0.0325	0.00721
ω_{22}	0.0361	0.00652	0.0361	0.00478
ω_{88}	0.0361	0.00579	0.0361	0.00544
ω_{99}	0.00466	0.00312	0.00466	0.00451

See Section 3.3.1 for a full explanation of the model. To help with identification of parameters, the most general form of the model is provided here:

$$V2/F = \theta_1 \times \theta_8{}^{**}C \times [(LBW/61)^{**}(1 + \theta_{15}H + \theta_{17}C)][(age/29)^{**}(\theta_{19} + \theta_{21}C)] \times \exp(\eta_8(1 + \theta_{24}C) + \eta_1(1 + \theta_{25}C))$$

$$CL/F = \theta_2 \times \theta_9{}^{**}C \times [(LBW/61)^{**}(\theta_{16}(1 + \theta_{18}H))] \times [\theta_{23}{}^{**}(RED\times C) \times (age/29)^{**}(\theta_{20}H + \theta_{20}\theta_{22}RED\times C)] \times \exp(\eta_8(1 + \theta_{24}C) + \eta_2(1 + \theta_{26}C) + \eta_9 RED\times C)$$

$\eta_j \sim N(0, \omega_{jj})$, j = 1, 2, 8, 9

H = 1 for Healthy Volunteers and 0 for Patients; C = 1 – H; RED = 1 if DAY > 2 and 0 otherwise.

Source: sponsor's Population pharmacokinetics of subcutaneous pasireotide in healthy volunteers and in Cushing's disease patients Modeling Report, Page23

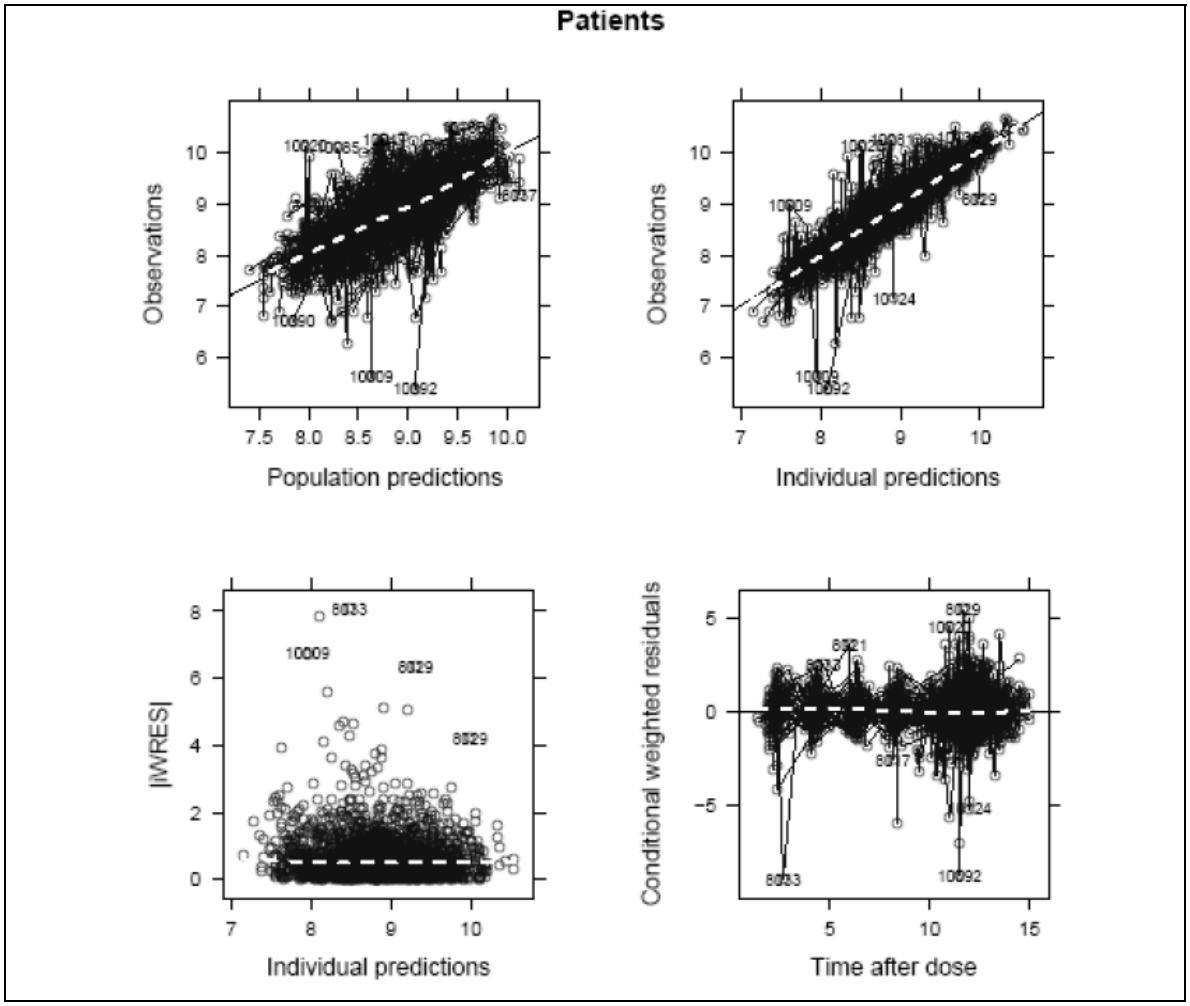
Reviewer's comments:

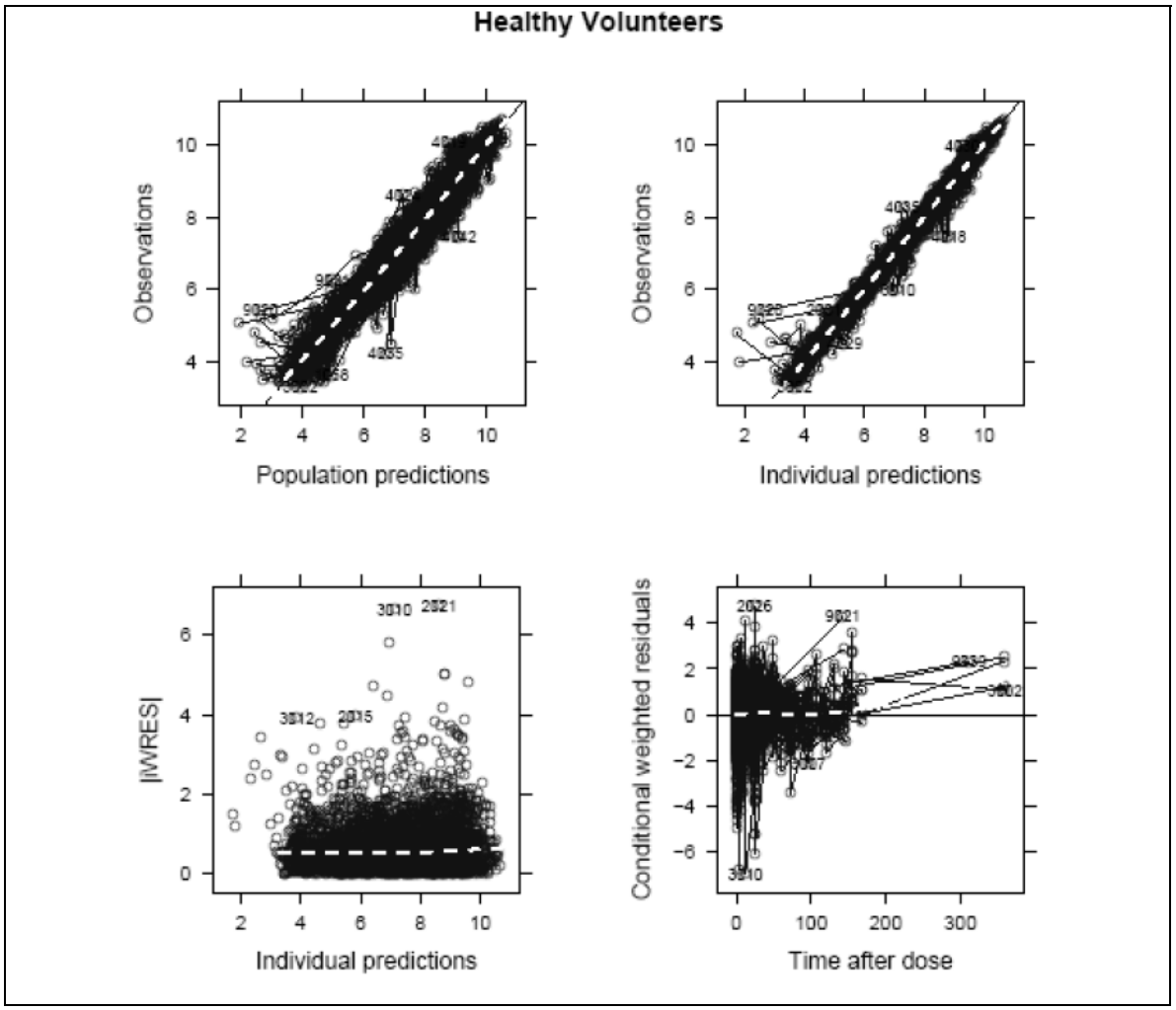
1. The population PK model can describe adequately the observed data for patients and HV (Figure 10).

2. Age, body weight, race (Caucasian vs Non-Caucasian) and gender has no meaningful effect on clearance. Age and body size has no meaningful effect on clearance. In the studied lean body weight range 33 to 83 kg, the AUCss is predicted to range from 67% to 134% of that of the typical patient of 49 kg. In the studied age range 18 to 73 years, the area under the curve at steady state for one dosing interval of 12 hours (AUCss) is predicted to range from 86% to 110% of that of the typical patient of 41 years.

3. The estimates of variance component ω2 for random effect were mistakenly reported as ω by sponsor (e.g., in Table 3). But this does not affect the validity of the aforementioned conclusions based on estimates of fixed effect.

Figure 10: Diagnostic plots for patients and HV





Source: sponsor's Population pharmacokinetics of subcutaneous pasireotide in healthy volunteers and in Cushing's disease patients Modeling Report, Page20, 21

4 REVIEWER'S ANALYSIS

4.1 Objectives

Analysis objectives are:

1. Exposure-response analysis for efficacy endpoints and explore other significant predictors for efficacy.
2. Exposure-response analysis for safety endpoints and explore other significant predictors for safety.

4.2 Methods

The exposure metric used in ER analysis was observed steady state pre-dose Cmin (or average Cmin) of each individual at a corresponding time of interest (e.g., Month 3 or 6).

The efficacy assessment was based on mean of urinary free Cortisol (mUFC) values. At baseline, months 3, 6 and 12 four 24-hour urine samples were collected. The results from the 4 samples per timepoint were averaged to obtain the baseline, Month 3, Month 6 and

Month 12 mean urinary free cortisol (mUFC) levels, respectively. The 4 urine samples were taken within 14 days of each other; these 14 days had to be within the last 21 days prior to start of study treatment at baseline and immediately prior to the visit at months 3, 6 and 12.

The primary efficacy variable was defined as the proportion of responders to pasireotide in each dose arm. A responder was defined as a patient who attained mUFC ≤ ULN (145 nmol/day) at Month 6 and whose dose was not increased relative to the randomized dose prior to Month 6. A controlled patient was defined as a patients who attained mUFC ≤ ULN (145 nmol/day) regardless of the dose escalation.

The safety endpoint in this ER analysis is the proportion of the patients who had post-baseline increase of more than 1% in HbA1C. The other safety endpoint is the proportion of patients who had abnormal liver function test.

4.2.1 Data Sets

Data from the pivotal trial (Study B2305) were used for this analysis to focus on risk/benefit profile under long term treatment (>2 months) in Cushing's disease patients.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
B2305	aeffvis.xpt	\\cdsesub1\EVSPROD\NDA200677\\0000\m5 \datasets\som230b2305\analysis\
B2305	jnpkef5.xpt	
B2305	apk.xpt	
B2305	agluc.xpt	
B2305	aeffsum.xpt	
B2305	alrs.xpt	

4.2.2 Software

SAS 9.2 and S-Plus 6.2 were used for analyses

4.2.3 Models

A multivariate logistic regression was conducted to assess the exposure-response relationship for efficacy and safety endpoints and identify the covariates that predict response. The following covariates were included in the analysis: baseline mUFC, baseline HbA1C, baseline ALT, prior medication, prior pituitary irradiation, prior pituitary surgery, gender, race, age, BMI.

4.3 Results

Patients with higher baseline mUFC tend to have more mUFC reduction compared to patients with lower baseline mUFC. As shown in **Figure 12**, there is no clear association between the pasireotide concentration and mUFC reduction (absolution change or

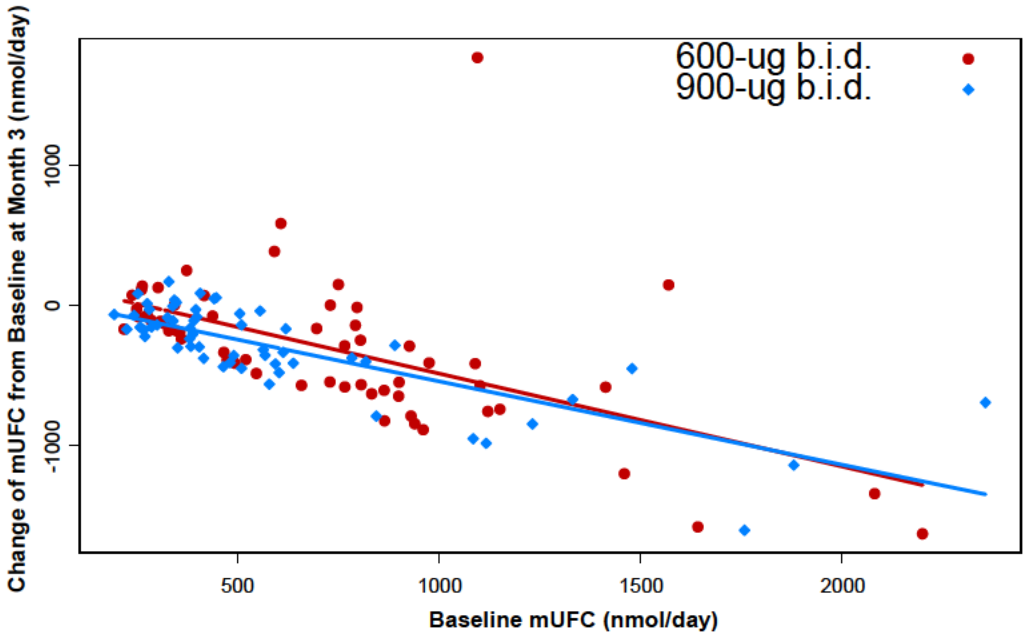
percentage change from baseline mUFC) at Month 3. Despite patients with higher baseline mUFC tend to have more mUFC reduction (Figure 11), such reduction is not sufficient to lower the mUFC below the ULN from high baseline mUFC. Results based on E-R analysis for efficacy using normalization of muFC (i.e., yes or no) as efficacy measure were discussed in Section 1.

Same conclusion was reached using other exposure metrics, such as trough concentration at the time of interest. Overall, results of exposure-response analysis using mUFC reduction (continuous outcome) and responder (binary outcome) as efficacy measure are consistent with each other, suggesting that higher exposure will not provide better efficacy benefit than lower exposure with respect to mUFC reduction or normalization of mUFC. Therefore, 900 ug b.i.d. dose is not expected to have better efficacy profile than 600 ug b.i.d. dose.

Results based on E-R analysis for safety using post-baseline hyperglycemia (i.e., >1% HbA1C increase from baseline) as safety measure were discussed in Section 1. In addition, no evident E-R relationship for ALT abnormality was identified (Figure 13).

To summarize, E-R analysis suggests that 600 ug b.i.d. dose should be recommended as initial dose for patients irrespective of diabetic status.

Figure 11: Change of mUFC at Month 3 by dose group



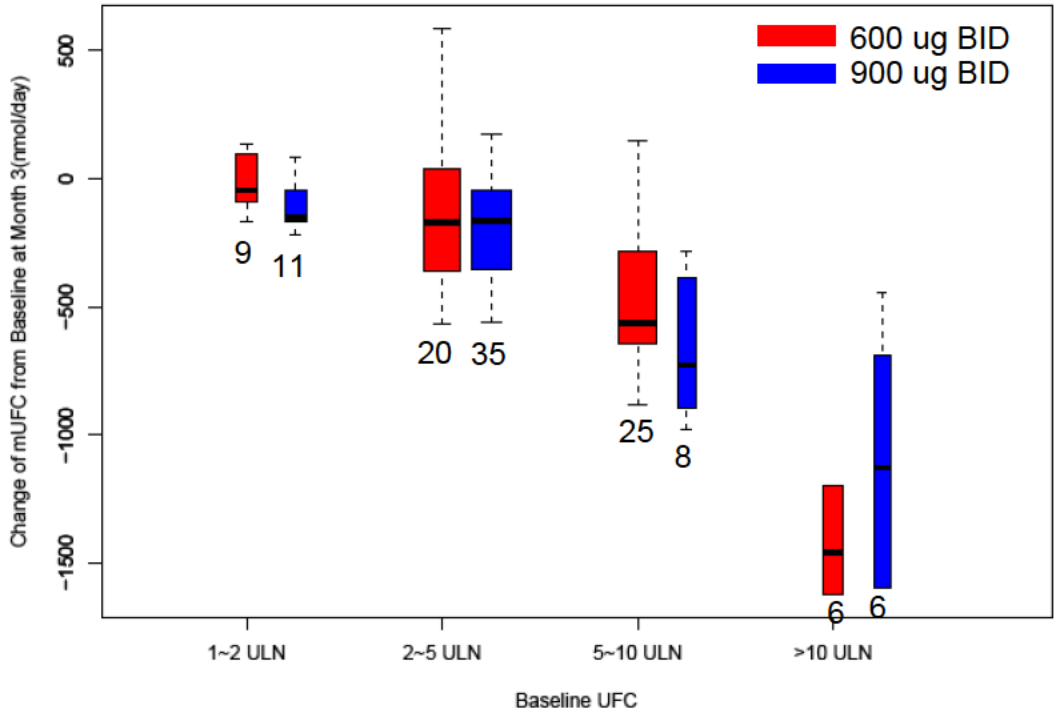


Figure 12: No Evident Relationship between Exposure and Reduction of mUFC

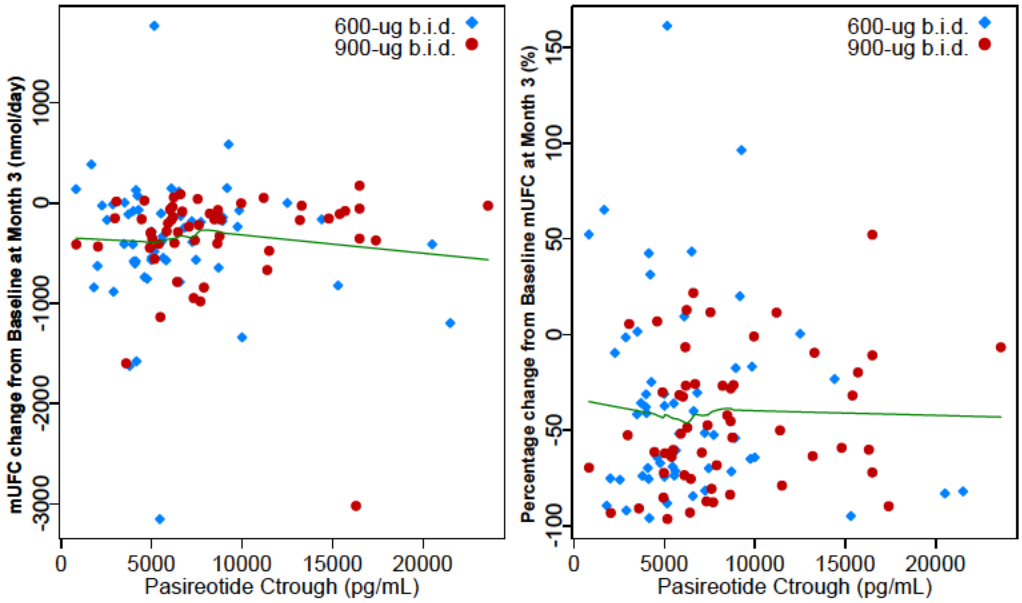
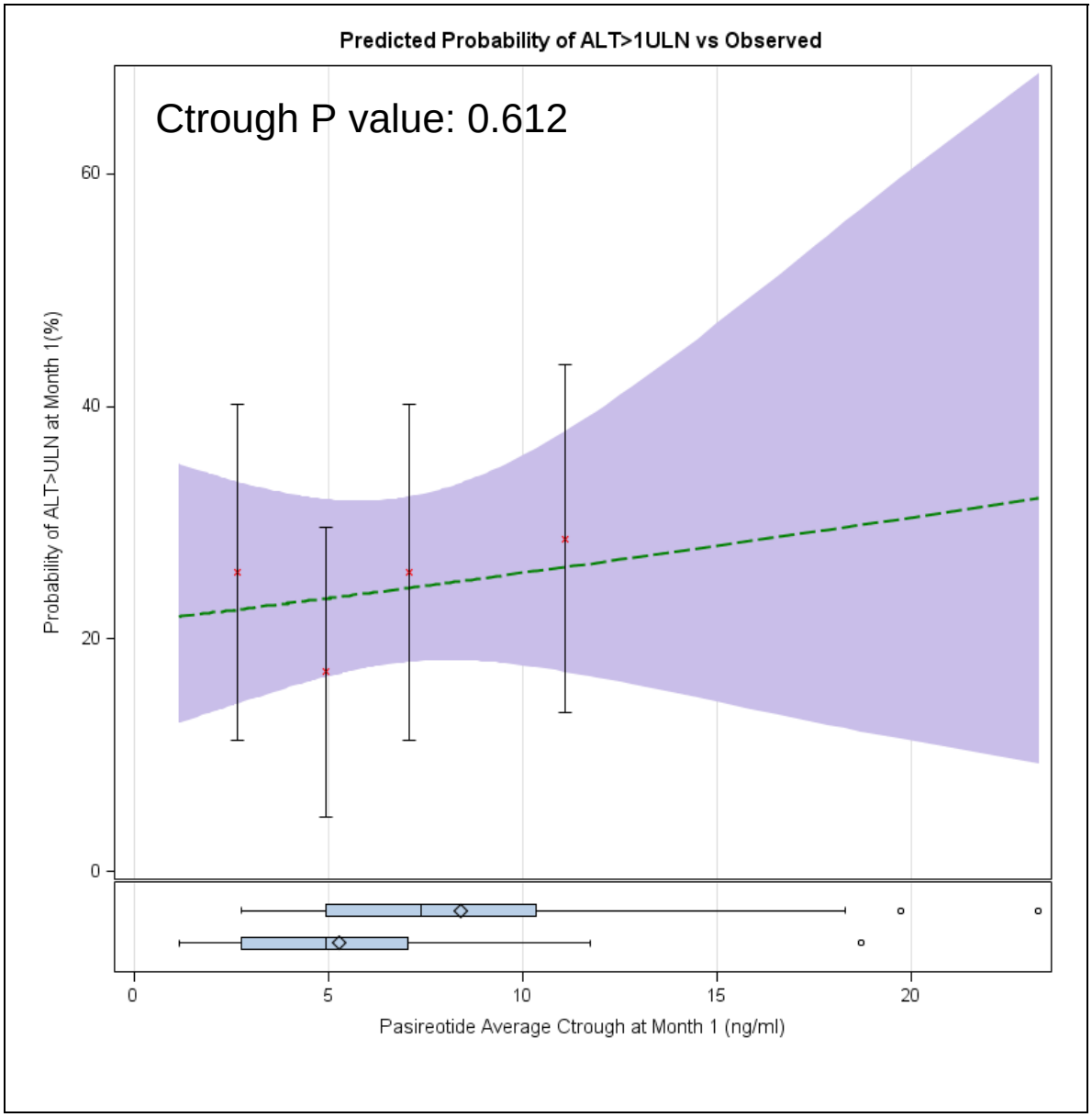


Figure 13: No Evident Relationship between Exposure and ALT Abnormality



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Efficacy2.ssc	E-R using mUFC as continuous measure	<\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pasireotide_ NDA200677_JYU\ER_Analyses>
ER_Primary_MeanConc90.sas	E-R using average Ctrough by Month 3	
ER_Primary_MeanConc180.sas	E-R using average Ctrough by Month 6	
ER_HbA1C.sas	E-R for HbA1C	
ER_Liver.sas	E-R for liver toxicity	
UFC.r	UFC reduction by dose and baseline mUFC	
ER_Explore.sas	Explore other factors affecting safety	

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

/s/

SANG M CHUNG
10/25/2012

JINGYU YU
10/25/2012

NITIN MEHROTRA
10/25/2012

IMMO ZADEZENSKY
10/25/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	200-677	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Date:	February 17, 2012		
Division:	DMEP	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Novartis		
Trade Name:	Signifor®	**Date Assigned:**	February 21, 2012
Generic Name:	Pasireotide	**Date of Review:**	October 10, 2012
Indication:	Treatment of patients with Cushing's disease	**Type of Submission:** Original New Drug Application, Resubmission/After Withdrawal	
Formulation/strengths	Injection/ 0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL		
Route of Administration	Subcutaneous		

SUBMISSION:

Pasireotide (Signifor®, SOM230), a somatostatin analog, is a peptide hormone commonly known as somatotropin release-inhibiting factor. Pasireotide solution for injection is an immediate-release dosage form for subcutaneous (s.c.) administration via the parentral route. The formulation is an aqueous solution containing the drug substance pasireotide diaspartate formulated in a buffer system. Pasireotide is intended for the treatment of Cushing's disease.

This NDA was originally submitted on 21-June-2011. On 19-August-2011, the Applicant withdrew the NDA due to manufacturing issues that would have led to a Refuse-to-File action. The Applicant proposed to resubmit the NDA with a revised drug product section to support the registration of the ampoule drug product and FDA agreed.

Pasireotide s.c. is an immediate-release dosage form. The proposed market formulation is a solution for injection in an ampoule. The Applicant is requesting approval of three dosage strengths 0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL supplied in glass ampoules for twice daily subcutaneous injection.

The Biopharmaceutics review will focus on the biowaiver for the 0.3 mg/mL.

BIOPHARMACEUTIC INFORMATION:

The pivotal Phase III study [B2305] supporting this submission is a randomized, double-blind study assessing the safety and efficacy of pasireotide s.c. 0.6 mg b.i.d. versus pasireotide s.c. 0.9 mg b.i.d over a total treatment period of 12 months, in patients with de novo, persistent or recurrent Cushing's disease. The Applicant stated that the composition of the product used in the pivotal study supporting this application is identical to the intended market form.

The composition of Pasireotide 0.3 mg, 0.6 mg and 0.9 mg solution for injection is provided in Table 1.

Table 1: Declared content of one ampoule of Pasireotide 0.3 mg, 0.6 mg and 0.9 mg solution for injection

Ingredient	Amount per ampoule (mg)			Function	Reference to standards
	0.3 mg	0.6 mg	0.9 mg		
Pasireotide diaspartate (SOM230 diaspartate)	0.3762 1	0.7524 2	1.1286 3	Active ingredient	Novartis
Mannitol	49.50	49.50	49.50	(b) (4)	Ph. Eur. / USP
Tartaric acid	1.501	1.501	1.501		Ph. Eur. / NF
Sodium hydroxide	ad pH 4.2	ad pH 4.2	ad pH 4.2		Ph. Eur. / NF
Water for injections / Water for injection	ad 1 ml	ad 1 ml	ad 1 ml		Ph. Eur. / USP
(b) (4)					

Note: Each ampoule contains an overfill of 0.1 ml to allow accurate administration of 1 ml from the ampoule.

1 corresponds to 0.3 mg Pasireotide free base (salt/base ratio: 1.254)

2 corresponds to 0.6 mg Pasireotide free base (salt/base ratio: 1.254)

3 corresponds to 0.9 mg Pasireotide free base (salt/base ratio: 1.254)

Reviewer's Note:

The 0.3 mg dosage strength is proportionally similar in its active and inactive ingredients to the strengths administered in the clinical study (0.6 and 0.9 mg/mL). Therefore, a biowaiver can be granted for the lower strength (0.3 mg/mL) because the drug product is proportional to the higher strengths and is a parentral solution intended solely for administration by injection.

RECOMMENDATION:

From the Biopharmaceutics viewpoint, NDA 200-677 for Pasireotide (Signifor®) s.c. Injection, 0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL, is recommended for APPROVAL.

Signature
Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: *NDA 200-677 DARRTS/ RLostritto*

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

/s/

HOUDA MAHAYNI
10/10/2012

ANGELICA DORANTES
10/10/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 200677**	**Brand Name**	**SIGNIFOR®**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Pasireotide**
Medical Division	**DMEP**	**Drug Class**	**Somatostatin analogue**
OCP Reviewer	**Zhihong Li**	**Indication(s)**	**Cushing's disease**
OCP Team Leader	**Jayabharathi Vaidyanathan**	**Dosage Form**	**Sterile solution for injection**
Pharmacometrics Reviewer	**TBD**	**Dosing Regimen**	**0.3, 0.6, and 0.9 mg/mL, BID**
Date of Submission	**6/21/2011**	**Route of Administration**	**S.C.**
Estimated Due Date of OCP Review	**2/17/2012**	**Sponsor**	**Novartis Pharmaceuticals, Inc.**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**4/21/2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		**ICPP(EU) R01-0742-01**
I. Clinical Pharmacology		**15**		**B2305, B2208, B2208E1. B2101, B2102, B2106, B2107, B2108, C2101, B2112, B2113, B2114, B2124, B2125, B2216.**
Mass balance:	**X**	**1**		**B2112**
Isozyme characterization:	**X**	**2**		**DMPK(CH) R01-389, DMPK R0400850**
Blood/plasma ratio:	**X**	**1**		**R99-2082**
Plasma protein binding:	**X**	**1**		**DMPK(CH) P99-2082**
Pharmacokinetics (e.g., Phase I) -	**X**	**13**		**B2305, B2208, B2208E1. B2101, B2102, B2106, B2108, C2101, B2112, B2113, B2114, B2124, B2125.**
Healthy Volunteers-		**12**		**B2101, B2102, B2106, B2107, B2108, C2101, B2112, B2113, B2114, B2124, B2125, B2216.**
single dose:	**X**	**5**		**B2101, B2106, C2101, B2112, B2114**
multiple dose:	**X**	**6**		**B2102, B2106, B2107, B2108, B2113, B2124, B2125, B2216**
Patients-		**3**		**B2305, B2208, B2208E1.**
single dose:		**0**		
multiple dose:	**X**	**3**		**B2305, B2208, B2208E1.**
Dose proportionality -	**X**	**5**		**B2101, B2106, C2101, B2102, B2113**
fasting / non-fasting single dose:	**X**	**3**		**B2101, B2106, C2101**
fasting / non-fasting multiple dose:	**X**	**3**		**B2106, B2102, B2113**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**		**B2114**
PD -	**X**	**5**		**B2101, B2102, B2113, B2125, B2216**
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**6**		**B2101, B2102, B2113, B2125. B2208, B2208E1.**
Phase 3 clinical trial:	**X**	**1**		**B2305**
Population Analyses -				
Data rich:	**X**	**1**		**Report: PopPKHV**
Data sparse:	**X**	**6**		**Report: PopPKCU1, PopPKCU2, PopPKCU3, PopPKUFC, PopPKGLU, PopPKPD**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**16**		**ICPP(EU) R01-0742-01. B2305, B2208, B2208E1. B2101, B2102, B2106, B2107, B2108, C2101, B2112, B2113, B2114, B2124, B2125, B2216.**

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Pediatric plan isn't submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

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

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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

None.

Zhihong Li, Ph.D.	8/011/2011
Reviewing Clinical Pharmacologist	Date
Jayabharathi Vaidyanathan, Ph.D.	8/011/2011
Team Leader/Supervisor	Date

RECOMMENDATIONS:

- This NDA application is fileable from a clinical pharmacology perspective
- No comments in the 74-day letter
- No DSI inspection needed for Clinical Pharmacology studies

BACKGROUND:

In accordance with 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 USC §355) and 21 CFR §314.50, Novartis Pharmaceuticals, Inc. has submitted this original New Drug Application (NDA 200677) for pasireotide injection for the treatment of Cushing's disease to be marketed under the proposed proprietary name SIGNIFOR®.

Pasireotide (SOM230), a novel somatostatin analog, is a peptide hormone commonly known as somatotropin release-inhibiting factor. It is supplied as a sterile solution in a single-dose, 1 mL pre-filled glass syringe containing pasireotide in 0.3 mg/mL, 0.6 mg/mL, or 0.9 mg/mL strengths for BID subcutaneous injection.

A total of 19 clinical studies including 15 clinical pharmacology studies or studies with clinical pharmacology components are submitted in the NDA database. The conducted clinical pharmacology studies meet the regulatory requirements for filing and this application is fileable from a clinical pharmacology perspective. The filing meeting was held on 8/09/2011.

The key clinical studies that contributed to safety and efficacy database in Cushing's disease include 3 studies, a Phase III pivotal study B2305, a Phase II POC study B2208 with its extension B2208E1. Given the rarity of Cushing's disease and the relatively small size of the pivotal study, additional safety data from 4 studies are presented for patients with acromegaly (Study B2103, Study B2201, and Study B2201E) and carcinoid syndrome (Study B2202).

Table 1 lists all Phase I, II, and III studies with PK, PD and PK/PD components.

Table 1: Summary of Phase I, II, and III studies with PK, PD and PK/PD analyses in healthy volunteers, subjects with varying degrees of hepatic impairment, and Cushing's disease patients

Study	Objectives	Dose	No. of subjects
Healthy volunteers			
[B2101].	Safety, tolerability, PK, PD	1, 2.5, 10, 30, 100, 200, 300, 600, 1200 µg single dose	72
[B2102].	Safety, tolerability, PK, PD	50, 200, 600 µg q.d. x 14 days	33
[B2106].	Safety, tolerability, PK	900, 1200, 1500 µg single dose 450, 600, 750 µg twice a day x 1 day	17
[B2107].	Safety, tolerability	150, 300, 600, 900, 1200, 1500 µg q.d. x 8 days 150, 300, 450, 600, 750 µg b.i.d, x 8 days	66
[B2108].	Safety, tolerability, PK	450, 900, 1350, 1800, 2025, 2250 µg/day continuous infusion x 7 days	44
[B2112].	ADME, PK, safety	600 µg single dose	4
[B2113].	Cardiac safety (QT/QTc), PK, PD	Part I: 900, 1200, 1500, 1800, 1950, 2100 µg b.i.d. x 5 days Part II: 1950 µg b.i.d. x 5 days	128
[B2124].	Blood glucose metabolism, safety, PK	600 µg b.i.d. x 7 days	90
[B2125].	Cardiac safety (QT/QTc), safety, PK	600 µg b.i.d. x 5 days 1950 µg b.i.d. x 5 days	112
[B2216].	Blood glucose, PD, safety	600, 900, 1200 µg b.i.d, x 8 days	45*
[C2101].	Safety, tolerability, PK	300 µg single dose	78
Subjects with varying degrees of hepatic impairment			
[B2114].	Hepatic impairment, PK, safety	600 µg single dose	34
Cushing's disease patients			
[B2208].	Efficacy, safety, PK, PD	600 µg b.i.d. x 15 days	39
[B2208E1].	Efficacy, safety, PK, PD	300-900 µg b.i.d.; dose titration allowed	19
[B2305].	Efficacy, safety, PK, PD	300, 600, 900, 1200 µg b.i.d.; dose titration allowed	162

q.d.: once daily; b.i.d.: twice a day; QTc: corrected QT interval

* Study B2216: Although 45 subjects had safety evaluations in all three dose groups, only 38 subjects in the 600µg and 900µg dose groups were included in the blood glucose and PD analyses.

Source: [SCP Table 2-1], [SCP Table 2-2].

Six studies (B2101, B2102, B2106, B2107, B2108, and C2101) are single dose and multiple dose safety, tolerability, PK and PD studies. One study (B2112) is a mass balance study. Two studies (B2113 and B2125) are TQT studies. Two studies (B2124 and B2216) are PD studies on blood glucose. One study (B2114) is a PK study in patients with hepatic impairment.

Following single-dose and multiple-dose s.c. administration of pasireotide in healthy volunteers, pasireotide showed rapid absorption (T_{max}: 0.25-0.5 hours), extensive distribution (Vz/F >100 L), and low clearance (CL ~6.7 L/hr). The AUC accumulation ratio of pasireotide to steady state was approximately 1.20-1.36 upon q.d. dosing for 14 days (Study B2102). Based on the AUC accumulation ratio, the calculated effective half-life ($t_{1/2,eff}$) for pasireotide was approximately 12 hrs.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

In Cushing's disease patients, pasireotide showed a lower clearance (CL ~3.8 L/hr) than that in healthy volunteers. The PK exposures in Cushing's disease patients were approximately 2-fold higher than those in healthy volunteers. The PK exposures were approximately dose-proportional in healthy volunteers and dose-proportional in Cushing's disease patients.

The mass balance study (B2112) showed that in humans, pasireotide was eliminated mainly as unchanged form in feces and urine; in the total radioactivity recovery (~56%, over a 10 day excreta collection period), most of the excretion was via the fecal route (~48%) with a minimal amount detected in urine (~8%).

PK study (B2114) from subjects with hepatic impairment (mild, moderate, and severe) showed that compared to subjects with normal hepatic function, pasireotide exposure (C_{max} and AUC) showed a moderate increase in patients with hepatic impairment, and the severity of hepatic impairment correlated with the extent of pasireotide exposure increase.

Study B2113 and Study B2125 are two TQT studies. Both studies showed that pasireotide prolonged QT and reduced heart rate (HR). In Study B2113, when given at supra-therapeutic doses of 1950 μg s.c. b.i.d., pasireotide showed a peak effect on QTcF prolonging at 2 hours post-dose with a 17.5 ms mean difference versus placebo (90%CI: 15.53; 19.38). Maximum change from baseline of HR reduction is 10.7 bpm. In Study B2125, the maximal placebo-subtracted change from baseline in QTcI is 13.19 ms (90% CI: 11.38; 15.01) for pasireotide 600 μg b.i.d., and 16.12 ms (90% CI: 14.30; 17.95) for pasireotide 1950 μg b.i.d. Both pasireotide doses decreased heart rate, with a maximal difference to placebo observed at 1 hour for pasireotide 600 μg b.i.d. (-10.39 bpm), and at 0.5 hours for pasireotide 1950 μg b.i.d. (-14.91 bpm).

Population PK/PD analysis indicated a trend in which urinary free cortisol (UFC) decreases with increasing pasireotide trough concentration and a positive correlation between pasireotide exposure and fasting plasma glucose levels in Cushing's disease patients.

The formulation used to characterize the safety and efficacy of pasireotide in the Phase III Study B2305 is solution for injection in ampoule, it is essentially identical to the intended marketing formulation pre-filled glass syringe except for the primary packaging. The sponsor requested biowaiver for the to-be-marketed formulation and bioequivalence (BE) study was not conducted to bridge these two formulations.

Pasireotide is proposed for s.c. administration and no food effect study was conducted.

Pasireotide is analyzed in human plasma using a radioimmunoassay (RIA), the mean inter-day accuracy for quality control samples was in the range of 82.8 - 95.2%. The overall precision was in the range of 6.1 - 20.1%.

In nonclinical studies, the distribution of pasireotide between blood cell and plasma showed that pasireotide was primarily located in the plasma component (91%), and distribution in blood was independent of concentration. The extent of plasma protein binding observed with pasireotide

was moderate (88%) and concentration-independent at therapeutic levels (i.e. < 0.05 μM) in Cushing's disease patients.

Pasireotide is highly metabolically stable. At therapeutic dose levels, pasireotide is not expected to be a substrate, inhibitor, or inducer of any major CYP450 enzymes; not a substrate of BCRP, OCT1, OATP1B1, OATP1B3 or OATP2B1. Pasireotide is likely to be a substrate of P-glycoprotein (P-gp), but P-gp may not play a significant role in the absorption, distribution or elimination of pasireotide.

Potential key clinical pharmacology review issues include:

- Exposure/dose-response analysis on primary efficacy endpoint (UFC) and selected safety endpoints (such as HbA1c) to support dosage in the general patient population and dose individualization in specific patient populations such as pre-diabetes/diabetes patients, patients with renal impairment, geriatric patients. Effect of other covariates (such as body weight, gender etc.) will also be explored
- PK in patients with hepatic impairment (dedicated study)
- PK, ADME, DDI and metabolic characterization
- QT analysis (consult QT-IRT)

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

/s/

ZHIHONG LI
08/17/2011

JAYABHARATHI VAIDYANATHAN
08/17/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 200-677 (000)	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DMEP		
Sponsor:	Novartis	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Signifor®	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Pasireotide	**Date Assigned:**	June 22, 2011
Indication:	Treatment of patients with Cushing's disease	**Date of Review:**	August 12, 2011
Formulation	Pre-filled syringe		
Route of Administration	Subcutaneous		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
June 21, 2011	June 21, 2011	June 22, 2011	December 21, 2011
Type of Submission:	Original NDA		
Type of Consult:	Biowaiver Request ---**FILING REVIEW**		

REVIEW SUMMARY:

Pasireotide (Signifor®, SOM230), a somatostatin analog, is a peptide hormone commonly known as somatotropin release-inhibiting factor. It is intended for the treatment of Cushing's disease.

Pasireotide solution for injection is an immediate-release dosage form for subcutaneous (s.c.) administration via the parenteral route. The sponsor seeks approval of three dosage strengths 0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL supplied in single dose pre-filled syringes for twice daily subcutaneous injection. The formulation is an aqueous solution containing the drug substance pasireotide diaspartate formulated in a buffer system.

The composition of Pasireotide 0.3 mg, 0.6 mg and 0.9 mg solution for injection is provided in Table 1 below.

Table 1: Declared content of one pre-filled syringe of Pasireotide 0.3 mg, 0.6 mg and 0.9 mg solution for injection

(b) (4)

The three dosage strengths (0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL) were used to characterize the efficacy and safety of pasireotide in the pivotal Phase III trial in cushing's disease patients. The composition of the product used in the pivotal study supporting this application is identical to the intended market form but they differ in primary packaging. The primary package of the clinical form was glass ampoules, while the one for the market form is a pre-filled glass syringe. The sponsor is requesting a biowaiver to conduct a bioequivalence study to link the pivotal study form and the intended market form because both forms are essentially identical with the exception of the primary packaging.

The biopharmaceutics review focuses on the biowaiver request.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 200-677(000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. There are no comments to be conveyed to the sponsor at this time.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200-677, ADorantes, JJohnson, KSharma, AAl Hakim, STran

---

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

/s/

HOUDA MAHAYNI
08/12/2011

PATRICK J MARROUM
08/12/2011