FDA BRIEFING DOCUMENT

NDA 200677

PASIREOTIDE INJECTION: 600 MCG, 900 MCG

SPONSOR: NOVARTIS PHARMACEUTICALS

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING

NOVEMBER 7, 2012

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 200677 (pasireotide) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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To: Endocrinologic and Metabolic Drugs Advisory Committee

Topic: Signifor (pasireotide for injection – NDA 200677)

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1. Role of medical therapy in Cushing's disease and history of drug approval for the Cushing's disease and Cushing's syndrome indications

Cushing's disease is the most common cause of endogenous hypercortisolism and accounts for as many as 70% of all cases of endogenous Cushing's syndrome. Caused mostly by histologically benign ACTH-secreting pituitary tumors, Cushing's disease has the potential of being cured by surgical interventions that remove successfully the entire tumoral tissue responsible for the excess ACTH secretion. In practice, however, even in the hands of the most experienced surgeons, remission rates do not exceed 65-90% for microadenomas, and are below 65% for macroadenomas. Even in patients who achieve clinical remission following surgical interventions, recurrence rates are not insignificant: for microadenomas 5-10% recurrence rates at 5 years and 10-20% at 6 years, and 12-45% recurrence rates for macroadenomas. Time to recurrence is also shorter for macroadenomas[1]. For patients with persistent hypercortisolemia following initial

[1] Biller et al: Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement. J Clin Endocrinol Metab 93:2454-2462, 2008.

surgery and for patients whose hypercortisolemia recurs after an initial remission, the therapeutic options include additional pituitary surgery (which generally has lower success rates unless a previously unidentified adenoma can be isolated and removed), radiotherapy, medical therapy and, as a last resort, bilateral adrenalectomy (a definite but drastic treatment of hypercortisolism).

Medical therapy is used as an initial intervention occasionally in situations where a patient cannot undergo surgery because of poor general health, if a tumor's growth is extensive making it unresectable, if pre-operative control of severe hypercortisolemia is necessary, or if a patient refuses surgery. In most cases, however, medical management of hypercortisolism in Cushing's disease is secondary or complements other interventions, such as surgery and radiotherapy. To date, clinical practice experience reflected in standard medical literature and medical textbooks lists three large groups of pharmaceutical products that have been used for the treatment of hypercortisolemia in Cushing's disease. Based on the site of drug action they include 1) agents that suppress ACTH release at the level of the pituitary, 2) steroidogenesis inhibitors that act primarily in the adrenal gland blocking intermediary steps in the synthesis of cortisol with a subsequent reduction in cortisol output, and 3) glucocorticoid receptor antagonists.[2] The latter compete with cortisol binding at the level of the glucocorticoid receptor and thus block the action of cortisol in target tissues. Despite the fact that clinical investigations have been conducted and reported with several drug products belonging to the above listed categories, until recently no drug products have been approved for the treatment of hypercortisolism in Cushing's syndrome or Cushing's disease (of note, other metabolic and clinical manifestations of Cushing's syndrome/disease such as hyperglycemia, hypertension, dyslipidemia are being treated routinely in clinical practice with drugs approved for the respective indications).

Mifepristone, a glucocorticoid receptor antagonist, is the first FDA-approved drug product for the treatment of hypercortisolemia in Cushing's syndrome. It was approved on February 17, 2012, under the trade name Korlym for the treatment of hypercortisolism in patients with Cushing's syndrome who have failed surgery or are not candidates for surgery and have concomitant manifestations of glucose intolerance or type 2 diabetes mellitus. It has been estimated that this indication applies to approximately half of all patients with overt endogenous Cushing's syndrome (and likely to a similar percentage of Cushing's disease patients). Use of Korlym in the management of Cushing's syndrome is challenging because the mechanism by which the drug targets the clinical manifestations of hypercortisolemia is through inhibition of the glucocorticoid receptor, not through a reduction in circulating cortisol levels. Consequently, serum or urine cortisol levels cannot be relied upon as a measure of response to treatment. Instead, response to Korlym relies heavily on improvement in clinical signs and symptoms of excess cortisol.

The Korlym program targeted control of hyperglycemia and hypertension as relevant clinical outcomes in the management of patients with Cushing's syndrome. The reason that the Korlym indication has been limited only to those Cushing's syndrome patients who manifest glucose metabolism abnormalities is based on the fact that, as designed, the

[2] Nieman LK: Medical Therapy of Cushing's Disease. Pituitary 5: 77-82, 2002.

Korlym phase 3 clinical program met the regulatory requirements of demonstrating substantial evidence of effectiveness only in this subgroup of patients. Specifically, the mean reduction in oral glucose concentrations measured during an oral glucose tolerance test (a co-primary efficacy analysis in the Korlym pivotal trial) and the mean hemoglobin A1c decrease of 1.1% (a secondary efficacy analysis) that were demonstrated with Korlym at the end of 6 months of treatment in patients with Cushing's syndrome were not accompanied by a demonstrable reduction in blood pressure, a co-primary efficacy endpoint.[3] This may be due to the elevated cortisol levels and binding of cortisol to the mineralocorticoid receptor resulting in clinical signs and symptoms of hyperaldosteronism (i.e., hypertension and severe hypokalemia). Despite its demonstrated efficacy on glycemic control, Korlym treatment remains a complex medical intervention that will require attentive medical care to monitor some of the safety findings observed in the phase 3 trial and currently labeled, which include, among others, adrenal insufficiency, hypokalemia, and unwanted pregnancy termination (the latter resulting in a boxed warning). To date, Korlym remains the only drug approved and labeled specifically for the treatment of hypercortisolism in Cushing's syndrome (and Cushing's disease for that matter).

2. Pasireotide for the treatment of Cushing's Disease

On February 17, 2012, the FDA received a new drug application (NDA) for Signifor (pasireotide injection) for the treatment of hypercortisolemia in patients with Cushing's disease. Pasireotide, the active ingredient in Signifor, is a new molecular entity. Chemically it is a cyclic nonapeptide; functionally it is somatostatin analog. The proposed indication for Signifor is the "treatment of patients with Cushing's disease who require medical therapeutic intervention". If approved, Signifor would be the second labeled drug to treat specifically hypercortisolemia.

Similar to the endogenous somatostatins (somatostatin-14 and somatostatin-28), pasireotide exerts its pharmacological activity via binding to somatostatin receptors (SSTRs). Pasireotide exhibits, however, a different pattern of receptor binding and different receptor affinities when compared to the currently marketed somatostatin (SST) analogs, lanreotide and octreotide. Lanreotide and octreotide bind primarily to SSTR2 and are currently approved for the medical treatment of acromegaly; octreotide is also approved for the treatment of severe diarrhea associated with carcinoid tumors and VIP-secreting tumors. Pasireotide binds to a broader range of receptors (SSTR 1, STTR2, STTR3 and SSTR5) and has particular affinity for SSTR5, which has been shown to be expressed, albeit somewhat variably, on tumoral corticotrophs. The broader binding profile of pasireotide and, in particular, its high affinity to SSTR5 constitute the basis for developing pasireotide for the treatment of Cushing's disease.

[3] Most recent Korlym label and reviews for Korlym's approval are available at the FDA website: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ after typing in Korlym.

The Phase 3 program consisted of a single "pivotal" study, Study B2305, which was a randomized, two-arm, two-dose (600 μg twice a day (bid) and 900 μg bid), uncontrolled clinical trial conducted in 182 patients with Cushing's disease. It is important to note that this trial was not powered to demonstrate statistically significant differences between doses, but rather to statistically analyze response rates within the 600 μg bid and 900 μg bid treatment groups, by comparing each group's percentage of patients whose urinary free cortisol (UFC) normalized at the end of 6 months of treatment with a pre-specified "threshold" of 15%. The magnitude of this threshold (in essence a non-inferiority margin) was selected on advice obtained from clinical endocrinologists who indicated that based on their clinical practice experience any response rate >15% would represent a clinical improvement in Cushing's disease. The 900 μg dose was shown to meet the primary efficacy criterion having a response rate of 26% and a lower bound of the two-sided 95% CI of 17% which exceeded the pre-specified 15% criterion. The 600 μg dose was not shown to meet the primary efficacy criterion. Several additional analyses of efficacy that will be presented in the clinical review section indicate that the response observed with the 900 μg bid dose regimen was only slightly better than that observed with the 600 μg bid dose regimen, and that the additional benefit was modest clinically and statistically non-significant. Such analyses include mean and individual UFC changes on treatment relative to baseline, several categorical analyses of UFC reduction, and correlations between the average daily dose and UFC changes. The totality of data seems to suggest that both the 600 μg bid and 900 μg bid doses are effective and that they are not far apart on the dose response curve.

Additional evidence of pasireotide's efficacy as medical treatment in Cushing's disease is provided by changes in plasma ACTH and serum cortisol concentrations, since both showed a decline that is consistent with the reduction in urinary free cortisol observed during trial B2305. There were also improvements in clinical signs and symptoms of Cushing's disease, in subjective evaluations of Cushing's disease manifestations, as well as reductions in systolic and diastolic blood pressure, although one needs to recognize that these findings took place in the context of an uncontrolled clinical trial, and the confounding contribution of factors other than treatment itself cannot be formally ruled out.

The above-described efficacy results need to be considered in the context of the overall safety profile observed in the pasireotide clinical program and, in particular, in the Phase 3 clinical trial. It is noteworthy that clinical use of pasireotide was associated with elevations of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3X upper limit of normal (ULN) in 5% of patients enrolled in Study 2305, and four cases of AST/ALT increases >2xULN accompanied by a simultaneous increase in total serum bilirubin were observed in healthy volunteers and in one patient treated in a compassionate use program. Due to the absence of a control arm and a comprehensive hepatological evaluation, the task of providing a clear etiological explanation is daunting. In addition, the Phase 3 program documented a remarkable elevation in mean serum glucose concentrations and HbA1c levels (approximately 1.5% mean absolute change on treatment relative to baseline) that occurred early during pasireotide treatment and continued throughout the duration of the trial. This finding is of particular concern as one

of the goals of treating Cushing's disease is to ameliorate the clinical signs and symptoms related to hypercortisolemia, with glucose impairment/diabetes and its long-term complications contributing to the overall morbidity of this condition. This magnitude of HbA1c change is out of proportion to what has been observed with other somatostatin analogs approved to date for non-Cushing's indications. While some other safety findings such as gastrointestinal adverse events (nausea, diarrhea, abdominal pain, cholelithiasis), prolongation of QT interval, and adrenal insufficiency could be addressed via adequate description in the product labeling, the liver findings and the diabetogenic effect of pasireotide merit further discussion at this advisory committee meeting. To this goal, the FDA package will include, in addition to this memorandum, the following:

- A joint clinical and statistical review focusing on the efficacy and safety findings of pasireotide treatment in the pivotal phase 3 clinical trial, with references to other relevant studies conducted in the pasireotide clinical program
- A pharmacometrics review discussing exposure-response analyses based on data obtained in the pivotal study.
- A review of the quality of life data and of the instrument used to generate this information.

While reviewing the advisory committee meeting materials, please consider the following topics for discussion and the draft voting question:

3. Draft Topics for Discussion by Panel

I. Efficacy

Determination of efficacy for the pasireotide clinical development program was based on a demonstration that the proportion of responders (patients with mUFC < ULN) within each dose group exceeded a pre-specified non-inferiority margin of 15%. Accordingly, only the 900 ug bid dose group was able meet this efficacy criterion. Recognizing that this was a stringent definition, additional exploratory analyses were performed including the proportion of patients with mUFC ≤ ULN or with ≥ 50% reduction from baseline and a longitudinal analysis of change from baseline in mUFC and the treatment difference between the two dose groups. The following tables summarize these analyses.

Percentage of Patients with mUFC ≤ ULN or ≥ 50% Reduction from Baseline at Month 6

Treatment	Pasireotide 600µg n=82	Pasireotide 900µg n=80	Total n=162
	n (%) [95% Confidence interval]		
Month 6 (LOCF)	28 (34%) [24%, 44%]	33 (41%) [30%, 52%]	61 (38%) [30%, 46%]
Month 6 (Observed)	24 (29%) [19%, 39%]	29 (36%) [26%, 47%]	53 (33%) [25%, 40%]

Longitudinal Analysis of mUFC % Change from Baseline

	Pasireotide 600 µg bid N=82		**Pasireotide 900 µg bid N=80**		Treatment difference (900 mcg – 600 mcg)		
Month	LSM % change	SE	LSM % change	SE	LSM % difference	SE	p-value *
1	-59	(14)	-61	(14)	-4	(20)	0.84
2	-49	(12)	-61	(12)	-24	(18)	0.09
3	-51	(11)	-60	(11)	-18	(16)	0.19
4	-54	(14)	-64	(14)	-23	(21)	0.17
5	-53	(12)	-62	(13)	-20	(18)	0.19
6	-52	(11)	-58	(12)	-12	(17)	0.40

*P-value determined from MMRM model log mUFC change from baseline as dependent variable with randomized dose and month as fixed effects and log(baseline mUFC) as a covariate

Please comment on the findings from these additional exploratory analyses and their clinical relevance to management of patients with Cushing's disease.

II. Safety

a. Liver

Several patients had elevations in hepatic transaminases with pronounced early rise in bilirubin levels. Four patients receiving pasireotide outside of the pivotal trial developed biochemical Hy's law (ALT or AST > 3xULN and bilirubin > 2xULN). Three of the subjects were healthy volunteers: one enrolled in the thorough QT study and two in a study that evaluated the effect of antidiabetic medications on pasireotide-induced hyperglycemia. The fourth subject was a patient with Cushing's disease enrolled in a compassionate use program. All patients recovered without serious sequelae.

Please comment on whether routine monitoring should be recommended with pasireotide treatment.

Please discuss whether any additional studies/data are necessary to investigate the hepatic risk of this drug in patients with Cushing's disease.

b. Dysglycemia

One of the goals of treating Cushing's disease is to improve the clinical signs and symptoms of hypercortisolemia. Diabetes is a known complication of hypercortisolemia. While treatment with pasireotide reduced cortisol levels, it also impaired insulin secretion resulting in dysglycemia and marked increases in HbA1c from baseline.

Please comment on this adverse effect of pasireotide and how it will impact the medical management of Cushing's disease.

Please discuss whether a patient's baseline glycemic profile should inform the physician regarding:

- choice of pasireotide in the management of Cushing's disease

- dose selection
- duration of use

Draft Topic of Discussion by the Panel

1. Based on the information presented today, do you believe the applicant has provided sufficient evidence that the efficacy of pasireotide outweighs the safety concerns?

- If yes, please provide the rationale for your vote and whether any additional studies should be conducted post-marketing.
- If no, please provide the rationale for your vote and what additional data will be necessary pre-marketing.

JOINT CLINICAL AND STATISTICAL REVIEW
SIGNIFOR (pasireotide injection)

NDA 20677

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1. Introduction

1.1 Drug substance and drug product

The drug substance in Signifor (pasireotide injection) is pasireotide, a cyclohexapeptide analog of endogenous somatostatin. Pasireotide is a new chemical entity. To date, it has not been approved in the US for any indication. Pharmacologically, pasireotide exerts its activity via binding to four of the five known somatostatin receptors (SSTR), specifically: SSTR1, SSTR2, SSTR3, and SSTR5. Pasireotide is different from the currently marketed somatostatin receptor analogs octreotide and lanreotide in the pattern of SST receptor binding and in the affinity that it has for individual SST receptors. Of particular clinical relevance is preferential binding of pasireotide to SSTR5 which displays a high level of expression in corticotroph tumor cells, being less sensitive to down-regulation by glucocorticoids when compared to other SST receptors such as SSTR2. The consequence of pasireotide binding to the various SST receptors on the surface of pituitary tumors is a reduction in ACTH pituitary output with subsequent decline in adrenal cortisol production and the expectation of improvement of the biochemical and clinical signs of hypercortisolism.

The Signifor drug product contains pasireotide as a diaspartate salt (MW= 1313.41 Daltons) formulated in mannitol a (tonicity agent), tartaric acid (a buffering agent), sodium hydroxide (used for pH adjustment), and sterile water. Signifor is supplied as a sterile solution in a 1 mL glass ampoule to be used as single-dose; there are three pasireotide strengths: 0.3 mg/mL, 0.6 mg/mL, or 0.9 mg/mL. An immediate-release product, Signifor is intended to be injected subcutaneously at doses between 0.3 mg and 0.9 mg twice a day.

1.2 Indication

Novartis is proposing the following indication for Signifor:

> Signifor is indicated for the treatment of patients with Cushing's disease who require medical therapeutic intervention.

Of note, due to the low prevalence of Cushing's disease, pasireotide was granted orphan drug designation in 2009 by the Office of Orphan Products Development.

1.3 Pasireotide Clinical Program

In addition to the Phase 2 and 3 trials (Table 1), the pasireotide clinical development program included 7 Phase 1 studies and 5 special safety clinical studies that contributed to the understanding of the safety profile of pasireotide, particularly its glycemic, hepatic, and cardiovascular effects. The safety profile was also assessed using data from trials of pasireotide in other indications. The comprehensive list of studies that contributed to the safety and efficacy profile are provided in Appendix 1.

The main components of the clinical program conducted in patients with Cushing's disease were a proof-of-concept Phase 2 study (Study B2208 followed by an extension, Study B2208E1) and one "pivotal" Phase 3 study (Study B2305). Table 1, below provides an overview of the Phase 2/3 program.

Table 1: Overview of Phase 2/3 Trials

Trial	Description	# of patients	Status
B2208 (proof-of-concept)	Phase II, 15, day, open-label, single-arm, non-randomized, multicenter study to assess the safety, efficacy and PK of 600 μg pasireotide administered s.c. bid in patients with Cushing's disease	39	Completed
B2208E1 (extension to proof-of-concept)	Open-label extension to B2208 that assessed long-term safety, efficacy, and PK	19	Ongoing
B2305 (Pivotal study)	A 12 month Phase III, double-blind, randomized, multi-center study of 2 dose levels (600μg and 900μg) in Cushing's disease patients to assess efficacy, safety, QoL, PK, and PK/PD relationship. Primary efficacy analysis done at Month 6.	162	Extension is ongoing

s.c.: subcutaneous; bid: twice daily; QoL: quality of life; PK: pharmacokinetic; PD: pharmacodynamic
Adapted from Applicant's Summary of Clinical Safety, Table 1-1

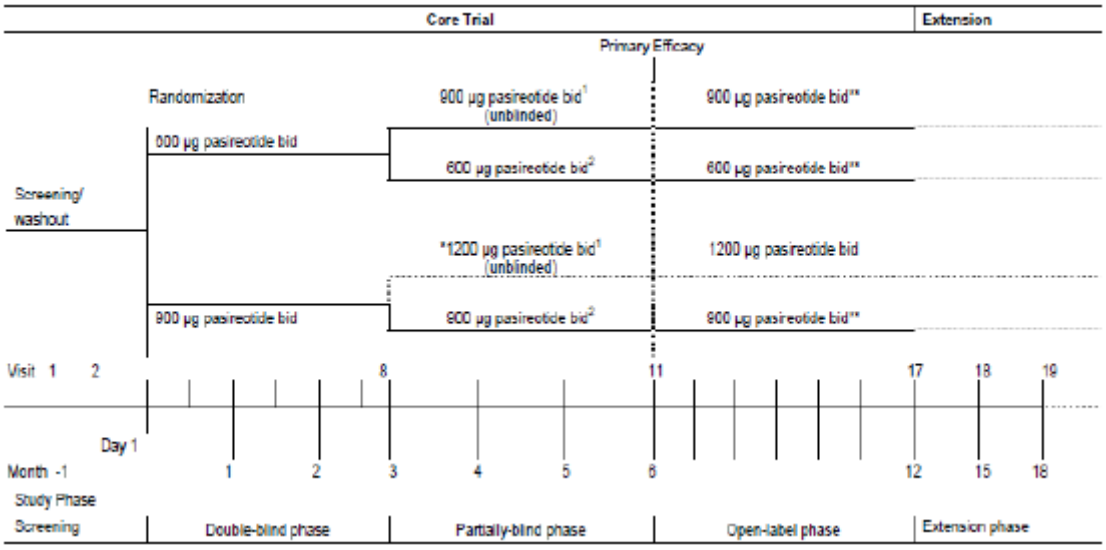
This briefing document will focus on the Phase 3 clinical program and will make references to other studies only as deemed necessary for the interpretation of the pivotal trial results, dose selection, and assessment of overall risk/benefit assessment.

1.3.1 Study B2305 – Trial Design and Patient Population

Pivotal study B2305 was a randomized, Phase III, 18-center, 6-month, double-blind, international clinical trial that assessed the safety and efficacy of two pasireotide dose regimens: 600 μg bid and 900 μg bid in patients with Cushing's disease. The study design is schematically represented in Figure 1, below. After a washout period from previous medical therapies for Cushing's disease, patients were randomized 1:1 to either 600 μg bid or 900 μg bid of pasireotide. At the Month 3 time point patients were allowed

to continue the same double-blind treatment as long as their mean urinary free cortisol[4] (mUFC) was reduced relative to baseline and, in addition, reached a level that was below twice the upper limit of normal (2 x ULN). Patients who did not meet these criteria were considered non-responders for the purpose of the primary efficacy analysis, were unblinded, and their doses increased by 300 µg bid to no more than 1200 µg bid daily; if they could not or did not undergo dose escalation they were discontinued from the trial. Patients who remained blinded continued treatment until Month 6 when they were unblinded and analyzed in the primary efficacy analysis. The primary efficacy analysis was a responder analysis, with a responder being defined as any subject who attained mUFC ≤ULN at the Month 6 time point and whose dose was not increased after Month 3. Any patient who completed 6 months of treatment was allowed participation in a 6-month open-label phase which could be further extended. During the open-label/extension phase patients were continued on the same dose or had their daily dosage further escalated to a maximum of 1200 µg bid in most sites, depending on their individual responses.[5] At any time during the trial, a subject's dose could be decreased for tolerability reasons.

Figure 1: Study Design for Study B2305



Applicant's Clinical Study Report

Study B2305 enrolled adult patients with Cushing's disease who demonstrated persistence of hypercortisolism despite prior pituitary resection or had recurrence of hypercortisolism after an initial favorable response to surgery. *De novo* Cushing's disease patients were allowed enrollment only if they were poor surgical candidates because of general bad health, if they had surgically unapproachable tumors, or if they refused surgery.

To support the diagnosis of Cushing's disease all patients had to have evidence of excess cortisol secretion (as evidenced by a baseline mean 24-hour urinary free cortisol at least

[4] Mean urinary free cortisol (mUFC) for each subject was calculated as an average of four 24 –hour samples per relevant timepoint: baseline; months 3, 6 and 12 (normal range was defined as 30-145 nmol/24 h). For Months 1,2,4,5, and 9 at least 2 collections were necessary.
[5] 900 µg bid at the Chinese sites.

1.5 times the upper limit of the laboratory normal range) and normal or above normal range morning plasma ACTH (≥ 5 ng/L). In addition to the required biochemical tests, the additional reports were required in the following individuals: 1) for patients with prior pituitary surgery, histopathology confirmation of an ACTH staining adenoma; 2) for patients with pituitary macroadenoma (pituitary tumor ≥ 1 cm), an MRI confirming the presence of the lesion; and 3) for patients with pituitary microadenoma (pituitary tumor < 1 cm), inferior petrosal sinus sampling (IPSS) with an inferior petrosal gradient for ACTH > 3 after corticotropin-releasing hormone (CRH) stimulation or > 2 if CRH stimulation was not performed.

Patients who received medical treatment for Cushing's disease prior to enrollment had to be washed out of such medications; wash out periods varied between drugs and depended on the half-life of each drug. Patients with evidence of glucose intolerance or diabetes mellitus were allowed enrollment as long as they were stable on diet and/or medication, but they were closely monitored with daily fasting blood glucose by fingerstick. Subjects with diabetes on antidiabetic drugs with an HbA1c over 8% were excluded. Criteria were in place for referral to a diabetes specialist for evidence of poor glycemic control.[6] Initiation or adjustment of antihyperglycemic medications was allowed as needed.

The trial protocol specified a long list of exclusion criteria that prevented enrollment of patients with other causes of hypercortisolism such as ectopic ACTH secretion, adrenal tumors or hyperplasia, or syndromes known to be associated with hormone over-secretion (Carney Complex, McCune-Albright, MEN-1). Also excluded were patients with several chronic and unstable conditions including but not limited to cardiac disease, chronic liver disease, QT prolongation syndromes/conditions, etc. Of note, patients who had received pituitary irradiation within the last ten years were excluded in order to avoid the potentially confounding effect of radiotherapy on efficacy analyses.

Although Study B2305 enrolled and randomized a total of 165 patients, three patients did not receive any study drug as they were screening failures. Of the remaining 162 randomized patients, 82 were in the 600 µg bid group and 80 in the 900 µg bid group. The stated primary objective of the trial was to assess the efficacy of pasireotide in the treatment of Cushing's disease in terms of independent response to pasireotide 600 µg s.c. bid and 900 µg s.c. bid (i.e. there was no prespecified comparison between the two dosing regimens). There were 14 secondary and exploratory analyses including, among others, assessments of UFC at different timepoints, measures of clinical improvement in signs and symptoms of Cushing's disease (including patient reported symptoms via a questionnaire), blood pressure changes, and assessments of pituitary tumor size via MRI scanning.

Mean UFC was calculated for each subject based on a number of 24-hour urine collections. The Protocol specified that at baseline, Months 3, 6, and 12 *at least three* 24-hour specimens were required for the mUFC calculation at each time point (the protocol required 4 collections for these timepoints). To compute mUFC for a subject at Months 1, 2, 4, 5, and 9, *at least two* 24-hour specimens were required.

[6] Any two consecutive HbA1c >8% or any single HbA1c>10%.

Safety assessments were mainly based on adverse events and standard chemistry and hematology laboratory measurements. Other important safety assessments included electrocardiograms, gallbladder ultrasounds, and vital signs.

1.3.2 Study B2305 –Baseline Characteristics, Patient Disposition, and Protocol Deviations

There were 162 randomized subjects in Study B2305. Of these, 55 subjects (34%) discontinued at or prior to Month 6. At Month 12 there were 48.1% of randomized subjects remaining in the trial.

Baseline characteristics

The following are the baseline demographic data of the randomized subjects (Table 2). Overall, characteristics were comparable between the 2 groups. The mean age at baseline was 40.2 years and the majority of subjects were female (77.8%) and Caucasian (78.4%). Very few black subjects (1.9%) were enrolled. There were very few patients over age 65.

Table 2: Baseline demographics by randomized dose group

	Pasireotide 600 µg bid N=82 n (%)	**Pasireotide 900 µg bid N=80 n (%)**	**Overall N=162 N (%)**
Age (years)			
Mean	40.5	39.9	40.2
SD	12.97	10.77	11.90
Median	39.0	41.0	93.0
Minimum, Maximum	18, 67	19,71	18, 71
Age			
<65 years	78 (95.1)	79 (98.8)	157 (96.9)
≥65 years	4 (4.9)	1 (1.3)	5 (3.1)
Sex			
Male	20 (24.4)	16 (20.0)	36 (22.2)
Female	62 (75.6)	64 (80.0)	126 (77.8)
Race			
Caucasian	65 (79.3)	62 (77.5)	127 (78.4)
Black	2 (2.4)	1 (1.3)	3 (1.9)
Asian	10 (12.2)	10 (12.5)	20 (12.3)
Native American	2 (2.4)	2 (2.5)	4 (2.5)
Other	3 (3.7)	4 (5.0)	7 (4.3)
Missing	0 (0.0)	1 (1.3)	1 (0.6)
Ethnicity			
Hispanic/Latino	29 (35.4)	22 (27.5)	51 (31.5)
Chinese	10 (12.2)	10 (12.5)	20 (12.3)
Mixed ethnicity	0 (0.0)	1 (1.3)	1 (0.6)
Other	43 (52.4)	46 (57.5)	89 (54.9)
Missing	0 (0.0)	1 (1.3)	1 (0.6)

Applicant's Clinical Study Report, Table 11-2

Table 3, below, summarizes disease characteristics for randomized subjects. With noted exceptions, characteristics were generally similar in the 2 groups. Of interest, there were obvious numerical differences in baseline mean UFC. Median UFC values differed as well: 730 nmol/24 hours and 487 nmol/24 hours for 600 µg and 900 µg, respectively. We assessed the statistical significance of the observed differences by comparing the baseline

mUFC values in the two groups using tests that accounted for the non-normality of the distributions. Baseline mUFC values were found to be not statistically different between the groups using the Wilcoxon test (p=.095) and an analysis of the log-transformed values (p=.10)

The majority of randomized subjects had persistent/recurrent disease and had prior surgery.

Table 3: Disease history and baseline characteristics by randomized dose group

	Pasireotide 600 µg bid N=82 n (%)	**Pasireotide 900 µg bid N=80 n (%)**	**Overall N=162 N (%)**
Time (months) to first pasireotide dose since diagnosis			
Mean	53.38 (63.79)	54.70 (62.79)	54.03 (63.11)
Median	35.48	29.70	33.99
Minimum, maximum	0.10-341.78	0.10-372.14	0.10-372.14
Cushing's Disease Status n (%)			
De novo	15 (18.3)	12 (15.0)	27 (16.7)
Persistent/recurrent	67 (81.7)	68 (85.0)	135 (83.3)
Any previous surgery			
No	18 (22.0)	16 (20.0)	34 (21.0)
Yes	62 (78.0)	64 (80.0)	128 (79.0)
Any previous pituitary irradiation n (%)			
No	79 (96.3)	76 (95.0)	155 (95.7)
Yes	3 (3.7)	4 (5.0)	7 (4.3)
Any previous medication n (%)			
No	45 (56.1)	38 (47.5)	84 (51.9)
Yes	36 (43.9)	42 (52.5)	78 (48.1)
Baseline mean UFC			
n	77	76	153
Mean (SD)	1156 (2630)	782 (926)	970 (1979)0)
Median	730	487	564.5
Minimum, maximum	219.50-22943.75	195.00-6122.75	195.00-22943.75

Applicant's Clinical Study Report, Table 11-3

The most common class of medications taken prior to starting study drug was thyroid hormones (24.4% in the 600 µg group and 31.3% in the 900 µg group). The use of antihyperglycemic medications at baseline (doses not recorded for the trial) was more frequent in the 600 µg group (24.4%) compared to the 900 µg group (16.3%).

Because trial B2305 allowed enrollment of patients with Cushing's disease who had an average baseline 24 hour urinary free cortisol > 1.5xULN, patients could be enrolled in the trial with a wide range of mUFC values, some relatively close to the upper limit of normal and some remarkably high (e.g. > 10X ULN). As such, normalization of UFC (the goal of treatment and the focus of the primary efficacy analysis) could be achieved with relatively small cortisol reductions for some patients and with significant reductions for others, depending on the specific baseline urinary cortisol level. Therefore, in order to understand the full range of efficacy changes, it is particularly important to understand the distribution of 24 hour urine cortisol values at baseline. Table 4, below, indicates that, while 41% of patients had a baseline mUFC in the > 2xULN to ≤ 5xULN range, a

sizeable proportion (38%) also had mUFC > 5xULN, and a smaller proportion (16%) had baseline levels between 1.5 and 2X ULN. When comparing the two randomization groups, a larger proportion of patients in the 600 µg bid group had mUFC > 5XULN (48% vs 28%), which may have contributed to the numerical imbalance in baseline mUFC levels between the 600 µg and the 900 µg arms.

Table 4: Number and percentage of enrolled subjects by baseline mUFC

Baseline mUFC category	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
> ULN to ≤ 2xULN	12 (14.6)	14 (17.5)	26 (16.0)
> 2xULN to ≤ 5xULN	26 (31.7)	40 (50.0)	66 (40.7)
> 5xULN to ≤ 10xULN	28 (34.1)	13 (16.3)	41 (25.3)
> 10xULN	11 (13.4)	9 (11.3)	20 (12.3)
Missing*	5 (6.1)	4 (5.0)	9 (5.6)

From Sponsor's Response to Information Request, Table 2-1

*Although these 9 subjects were considered to have "missing" baseline mUFC values in this table because they did not have the required 3 baseline 24 UFC urine collections, they were used in the primary efficacy analysis because they had two 24 hour urine collections in addition to other evidence supporting the diagnosis of Cushing's disease.

Patient Disposition

The following table summarizes patient disposition for Study B2305. At or prior to Month 6 (time point for primary efficacy analysis), a total of 55 subjects (34%) discontinued the trial. A total of 78 subjects (48.1%) completed the core study (Month 12).

Table 5: Subject disposition by randomized dose group

	Pasireotide 600 µg bid N=83 n (%)	Pasireotide 900 µg bid N=82 n (%)	Overall N=165 n (%)
Randomized	83 (100.0)	82 (100.0)	165 (100.0)
Randomized but not treated*	1 (1.2)	2 (2.4)	3 (1.8)
Randomized and treated	82 (98.8)	80 (97.6)	162 (98.2)
Discontinued at any time[#]	49 (59.8)	48 (60.0)	97 (59.9)
Reason for discontinuation			
Adverse event	13 (15.9)	15 (18.8)	28 (17.3)
Unsatisfactory therapeutic intervention	19 (23.2)	22 (27.5)	41 (25.3)
Subject withdrew consent	13 (15.9)	11 (13.8)	24 (14.8)
Protocol deviation	4 (4.9)	0	4 (2.5)
Discontinued at or prior to Month 3	14 (17.1)	15 (18.8)	29 (17.9)
Discontinued at or prior to Month 6	28 (34.1)	27 (33.8)	55 (34.0)
Reason for discontinuation			
Adverse event	9 (11.0)	11 (13.8)	20 (12.4)
Unsatisfactory therapeutic intervention	9 (11.0)	10 (12.5)	19 (11.7)
Subject withdrew consent	7 (8.5)	6 (7.5)	13 (8.0)
Protocol deviation	3 (3.7)	0	3 (1.9)
Discontinued between Month 6 and Month 12	15 (18.3)	14 (17.5)	29 (17.9)
Completed Month 12	39 (47.6)	39 (48.8)	78 (48.1)

*Three subjects were screening failures but investigator mistakenly chose the IVRS randomization option.
[#]Subjects who completed Month 12 and did not enter extension phase are not counted as discontinuations
From Applicant's Clinical Study Report Tables 10-1 and 14.1-1.3a

Adverse events and unsatisfactory therapeutic effect were the most common reasons for discontinuation. Discontinuations due to "unsatisfactory therapeutic response" were due to protocol-specific criteria (lack of efficacy, disease progression) in 25 of 41 subjects.

Protocol Deviations

The numbers of protocol deviations were similar in both dose groups. At Month 6, 58.5% and 57.5% of subjects in the 600 μg and 900 μg groups, respectively, had at least one protocol deviation. Most protocol deviations were not major and did not lead to discontinuation from the trial.

1.3.3 Statistical Analysis Plan

Primary efficacy analysis

In Study B2305, the pre-specified primary efficacy endpoint was the proportion of responders at Month 6 by individual dose group (pasireotide 600 μg s.c. bid or 900 μg s.c. bid) in the Full Analysis Set (FAS) consisting of all randomized patients who received at least one dose of pasireotide.

A responder was defined as a patient who had a mUFC ≤ upper limit of normal (ULN equal to 145 nmol/day) at Month 6 and whose dose was not increased prior to Month 6. Patients who discontinued before Month 3 were classified as non-responders in the primary efficacy analysis. For patients discontinued at or after Month 3 and before Month 6, the last available mUFC (at least 3 samples) was carried forward to Month 6 for the primary efficacy analysis.

Estimated response rates and corresponding 95% confidence intervals (based on the normal approximation to the binomial distribution) were to be summarized by treatment group. A dose was considered to be effective in lowering mUFC if the lower bound of the 95% CI exceeded the pre-specified 15% non-inferiority margin. The 15% threshold was agreed between the Division and the Applicant during the planning stages of the study as a proportion of patients who, if treated successfully, would demonstrate evidence of clinical benefit.

There was no plan to formally test for statistical differences in mUFC between dose groups. The Applicant did not perform sample size or power calculations for the purpose of comparing the dose groups. According to the protocol, differences between the two groups were to be assessed solely by frequencies and descriptive statistics.

The Hochberg sequential step-down procedure was to be used initially to control type 1 error for testing across the two doses. In protocol Amendment 6, the sponsor removed the Hochberg procedure in favor of nominal statistical tests and 95% CIs for each dose. The Agency has presented results for both 95% and 97.5% CIs, the latter for the purpose of controlling type 1 error across the two doses (see below).

Longitudinal analysis of mUFC

The applicant pre-specified a mixed model repeated measures (MMRM) statistical model for the purpose of analyzing mUFC as a continuous variable. The MMRM model used

mUFC change from baseline on the natural log scale as the dependent variable with randomized dose and month as fixed effects and log(baseline mUFC) as a covariate.

2. Review of Efficacy

2.1 Primary efficacy analysis

Table 6 below gives results for the primary efficacy endpoint. The Applicant's results shown match those performed by the Agency. The 900 µg dose met the primary efficacy criterion (lower bound of the two-sided 95% CI equal to 17% and greater than the non-inferiority margin of 15%) but the 600 µg dose did not. The 900 µg dose also satisfied the 15% non-inferiority margin when a 97.5% CI was used to assess efficacy. As stated previously, the larger CI was used for the purpose of controlling type 1 error across the two doses.

Table 6: Primary efficacy analysis (Month 6)

Treatment	Pasireotide 600µg n=82	Pasireotide 900µg n=80	Total n=162
n/N (%) patients with mUFC ≤ ULN	12/82 (15%)	21/80 (26%)	33/162 (20%)
[95% CI] Sponsor's analysis	[7%, 22%]	[17%, 36%]	[14%, 27%]
[97.5% CI] FDA analysis		[16%, 39%]	

FDA also conducted logistic regression analyses of the primary endpoint. The purpose of these supportive analyses was to directly compare the efficacy of the two doses and also to potentially incorporate adjustment for observed baseline imbalances in mUFC. The logistic model was used to estimate the odds ratio (OR), one analysis with adjustment for baseline ("adjusted model") and the other without ("unadjusted model"). As noted previously, baseline mUFC values were not statistically different between the groups ($p>.05$). We adjusted for baseline anyway because this is routinely done in analyses of clinical trial data, and the analysis adjusting for baseline could be compared with the unadjusted analysis. The results are shown in Table 7 below. The unadjusted model showed a statistical trend for dose response (OR=2.1, p=0.07). By comparison, the adjusted model resulted in a slightly lower OR and did not show a statistical trend (OR=1.9, p=0.13). However, the reduction in OR using the adjusted model (in the direction of equality) was small indicating that baseline adjustment had only a modest impact on the comparative efficacy in the two groups.

Table 7: Logistic Regression Analyses of Primary Endpoint at Month 6

Treatment	Pasireotide 600µg n=82	Pasireotide 900µg n=80	Odds Ratio (OR) [95% CI]
# of responders/n (%)	12/82 (15%)	21/80 (26%)	
Odds using unadjusted model [95% CI]	0.17 [0.09, 0.32]	0.36 [0.22, 0.59]	2.1 [0.94, 4.57] p=0.07
Odds using adjusted model with covariate log(baseline mUFC) [95% CI]	0.16 [0.09, 0.31]	0.30 [0.18, 0.52]	1.9 [0.83, 4.16] p=0.13

From Statistical Reviewer Lee Ping Pian

The assessment of the primary efficacy endpoint is dependent on reliable, multiple measurements of cortisol obtained from 24 hour urine collections. Although sensitivity and specificity for the 24 hour urine collection for urinary free cortisol are high, such collections are fraught with potential difficulty leading to error and falsely low UFC values. In order to confirm completeness of a 24 hour collection, 24 hour urine volume and creatinine were measured as well. There were 2 subjects, both in the 900 µg group, who had extremely low 24 hour urine creatinine values at Month 6 and were considered responders at the primary efficacy endpoint. A responder analysis was done excluding the 2 subjects with insufficient urine collections. This analysis did not widely differ than the analysis that included these subjects, indicating that the overall efficacy results were not impacted by these two subjects.

2.2 Exploratory analysis using alternate definition of responder

Given the stringent threshold required to meet the primary efficacy endpoint (normalization of mUFC) and the possibility that some patients who started with very high mUFC values at baseline may have important changes in mUFC even if they did not achieve normalization, we conducted a post-hoc categorical analysis, using an alternate and less restrictive definition of responder compared to the pre-specified primary efficacy endpoint (Table 8). Here, a responder is defined as a patient with mUFC ≤ ULN or ≥ 50% reduction from baseline. Clearly, with this definition, a higher percentage of subjects are considered responders. As many as 34% patients in the 600 µg bid and 41% in the 900 µg bid groups met this new criterion of efficacy at Month 6 (LOCF).

Table 8: Percentage of subjects with mUFC ≤ ULN or ≥ 50% reduction from baseline at Month 6

Treatment	Pasireotide 600µg n=82	Pasireotide 900µg n=80	Total n=162
	n (%) [95% Confidence interval]		
Month 6 (LOCF)	28 (34%) [24%, 44%]	33 (41%) [30%, 52%]	61 (38%) [30%, 46%]
Month 6 (Observed)	24 (29%) [19%, 39%]	29 (36%) [26%, 47%]	53 (33%) [25%, 40%]

2.3 Additional efficacy analyses of changes in mUFC

2.31 Changes in mUFC over time by randomization group

The following table summarizes descriptive statistics for mUFC at baseline and subsequent time points. The data are presented for all patients on trial with a mUFC calculated from at least 3 measurements per timepoint unless otherwise specified. Standard deviations for all values are very large, but clearly mean UFC values decreased in both dose groups.

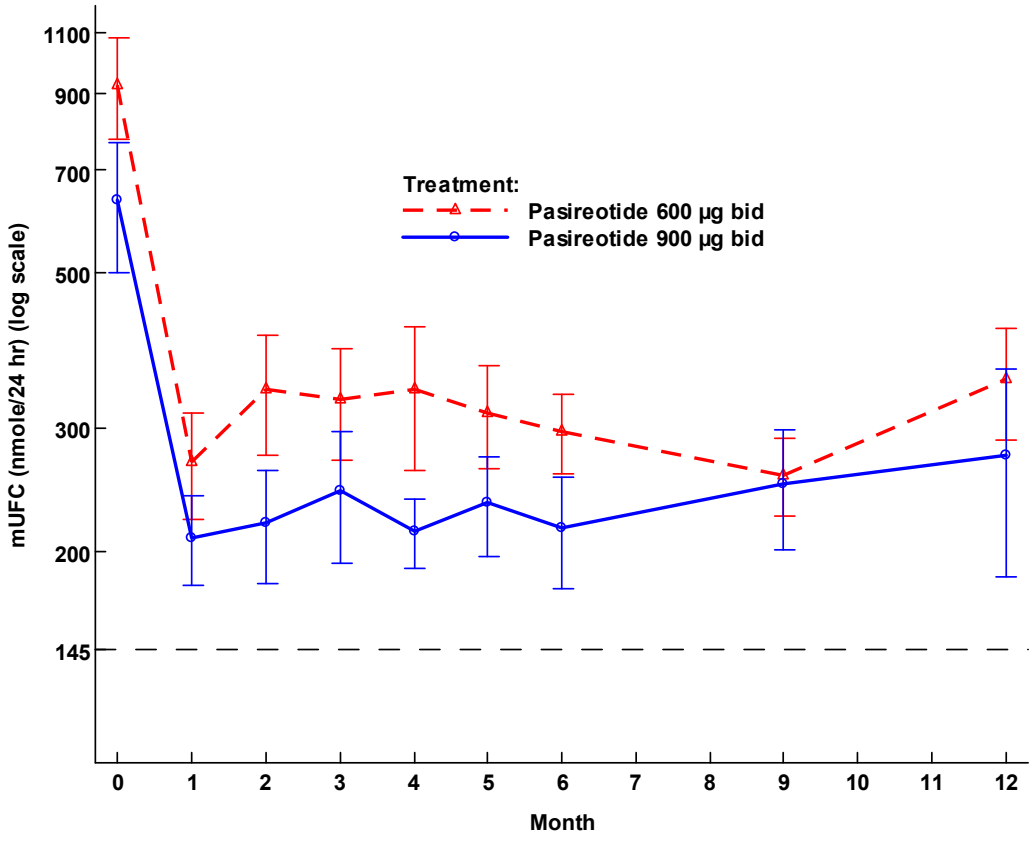
Table 9: Descriptive statistics for mUFC Values by Randomization Group through Month 6

Variable	SOM230 600µg				SOM230 900µg			
	N	**Mean**	**SD**	**Median**	**N**	**Mean**	**SD**	**Median**
mUFC at baseline	77	1156	(2630)	730	76	782	(926)	487
mUFC at Month 3	65	454	(489)	265	66	388	(667)	231
mUFC at Month 6	56	366	(330)	254	55	379	(753)	210
mUFC at Month 6 with LOCF*	69	461	(487)	280	67	381	(686)	270
Last mUFC for at least 2 samples**	78	503	(559)	288	76	427	(691)	227

*Mean UFC at month 6 with Last Observation Carried Forward (LOCF) applied. Mean UFC is only carried forward if it is between (and including) Month 3 and Month 6 and is calculated from a minimum of 3 samples.
** Last post-baseline mean UFC with at least 2 samples

The figure below depicts longitudinal changes in mUFC through Month 12 for Month 12 completers (39 subjects per treatment group). It is important noting that mUFC reduction is already seen by the Month 1 timepoint.

Figure 2: Mean (±SE) Urinary Free Cortisol (nmol/24h) at all Time Points up to Month 12 by Randomized Dose Group (Completers, n=39/group)



The longitudinal analysis below shows the percent changes in mUFC and treatment difference at various time points.

Table 10: Longitudinal analysis of mUFC % change from baseline

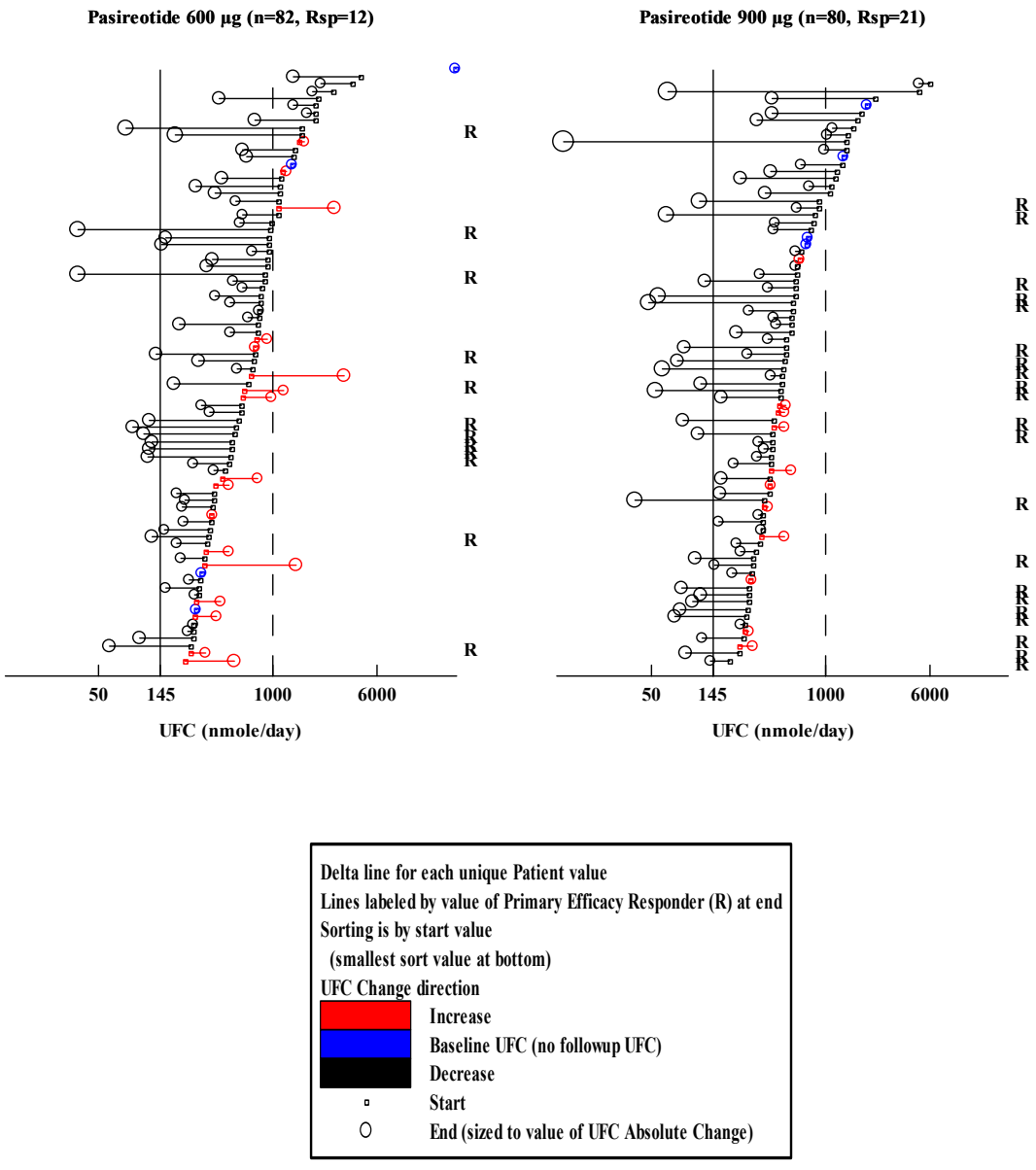
	Pasireotide 600 µg bid N=82		Pasireotide 900 µg bid N=80		Treatment difference (900 mcg – 600 mcg)		
Month	LSM % change	SE	LSM % change	SE	LSM % difference	SE	p-value *
1	-59	(14)	-61	(14)	-4	(20)	0.84
2	-49	(12)	-61	(12)	-24	(18)	0.09
3	-51	(11)	-60	(11)	-18	(16)	0.19
4	-54	(14)	-64	(14)	-23	(21)	0.17
5	-53	(12)	-62	(13)	-20	(18)	0.19
6	-52	(11)	-58	(12)	-12	(17)	0.40

*P-value determined from MMRM model log mUFC change from baseline as dependent variable with randomized dose and month as fixed effects and log(baseline mUFC) as a covariate

2.32 Individual UFC changes

Individual changes in mUFC from baseline are presented by randomized group in the figure below. Red lines represent increases from baseline, black lines (noticeable for the vast majority of patients) represent reductions. The upper limit of normal for urinary free cortisol (145 nmol/day) is indicated. In this graph individual values were calculated from a minimum of 2 measurements. Patients labeled with R are primary efficacy responders at Month 6.

Figure 3: Individual UFC Changes from baseline to Month 6 (LOCF, FAS) in Study 2305



2.33 Categorical efficacy analyses

The table below displays percentages of the primary efficacy responders by the following baseline mUFC categories (subjects with a minimum of 2 samples): 1-2 x ULN, 2-5 x ULN, 5-10 x ULN and >10 x ULN. The highest percentages of responders were in lower baseline UFC categories. There was only one responder in the highest baseline UFC category.

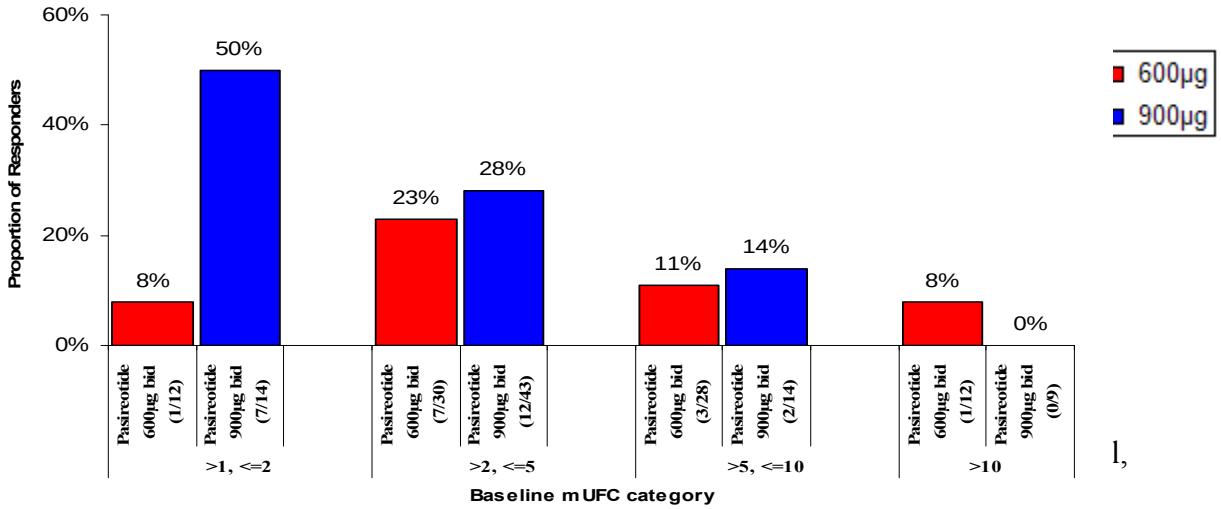
Table 11: Percentages of mUFC primary responders at Month 6 by baseline mUFC category (at least 2 samples) - FAS

Baseline UFC category	n/N (%) (CI*)	Pasireotide 600 µg bid (N=82)	Pasireotide 900 µg bid (N=80)	Overall N=162
> 1xULN to ≤2xULN	n/N (%)	1/ 12 (8%)	7/ 14 (50%)	8/ 26 (31%)
	95% CI	(0.2%, 38%)	(23%, 77%)	(14%, 52%)
> 2xULN to ≤5xULN	n/N (%)	7/ 30 (23%)	12/ 43 (28%)	19/ 73 (26%)
	95% CI	(9.9%, 42%)	(15%, 44%)	(16%, 38%)
> 5xULN to ≤10xULN	n/N (%)	3/ 28 (11%)	2/ 14 (14%)	5/ 42 (12%)
	95% CI	(2.3%, 28%)	(1.8%, 43%)	(4%, 26%)
> 10xULN	n/N (%)	1/ 12 (8%)	0/ 9 (0.0%)	1/ 21 (5%)
	95% CI	(0.2%, 38%)	-	(0.1%, 24%)

*95% CI from exact method

The figure below is a graphical display of the data shown in the table above.

Figure 4: Percentages of mUFC primary responders by baseline mUFC category.



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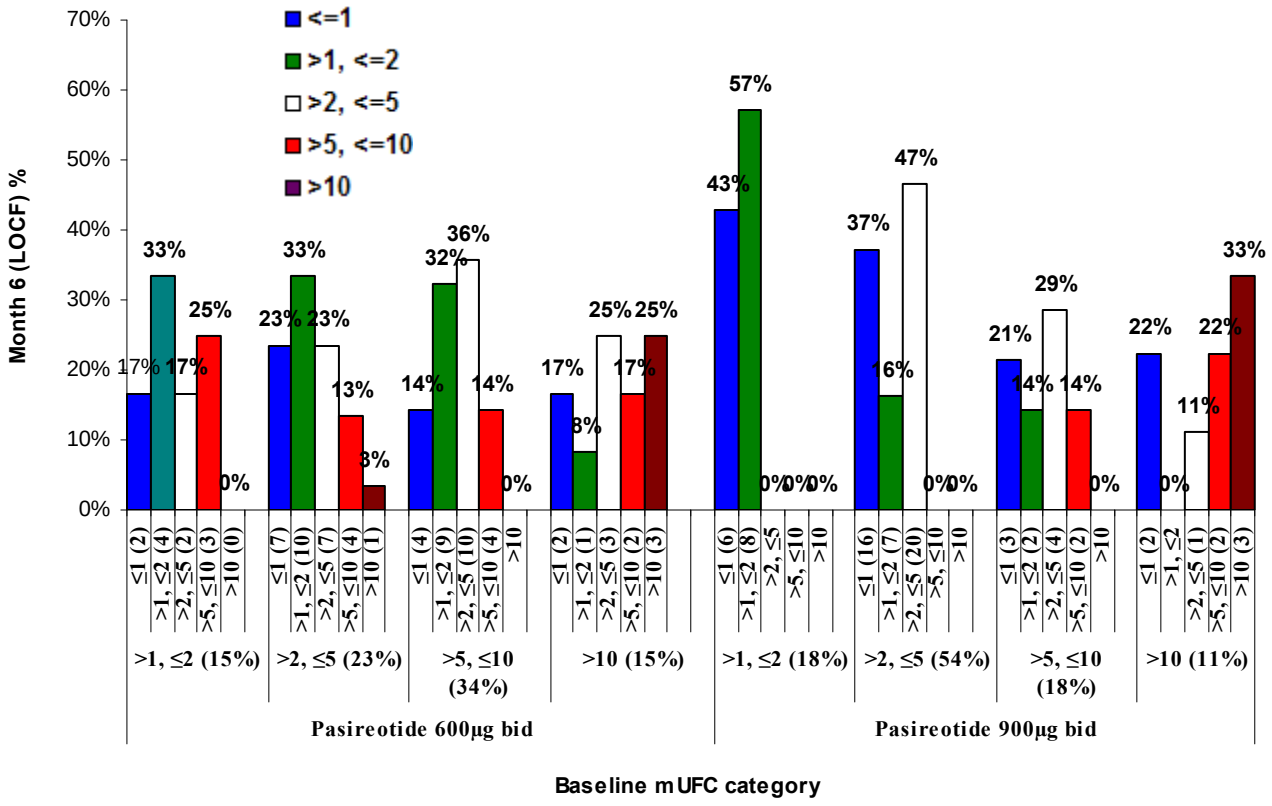
The table below presents shifts on treatment from baseline mUFC categories.

Table 12: Shifts on treatment from baseline UFC categories (1-2, 2-5, 5-10, > 10 ULN) by group – LOCF to Month 6

Baseline mUFC category	Pasireotide 600 µg bid (N=82)							Pasireotide 900 µg bid (N=80)						
	Baseline	Month 6 mUFC category						Baseline	Month 6 UFC					
	Total n (column %)	≤1 n (row %)	>1, ≤2 n (row %)	>2, ≤5 n (row %)	>5, ≤10 n (row %)	>10 n (row %)	Missing n (row %)	Total n (column %)	≤1 n (row %)	>1, ≤2 n (row %)	>2, ≤5 n (row %)	>5, ≤10 n (row %)	>10 n (row %)	Missing n (row %)
>1, ≤2	12 (15%)	2 (17%)	4 (33%)	2 (17%)	3 (25%)	0 (0%)	1 (8%)	14 (18%)	6 (43%)	8 (57%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>2, ≤5	30 (37%)	7 (23%)	10 (33%)	7 (23%)	4 (13%)	1 (3%)	1 (3%)	43 (54%)	16 (37%)	7 (16%)	20 (47%)	0 (0%)	0 (0%)	0 (0%)
>5, ≤10	28 (34%)	4 (14%)	9 (32%)	10 (36%)	4 (14%)	0 (0%)	1 (4%)	14 (18%)	3 (21%)	2 (14%)	4 (29%)	2 (14%)	0 (0%)	3 (21%)
>10	12 (15%)	2 (17%)	1 (8%)	3 (25%)	2 (17%)	3 (25%)	1 (8%)	9 (11%)	2 (22%)	0 (0%)	1 (11%)	2 (22%)	3 (33%)	1 (11%)
Total n (row %)	82 (100%)	15 (18%)	24 (29%)	22 (27%)	13 (16%)	4 (5%)	4 (5%)	80 (100%)	27 (34%)	17 (12%)	25 (31%)	4 (5%)	3 (4%)	4 (5%)

The figure below represents a graphical display of the same data shown in the table above. Of note, all subjects in the 900 µg bid group stayed in the same baseline mUFC category or shifted left (improved) after treatment. No patient worsened from their baseline mUFC category. By comparison, 10 (12%) subjects in the 600 µg bid group worsened from their baseline mUFC category

Figure 5: Shifts on treatment from baseline UFC categories (1-2, 2-5, 5-10, > 10x ULN) to Month 6 (LOCF)



2.34 Additional analyses of dose

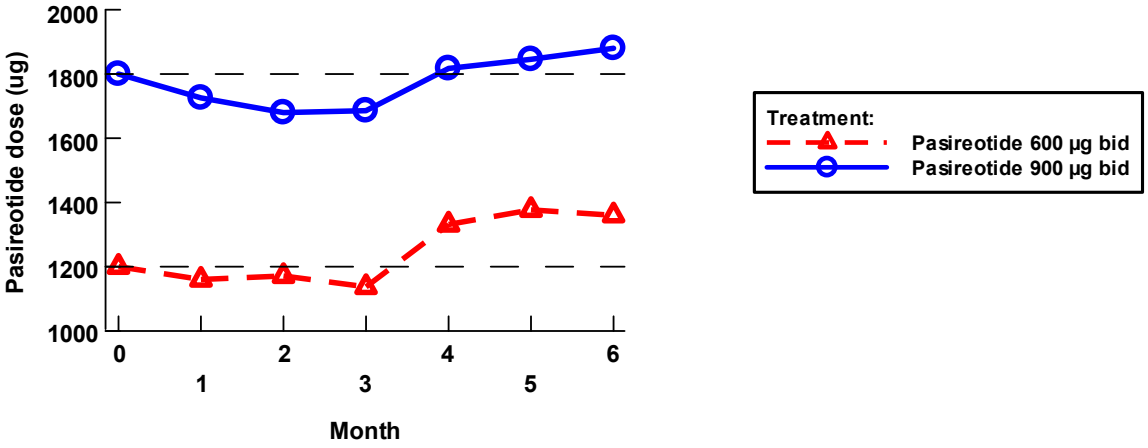
Mean dose

The table below presents data for dose by month. The figure that follows displays the mean dose over time.

Table 13: Mean total daily dose (SD) for both dose group through Month 6

	600 µg bid			900 µg bid		
	N	Mean total daily dose (SD)	Min, Max	n	Mean total daily dose (SD)	Min, Max
Month 1	75	1140 (191)	300, 1200	71	1741 (180)	1200, 1800
Month 2	69	1148 (199)	600, 1800	66	1695 (238)	900, 1800
Month 3	68	1125 (210)	300, 1200	67	1693 (254)	600, 1800
Month 4	64	1331 (420)	600, 1800	61	1820 (363)	1200, 2400
Month 5	60	1380 (446)	600, 1800	57	1837 (401)	900, 2400
Month 6	58	1360 (421)	600, 1800	57	1884 (366)	1200, 2400

Figure 6: Mean total daily dose (prior to visit day) over time – Month 6 completers



It should be noted that there were a total of 11 subjects who had normal mUFC levels at the Month 6 timepoint while on a dose lower than their randomized dose (decreased for tolerability reasons). A detailed discussion of these subjects is in Appendix 3.

Effect of dose change on responder status

For the purpose of the primary efficacy analysis, patients who did not normalize their mUFC by Month 3 or had the pasireotide dose increased above the randomization dose were considered non-responders. As already described, there were 12 responders in the 600 µg bid group and 21 in the 900 µg bid group. Twenty-four out of 80 (30%) patients in the 600 µg group required a dose increase at Month 3, and 12 (15%) patients in the 900 µg group had a dose increase at Month 3. Importantly, these dose increases did not result in many more patients with normalized mUFC. With a dose increase, only one additional subject in the 600 µg group and 2 additional subjects in the 900 µg group reached mUFC values below the upper limit of the normal range.

Dose-clinical response correlations

Patients were randomized to one of two doses but could have their dose titrated up or down starting at Month 3, depending on UFC response and tolerability. Therefore the range of possible daily doses was greater than the randomized doses. The first line of Table 14, below, summarizes descriptive data for the average daily dose. The average for each patient was calculated as the sum of daily doses divided by the number of days the drug was taken (up to 6 months in all patients who were exposed to study drug for at least a month). For example, the average daily dose for patients randomized to the 600 µg group (1200 µg daily) ranged from 600 to 1528 µg. With these data, we sought to estimate the linear relationship (i.e., correlation) between dose and efficacy as measured

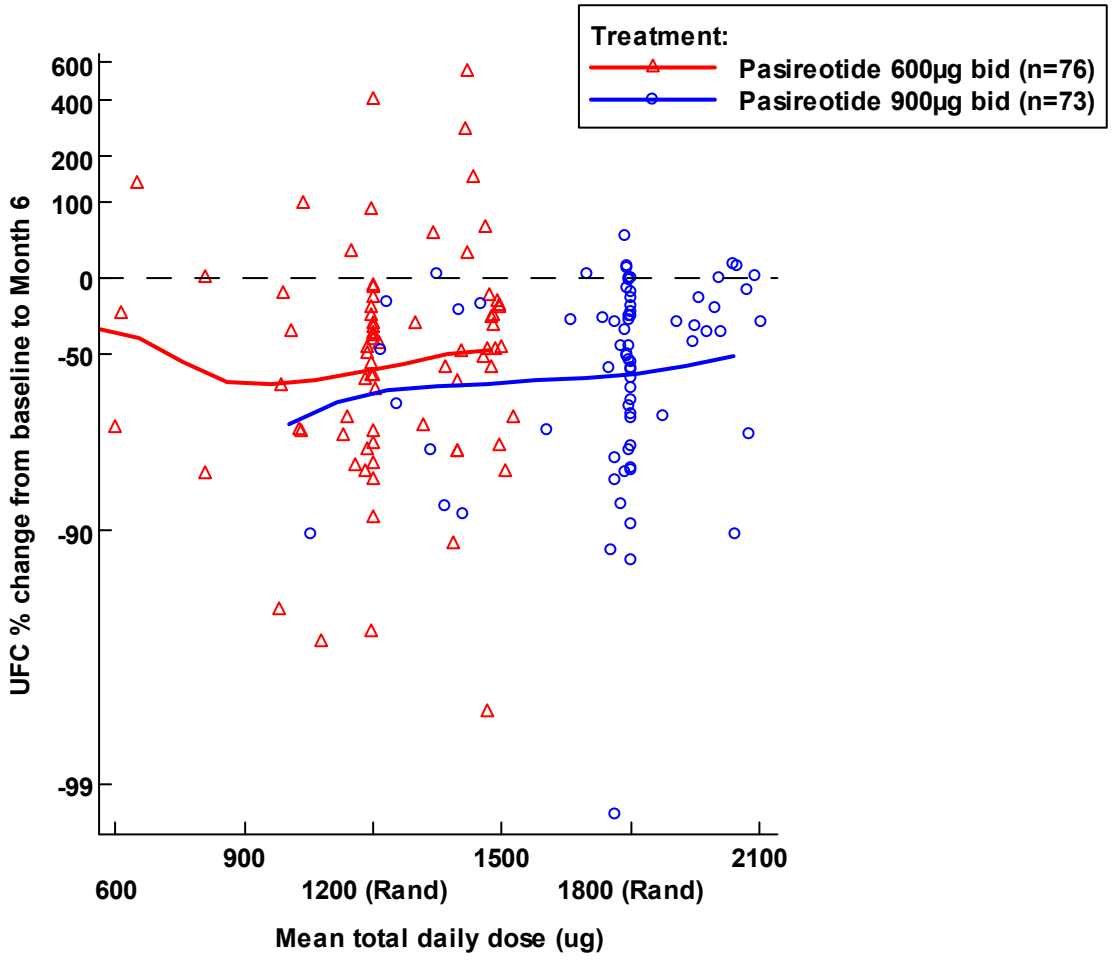
by mUFC. The second line of the table summarizes descriptive data for mUFC percent change from baseline. We computed sample correlations (r) between average daily dose and log(mUFC percent change) (3rd line of the table). The sample correlations were low (r=6% and 17% for 600 and 900 μg, respectively) and not statistically significant, indicating a weak relationship between dose and percent change mUFC. Furthermore, the observed correlations, although not significantly different from zero, were numerically positive indicating slightly reduced efficacy with increasing dose. This relationship is not unusual in dose titration designs such as this; the observed trend was likely the result of lack of efficacy in certain subjects. In other words, perhaps certain subjects would not respond despite up-titration of pasireotide.

Table 14: Correlation between average daily dose and percent change in mUFC from baseline in Study B2304

	600μg bid n=76			**900μg bid N=74**		
	Mean (SD)	Median	Min, Max	Mean (SD)	Median	Min, Max
Average daily dose	1238 (210)	1200	600, 1528	1761 (215)	1795	1055, 2103
mUFC % change	-23% (103%)	-48%	-98%, +542%	-44% (34%)	-46%	-99%, +45%
Correlation (r) (p-value testing ρ=0)	r =6% (p=0.6)			r =17% (p=0.14)		

Figure 7, below, provides additional insight into the relationship between average dose and mUFC. The figure displays individual patient data for the actual average daily dose (taking into account dose titration and therefore not the randomized dose) and mUFC percent change from baseline. The individual data in the figure are the same as in the previous table used to calculate the sample correlations. In this figure, we fit solid curves to the data for each randomized group. The fitted lines show a slight upward trend (in the direction of reduced efficacy) with increasing dose. This pattern is consistent with the slight positive correlations calculated in the previous analysis. As we noted in the discussion of the correlation results, this finding is not unusual in dose titration designs such as this.

Figure 7: Percent change in mUFC as a function of mean total daily dose



2.4 Secondary and exploratory endpoints

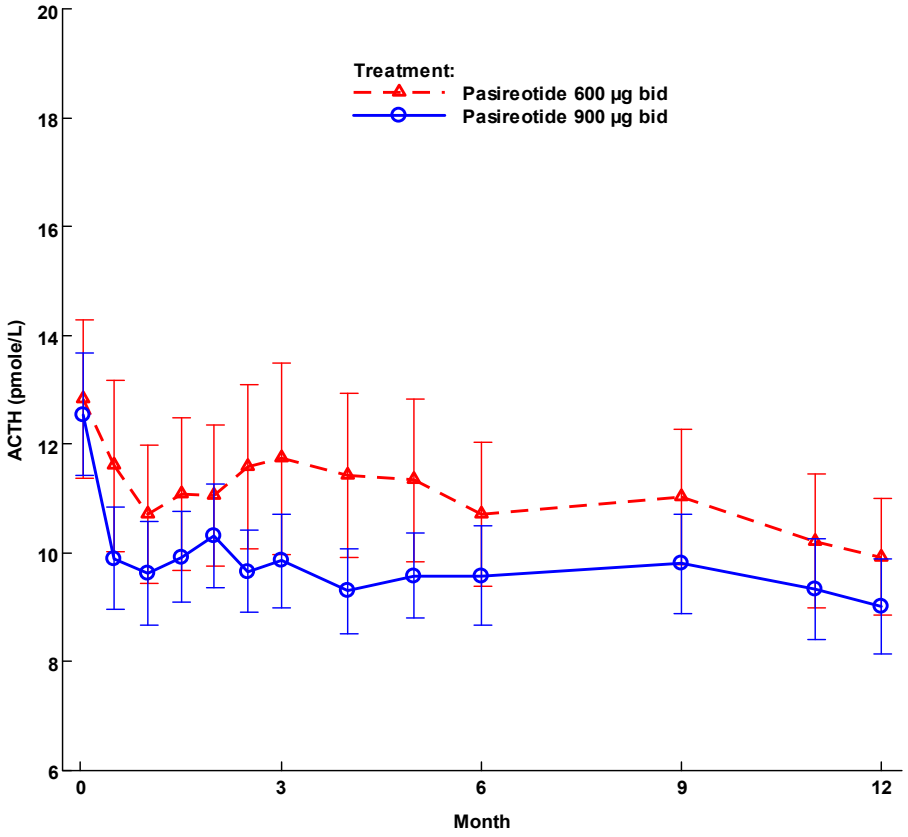
The pivotal trial had 14 secondary objectives including several additional efficacy analyses. Given that Study B2305 was an uncontrolled clinical trial, the efficacy analyses focus on changes from baseline to end-of-trial for different efficacy variables. It is important to recognize that any changes from baseline cannot be assumed with reasonable certainty to be drug-related since they may be due to unidentified confounders or simply to consistent medical attention received by patients during trial participation, including optimization of background medical treatments. This is in sharp contrast with the primary efficacy analysis which measures the laboratory endpoint, urinary free cortisol, which that is not expected to exhibit spontaneous improvement.

Therefore this review will present only some of the secondary efficacy analyses of particular interest such as changes in ACTH levels, blood pressure, and patient reported outcomes.

ACTH

Declines in mean plasma ACTH concentrations, displayed graphically in Figure 8, below, were consistent with the observed reductions in mUFC seen during the trial, and consistent with the known mechanism of action of pasireotide.

Figure 8: Mean ACTH plasma concentrations



Blood pressure changes

The table below summarizes the changes in blood pressure from baseline by randomized group. There were decreases in both systolic and diastolic blood pressure in both dose groups. Differences in systolic, but not diastolic blood pressure reductions were seen between the two dose regimens: 11.4 mm Hg reduction with the 900 µg bid dose vs. 6.8 mm Hg reduction with the 600 µg bid dose.

Table 15: Mean change from baseline in blood pressure by randomized dose group at Month 6

Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80		
n	**Baseline mean (SD)**	**mean (SD)**	**n**	**Baseline mean (SD)**	**mean (SD)**
Sitting systolic blood pressure, mmHg					
59	132 (20)	-6.8 (19.4)	57	138 (20)	-11.4 (15.9)
Sitting diastolic blood pressure, mmHg					
59	86 (13)	-4.2 (13.5)	57	89 (11)	-5.0 (11.6)

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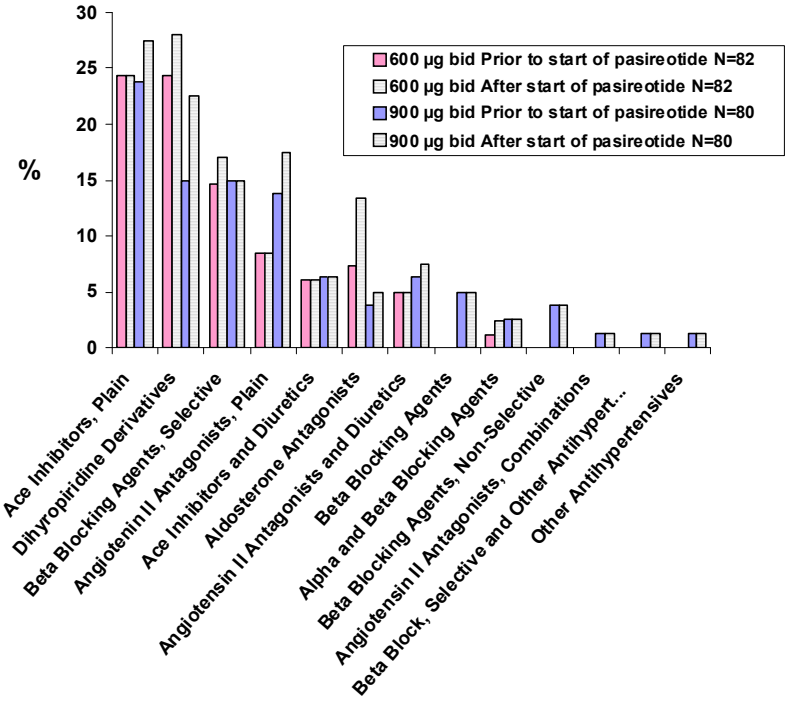
Patients enrolled in Study B2305 were allowed to use antihypertensive medications, and there were no restrictions to adding antihypertensive drugs during the trial. Information regarding the use of such drugs, including dose and duration, was not specifically collected. The general use of antihypertensives was, however, recorded in the same way as any concomitant medication. A general comparison of antihypertensives used at baseline versus during the trial is presented in Figure 9, which indicates that there was an increase in use in some categories of antihypertensives. Unfortunately, in the absence of a comparator group, the exact contribution of these changes in medication to the overall reductions in systolic and diastolic blood pressure cannot be accurately assessed.

Figure 9: Concomitant use of antihypertensive agent prior to and after the start of pasireotide dosing for both groups



Quality of life

A Cushing's syndrome health related quality of life (HRQL) questionnaire was used in this trial.[7] A critical assessment is provided in the Study Endpoints and Labeling Development (SEALD) review, attached to this briefing document.

This HRQL questionnaire is a novel single-domain 12 item instrument. It should be noted that this questionnaire was created by one of the trial investigators. Although the questionnaire generally seems to capture important elements for Cushing's disease patients, there is still insufficient information to adequately assess the content validity.

Items in the questionnaire are:

1) I have trouble sleeping
2) I have pain that keeps me from leading a normal life
3) My wounds take a long time to heal
4) I bruise easily
5) I am more irritable, I have sudden mood swings and angry outbursts
6) I have less self-confidence, I feel more insecure
7) I'm worried about the changes in my physical appearance due to my illness
8) I feel less like going out or seeing relatives or friends
9) I have had to give up my social or leisure activities due to my illness
10) My illness affects my everyday activities such as working or studying
11) It's difficult for me to remember things
12) I'm worried about my health in the future.

Each item is rated on a scale of 1-5, where '1' corresponds to 'always' or 'very much' and 5 to 'never' or 'never at all'. Therefore increasing scores indicates improvement. To simplify score interpretation, standardization on a scale from 0 (worst HRQol) to 100 (best HRQol) is done with a formula.

The following table summarizes changes from baseline in HRQL scores for Month 6. Subjects who completed one or more items at an assessment were considered evaluable for that visit. Baseline scores were similar for the 2 dose groups. Although standard deviations were large, mean and median increased from baseline for both groups, indicating improvement.

[7] Webb SM, Badia X, Barahona MJ, et al (2008) Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur J Endocrinol;158: 623-630.

Table 16: Change in HRQL score from baseline to Month 6 by randomized dose group

	Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80		
	Actual	**Change from baseline**	**Percent change from baseline**	**Actual**	**Change from baseline**	**Percent change from baseline**
Baseline						
n	81			78		
Mean (SD)	41.6 (20.41)			40.5 (20.11)		
Median	41.7			37.5		
Min, Max	6.3, 87.5			4.2, 87.5		
Month 6						
n	56	56	56	56	55	55
Mean (SD)	48.7 (21.08)	6.2 (16.02)	31.3 (79.99)	52.0 (19.11)	12.9 (14.80)	73.0 (181.06)
Median	50.0	7.3	13.2	54.2	8.3	30.0
Min, Max	0.0, 86.4	-35.4, 52.1	-100.0, 400.0	16.7, 91.7	-10.4, 52.1	-21.4, 1250.0

Sponsor's Clinical Study Report, Table 11-11

Nevertheless, because of the limitations of the instrument and the lack of a trial comparator, the clinical relevance of these data is unclear.

Tumor volume

Pituitary tumor volume was evaluated in a little over two-thirds of patients. There were no dramatic mean changes in tumor size. Tumor volume was determined from images obtained by pituitary MRI scanning with gadolinium. The interpretation was performed by 2 independent radiologists who were blinded to the treatment dose as well as to the timepoints of the MRI images of the first 6 months.

Overall, sample sizes for this analysis are small and therefore conclusions based on these data are limited. At Month 6, subjects in the 600 µg group showed a mean increase in tumor volume of 9.3% and the 900 µg group had a decrease of 19.0%.

The number of subjects in the "percent change from baseline" columns is nearly half of those in the "change from baseline" for both dose groups. This is because a total of 87 subjects did not have measurable tumor volume by MRI at baseline and the value was recorded as "0". Since the calculation of the percent change from baseline depends on the baseline value, if the baseline value=0 the calculation cannot be performed.

Table 17: Change in pituitary volume (cm3) by randomized dose group

	Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80		
	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
Baseline						
n	82			78		
Mean (SD)	0.89 (3.54)			0.20 (0.43)		
Median	0.01			0.03		
Min, max	0.00, 22.83			0.00, 2.99		
Month 6						
n	57	52	25	54	50	28
Mean (SD)	0.55 (2.16)	0.06 (0.27)	9.3 (44.02)	0.18 (0.42)	-0.04 (0.15)	-19.0 (36.82)
Median	0.00	0.00	12.6	0.02	0.00	-28.90
Min, max	0.00, 13.99	-0.32, 1.57	-83.0, 89.5	0.00, 2.24	-0.75, 0.50	-100.0, 57.0

Source: Sponsor's Clinical Study Report, Table 14.2-2.8

2.5 Efficacy conclusions

Study 2305 provides evidence of efficacy for pasireotide in patients with Cushing's disease. The primary endpoint for this pivotal trial -- response defined by normalization of mUFC without a dose increase -- was a stringent one. The pre-specified primary efficacy analysis stipulated that response rates be estimated within individual treatment groups and each rate compared with a pre-specified non-inferiority margin of 15%. The 900 µg dose (given twice daily) met the primary efficacy criterion. The estimated response rate for 900 µg was 26% with the lower bound of the two-sided 95% CI equal to 17%, which exceeded the 15% benchmark. The two-sided 97.5% CI, which FDA computed for the purpose of controlling type 1 error across the two doses, had a lower bound of 16% which also met the primary efficacy criterion.

The 600 µg dose (given twice daily) did not meet the primary efficacy criterion. It is important to recognize, though that this difference in results between the doses – significance vs. non-significance – is not sufficient for declaring that the two doses are different statistically. Although Study B2305 was dose-randomized, it was inadequately powered to differentiate statistically between doses and there was no plan to formally test for statistical differences in mUFC between dose groups. Despite the differences in the results for the primary endpoint, both doses were associated with consistent reductions from baseline in mUFC, and relatively large proportions of patients in each dose group exhibited > 50% reductions or normalization of mUFC (34% for the 600 µg bid and 41% for the 900 µg bid group). Graphic displays of individual responses also indicated that most patients in each of the two groups have had reductions in mUFC relative to baseline. The totality of analyses we conducted in order to more fully describe the relationship between average daily or randomized dose and response indicates some additional efficacy for 900 µg compared to 600 µg although we would characterize the additional benefit as modest clinically and statistically non-significant.

Regarding baseline mUFC, we chose to adjust for baseline in some of the analyses comparing the two doses. The range of baseline mUFC values was very large and showed substantial variability. It should be remembered, however, that the primary analysis did not pre-specify any adjustment for or reliance on baseline mUFC values. Furthermore, there was no statistical evidence pointing to a difference in baselines. Our analyses comparing the two doses which adjusted for baseline mUFC did not differ substantially from the unadjusted analyses.

The trial did not have a placebo group and therefore did not account for possible regression to the mean with possible inflation of the response rate that might have occurred in each group given the fact that some patients were entered with very high baseline mUFC values. However, the treatment goal was a fixed ULN of 145 nmol/day, the achievement of which was difficult for high baseline values and therefore was likely unaffected by modest regression to the mean.

An important characteristic of pasireotide treatment is that in both dose groups mUFC reached a nadir by the Month 1-Month 2 timepoints. Given the unfavorable glycemic changes associated with pasireotide use in a large proportion of patients, an issue that will be discussed in detail in the following section of this review, this observation has important clinical practice implications for deciding early in the course of treatment whether the benefit on cortisol reduction outweighs the risk of hyperglycemia in individual patients.

Another interesting observation from this trial was the minimal effect that dose increases had on efficacy. Patients who failed to respond to the 600 µg bid dose did not show a clear benefit when their dose was increased to 900 µg bid. This may simply be a reflection of the fact that the 900 µg bid regimen, although slightly better than the 600 µg bid regimen in the primary and other efficacy analyses, had only a modest additional benefit, thus pointing out to the fact that the two doses may not be very far away on the dose-response curve. Such a fact may suggest an explanation for why the pharmacometric modeling used in several exposure-response analyses provided in another section of this briefing package failed to identify differences between the 600 µg bid and the 900 µg bid regimens. Yet another possible explanation may relate to inherent methodological differences between these two approaches: one being an analysis of efficacy in the context of randomized groups in a clinical trial, the other being post hoc data modeling.

Finally, although some favorable trends were observed in a few secondary efficacy endpoints (e.g. blood pressure, BMI, waist circumference, quality of life questionnaire), methodological limitations imposed by the uncontrolled design of the clinical study limit the ability to draw firm conclusions.

3. Review of Safety

3.1 Drug Exposure

In the Phase 3 program safety information was obtained using two dosing regimens: 600 μg b.i.d (1200 μg daily) and 900 μg b.i.d (1800 μg daily) to which patients were exposed for a mean duration of 10.77 months for both groups combined, with similar exposure for each dose regimens. The actual range of total daily doses was 596 to 2163 for the 600 μg b.i.d. group, and 514 to 2273 for the 900 μg b.i.d. group; the mean dose of 1334.9 ± 325.3 μg/day was slightly above the randomized dose for the 600 μg b.i.d. group, and the mean daily dose of 1758.4 ± 286.4 μg/day was only slightly below the randomized dose for the 900 μg b.i.d. group.

The safety information evaluated in the Phase 3 program included standard collection of adverse events, ECGs, gallbladder ultrasounds, pituitary MRIs, and adverse events of special interest which are described below. Additional safety information was obtained with pasireotide in Phase 1 and 2 studies, as well as in several safety studies. This review focuses, however, on safety data obtained in the pivotal trial 2305 which includes the target patient population for which Signifor has been developed and represents the longest continuous exposure to the study drug to date. Therefore, in this review, safety analyses refer to the pivotal Study 2305, unless specified otherwise.

3.2 Deaths

There were no deaths during active pasireotide treatment. One patient (treatment failure) died from complications of bilateral adrenalectomy two months after being discontinued from the study.

3.3 Non-fatal serious adverse events

Serious adverse events (SAEs) were reported for almost a quarter of subjects (24.7% overall; 23.2% for 600 μg b.i.d., and 26.3% for 900 μg b.i.d). About 5% of SAEs resulted in discontinuation (3.7% for the 600 μg and 6.3% for 900 μg arm, respectively).

The most common reported SAE across dose groups were, in descending order, pituitary-dependent Cushing's syndrome (3.7%)[8], diabetes mellitus (2.5%), hyperglycemia (2.5%),

[8] Of the 9 patients who had SAEs related to pituitary-dependent Cushing's syndrome or pituitary adenomas, 8 were discontinued from the trial and underwent surgical interventions (either pituitary surgery or bilateral adrenalectomy) because of uncontrolled disease. Because these patients' surgeries took place within 30 days from the end of the trial they were reported as SAEs.

cholelithiasis (2.5%), benign pituitary tumor (1.9%), adrenal insufficiency (1.2%), disease progression (1.2%), drug ineffective (1.2%), uterine polyp (1.2%), and hypotension (1.2%). Several other SAEs were seen each in only one patient (0.6%). Some SAEs were anticipated based on the known mechanism of action of the drug, prior experience with pasireotide in the clinical development program, and the known safety profile of somatostatin analogues in general. These include adrenal insufficiency, gastrointestinal disorders (abdominal pain, constipation, increased lipase, food intolerance) including hepatobiliary disease (cholelithiasis, cholecystitis, acute cholecystitis), QT prolongation, and carbohydrate metabolism related (diabetes mellitus, hyperglycemia, hypoglycemia, type 2 diabetes).

Of interest, drug-related SAEs (11.7% across groups) were almost twice more frequent in the 900 µg b.i.d. group (15.0%) vs. the 600 µg b.i.d. group (8.5%); they mostly included SAEs related to metabolism and nutrition disorders (predominantly diabetes and hyperglycemia).

3.4 Trial discontinuations due to adverse events

Of the 162 patients exposed to pasireotide across both treatment arms, 17.3% patients (15.9% for 600 µg b.i.d vs. 18.8% for 900 µg b.i.d) discontinued because of adverse events. The specific adverse events were: adrenal insufficiency (1 patient), pituitary-dependent Cushing's syndrome (1), diarrhea (3), fecal incontinence (1), nausea (2), asthenia (1), fatigue (2), cholelithiasis (1), increased alanine aminotransferase (2, both in the 900 mcg b.i.d. group), increased aspartate aminotransferase (1 in the 900 mcg. b.i.d. group), increased blood immunoglobulin E (1), QT prolongation (in the 900 mcg. b.i.d. group), increased gamma-glutamyltransferase (5), hepatic enzyme increased (1), increased lipase (1), diabetes mellitus (4, two per each dose group), hyperglycemia (5; similar by dose), type 2 diabetes (1), benign pituitary tumor (1), cranial nerve paralysis (1), tongue paralysis (1), tremor (1), pregnancy (1), confusional state (1), urinary incontinence (1), urticaria (1), hot flush (1), hypotension (1).

3.5. Treatment-emergent adverse events

Almost all patients (98.1%) had at least one treatment-emergent (TEAE), and the frequency of such adverse events was similar for the 2 groups (97.6% for the 600 b.i.d. arm and 98.8% for the 900 b.i.d. arm). The majority of patients (95.7%) had at least one TEAE considered to be related to the study drug (96.3% 600 µg b.i.d. and 95.0% 900 µg b.i.d.). The observed high incidence of adverse should not be surprising given the morbidity associated with Cushing's syndrome in general and the length of exposure in the trial.

Most frequent treatment-emergent adverse events (i.e. TEAEs present in > 50% of patients) were in the gastrointestinal disorders (80.9%), metabolism and nutrition disorders (74.7%), and general disorders and administration site conditions (54.3%)

system organ class. Regardless of the overall frequency, the percentage of TEAEs was generally comparable between dose groups with the exception of psychiatric disorders, injury, poisoning & procedural complications, blood and lymphatic system disorders, ear and labyrinth disorders (however, the number of the patients contributing events in some of these groups was relatively small and therefore such group imbalances may simply reflect variability due to small numbers).

Across both treatment arms, the most frequent individual adverse events (≥ 15%) were, in decreasing order, diarrhea (58%), nausea (52%), hyperglycemia (40%), cholelithiasis (30 %), headache (28%), abdominal pain (24%), fatigue (19%) and diabetes mellitus (18%).

There were several adverse events associated with disturbances in glucose metabolism. They included, in decreasing order of overall frequency, hyperglycemia (40.1%), diabetes mellitus (17.9%), increased glycosylated hemoglobin (11.1%), and type 2 diabetes mellitus (9.3%). Gastrointestinal adverse events, which are known effects of somatostatin analogues, were also quite frequent: diarrhea (58.0%), nausea (51.9%), cholelithiasis (30.2%), abdominal pain (24.1%), upper abdominal pain and decreased appetite (9.9%). Of note, though, adverse events related to elevation of liver function tests were also present in 10.5% of all patients and included increases in alanine aminotransferase and gammaglutamyltransferase.

Taking into account the severity of the reported TEAEs, the most frequent Grade 3/4 TEAEs across both treatment arms were hyperglycemia (13%), diabetes mellitus (7.4%), type 2 diabetes mellitus (4.3%), increased gammaglutamyltransferase (3.7%) and diarrhea (3.1%).

Adverse events that triggered dose adjustment or study interruption

Dose adjustment or temporary interruption of study drug because of an adverse event was seen in almost one-third of patients (55/162). The most common adverse events responsible for this course of action were nausea, diarrhea, hyperglycemia and adrenal insufficiency[9].

Finally, the most common AEs requiring additional therapy were (in the 600 μg vs. 900 μg bid groups) hyperglycemia (26.8% vs. 30.0% of patients), headache (17.1% vs. 21.3% of patients), nausea (8.5% vs. 22.2% of patients), diabetes mellitus (13.4% vs. 18.8%), and diarrhea (14.6% vs. 7.5% of patients).

[9] Less frequent AEs were AV block, sinus tachycardia, vertigo, pituitary-dependent Cushing's syndrome, abdominal pain, vomiting, asthenia, fatigue, influenza-like illness, malaise, biliary colic, cholecystitis, bronchitis, gastroenteritis, viral infection, influenza, therapeutic agent toxicity, ALT increase, AST increase, decreased blood cortisol, decreased urinary free cortisol, increased gammaglutamyltransferase, increase lipase, decreased weight, decreased appetite, diabetes mellitus, food intolerance, hyperglycemia, hypertryglyceridemia, hypoglycemia, lipomatosis, arthralgia, myalgia, dizziness, headache, migraine, presyncope, tremor, nocturia, polyuria, renal colic, uterine polyp, epistaxis, oropharyngeal pain, erythema, hyperhydrosis, skin striae, urticaria, hypotension.

3.6 Adverse events of special interest

The Sponsor categorized these AEs as follows:

- somatostatin analogue class effects: gastrointestinal reactions, QT prolongation, bradycardia, hyperglycemia, gallbladder and biliary disorders, hematological abnormalities, liver safety related, injection site reactions, pancreatitis, hypopituitarism
- Cushing's disease effects: adrenal hypocortisolism/cortisol withdrawal syndrome
- risks observed in pre-clinical studies: coagulation abnormalities, hypotension, hypocalcemia, rhabdomyolysis and gastrointestinal erosions/bleeding

The following table summarizes these AEs. At least one AE of special interest was reported for over 96% of subjects. Hyperglycemia, gastrointestinal, biliary, and liver AEs were most common.

Table 18: Adverse events of special interest by category and randomized dose group, up to data cut-off

	Pasireotide 600 µg bid N=82 n (%)	**Pasireotide 900 µg bid N=80 n (%)**	**Overall N=162 n (%)**
Subjects with at least one AE of special interest	79 (96.3)	77 (96.3)	156 (96.3)
Hyperglycemia-related AEs	61 (74.4)	57 (71.3)	118 (72.8)
Diarrhea related AEs	48 (58.5)	46 (57.5)	94 (58.0)
Nausea related AEs	39 (47.6)	46 (57.5)	85 (52.5)
Gallbladder and biliary related AES	27 (32.9)	29 (36.3)	56 (34.6)
Liver safety related AEs	17 (20.7)	9 (11.3)	26 (16.0)
Injection site reaction related AEs	11 (13.4)	13 (16.3)	24 (14.8)
Bradycardia related AEs	15 (18.3)	8 (10.0)	23 (14.2)
Pancreatitis related AEs	11 (13.4)	10 (12.5)	21 (13.0)
Hypocortisolism related AEs	7 (8.5)	6 (7.5)	13 (8.0)
QT-prolongation related AEs	6 (7.3)	7 (8.8)	13 (8.0)
Constipation related AEs	7 (8.5)	4 (5.0)	11 (6.8)
Low blood cell related AEs	4 (4.9)	5 (6.3)	9 (5.6)
Hypothyroidism related AEs	4 (4.9)	3 (3.8)	7 (4.3)
Coagulation related AEs	1 (1.2)	2 (2.5)	3 (1.9)
Diabetes insipidus related AE	0 (0.0)	1 (1.3)	1 (0.6)

From Sponsor's Clinical Study Report, Table 12-8

The remainder of the discussion in this document focuses on the adverse events considered to be most vital in the safety assessment of this novel somatostatin analogue: hyperglycemia, liver test elevations, gastrointestinal events, hypocortisolism, bradycardia and QT prolongation, pancreatitis, and PTT/PT-INR elevations.

3.7. Glucose metabolism

Along with treatment-emergent adverse events such as hyperglycemia and diabetes (already summarized in Sections 3.3, 3.4 and 3.5 of this review), fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) were two key measures of glycemia monitored and analyzed in Study 2305.

3.71 Fasting Plasma Glucose

Mean fasting plasma glucose values by randomization group and time on trial are presented in Table 19, below. Baseline mean FPG values were in the normal range (i.e < 100 mg/dl); specifically they were 98.6 and 97.0 mg/dL, respectively for the 600 and 900 µg bid groups. A distinct elevation of mean FPG values was noticeable at the first post-baseline assessment at two weeks, and the FPG remained elevated throughout the trial. At early timepoints (primarily through Month 2) the mean FPG reached the diabetic range, and even though mean FPG decreased somewhat with time they did not normalize and remained at least in the pre-diabetic range throughout Month 12.[10]. Of note, one cannot support the conclusion that there was a decline in mean FPG between Month 3 and Month 12 because a significant number of patients discontinued the trial for a variety of reasons, including hyperglycemia and diabetes.

Table 19: Summary of mean fasting plasma glucose by randomized group and visit—Study 2305 (Safety analysis set)

	Pasireotide 600 µg bid		**Pasireotide 900 µg bid**	
Visit	N	Mean (SD)	N	Mean (SD)
Baseline	79	98.6 (23.6)	79	97.0 (18.7)
Month 0.5	78	136.0 (57.0)	76	149.2 (68.1)
Month 1	76	138.8 (68.6)	72	153.4 (71.5)
Month 1.5	74	131.4 (57.0)	69	143.6 (57.0)
Month 2	70	133.7 (51.4)	67	138.4 (60.3)
Month 3	69	122.0 (41.5)	66	124.7 (52.1)
Month 4	68	122.1 (41.8)	61	124.9 (43.1)
Month 5	62	121.3 (33.9)	57	128.5 (46.3)
Month 6	57	125.1 (34.6)	55	128.0 (54.6)
Month 9	46	126.9 (35.9)	48	119.4 (33.1)
Month 12	39	120.9 (40.5)	38	114.4 (36.3)

From Sponsor's Full Clinical Study Report, Table 12-14

[10] The 2013 American Diabetic Association definitions:

- Diabetic: patients taking anti-diabetic medication or prior history of diabetes mellitus or HbA1c≥6.5% or FPG ≥126 mg/dL.
- Pre-diabetic: non-diabetic patients with 100 mg/dL≤FPG<126 mg/dL or 5.7%≤HbA1c<6.5%
- Normal glucose tolerance: non-diabetic or non-pre-diabetic patients with FPG<100 mg/dL and/or HbA1c<5.7%

Shifts in fasting blood glucose from baseline to Month 6 are summarized in the table below, which reproduces one of the applicant's analyses. Overall, 63% of subjects had normal FPG levels (i.e. <100 mg/dL) at baseline. At data cutoff, in this subgroup approximately 46% still had normal values.

Table 20: Shift in fasting glucose from baseline to Month 6 (LOCF) by randomized dose group—Study 2305 (safety analysis set)

Dose group	Baseline		Month 6 (LOCF)				
		n (%)	FPG<100 mg/dL n (%)	100≤FPG <126 mg/dL n (%)	126≤FPG <200 mg/dL n (%)	FPG≥ 200 mg/dL n (%)	Missing n (%)
600 µg bid	FPG<100 mg/dL	53 (65)	23 (43)	16 (30)	12 (23)	1 (2)	1 (2)
	100≤FPG<126 mg/dL	20 (24)	2 (10)	6 (30)	10 (50)	1 (5)	1 (5)
	126≤FPG<200 mg/dL	5 (6)	1 (20)	1 (20)	2 (40)	1 (20)	0
	FPG≥200 mg/dL	1 (1)	0	0	1 (100)	0	0
	Missing	3 (4)	2 (67)	0	1 (33)	0	0
	Total	82 (100)	28 (34)	23 (28)	26 (32)	3 (4)	2 (2)
900 µg bid	FPG<100 mg/dL	49 (61)	24 (49)	13 (27)	10 (20)	2 (4)	0
	100≤FPG<126 mg/dL	27 (34)	5 (19)	6 (22)	12 (44)	3 (11)	1 (4)
	126≤FPG<200 mg/dL	3 (4)	0	1 (33)	0	2 (67)	0
	FPG≥200 mg/dL	0	0	0	0	0	0
	Missing	1 (1)	1 (100)	0	0	0	0
	Total	80 (100)	30 (38)	20 (25)	22 (28)	7 (9)	1 (1)
Overall	FPG<100 mg/dL	102 (63)	47 (46)	29 (28)	22 (22)	3 (3)	1 (1)
	100≤FPG<126 mg/dL	47 (29)	7 (15)	12 (26)	22 (47)	4 (9)	2 (4)
	126≤FPG<200 mg/dL	8 (5)	1 (13)	2 (25)	2 (25)	3 (38)	0
	FPG≥200 mg/dL	1 (0.6)	0	0	1 (100)	0	0
	Missing	4 (2)	3 (75)	0	1 (25)	0	0
	Total	162 (100)	58 (36)	43 (27)	48 (30)	10 (6)	3 (2)

3.7.2 Hemoglobin A1 c

The values of mean HbA1c by randomization group and time on trial are summarized below. Baseline values were slightly above the normal upper limit of 5.7% and at the lower end of pre-diabetes value range. HbA1c sharply increased in the diabetes range in both dose groups and never returned to baseline values.

Table 21: Summary of mean HbA1c (%) by randomized group and visit (Safety analysis set)

	Pasireotide 600 µg bid		Pasireotide 900 µg bid	
Visit	n	Mean (SD)	N	Mean (SD)
Baseline	78	5.83 (0.78)	76	5.76 (0.79)
Month 2	73	7.24 (1.65)	66	7.41 (1.50)
Month 4	68	7.23 (1.49)	61	7.15 (1.17)
Month 6	59	7.24 (1.42)	56	7.34 (1.18)
Month 8	49	7.31 (1.46)	46	7.36 (1.38)
Month 10	43	7.37 (1.35)	47	7.15 (1.33)
Month 12	40	7.25 (1.32)	38	7.21 (1.60)

From Sponsor's Clinical Study Report, Table 12-16

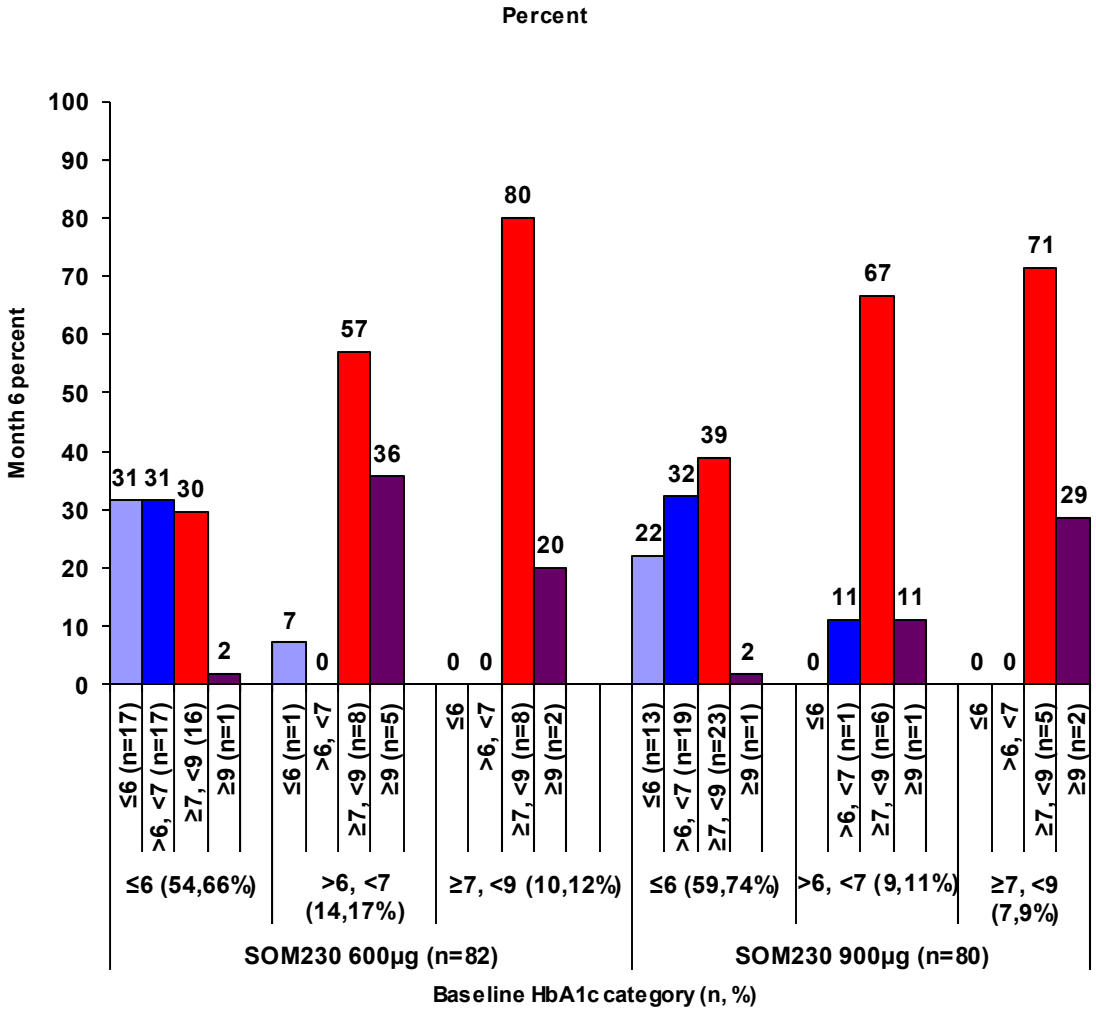
Shifts from baseline HbA1c levels are summarized below. Nearly 70% of subjects overall had a normal HbA1c level below 6% at baseline. In this subgroup only 27% stayed below 6% at the last measured value. Similar trends were seen for both dose groups.

Table 22: Shift in HbA1c from baseline to last value up to Month 6 by randomized dose group (safety analysis set, LOCF)

Dose group	Baseline		Month 6 (LOCF)				
		n (%)	HbA1c≤6 n (%)	6<HbA1c<7% n (%)	7%≤HbA1c<9% n (%)	HbA1c≥9% n (%)	Missing n (%)
600 µg bid	HbA1c≤6	54 (66)	17 (32)	17 (32)	16 (30)	1 (2)	3 (6)
	6<HbA1c<7%	14 (17)	1 (7)	0	8 (57)	5 (36)	0
	7%≤HbA1c<9%	10 (12)	0	0	8 (80)	2 (20)	0
	HbA1c≥9%	0	0	0	0	0	0
	Missing	4 (5)	1 (25)	2 (50)	0	0	1 (25)
	Total	82 (100)	19 (23)	19 (23)	32 (39)	8 (10)	4 (5)
900 µg Bid	HbA1c≤6	59 (74)	13 (22)	19 (32)	23 (39)	1 (2)	3 (5)
	6<HbA1c<7%	9 (11)	0	1 (1.3)	6 (67)	1(11)	1 (11)
	7%≤HbA1c<9%	7 (9)	0	0	5 (71)	2 (29)	0
	HbA1c≥9%	1 (1)	0	0	0	1 (100)	0
	Missing	4 (5)	0	1 (25)	3 (75)	0	0
	Total	80 (100)	13 (16)	21 (26)	37 (46)	5 (6)	4 (5)
Overall	HbA1c≤6	113 (70)	30 (27)	36 (32)	39 (35)	2 (2)	6 (5)
	6<HbA1c<7%	23 (14)	1 (4)	1 (4)	13 (76)	4 (24)	0
	7%≤HbA1c<9%	17 (11)	0	0	12 (7.4)	3 (1.9)	0
	HbA1c≥9%	1 (1)	0	0	0	1 (100)	0
	Missing	8 (5)	1 (13)	3 (38)	3 (38)	0	1 (13)
	Total	162 (100)	32 (20)	40 (25)	69 (43)	13 (8)	8 (5)

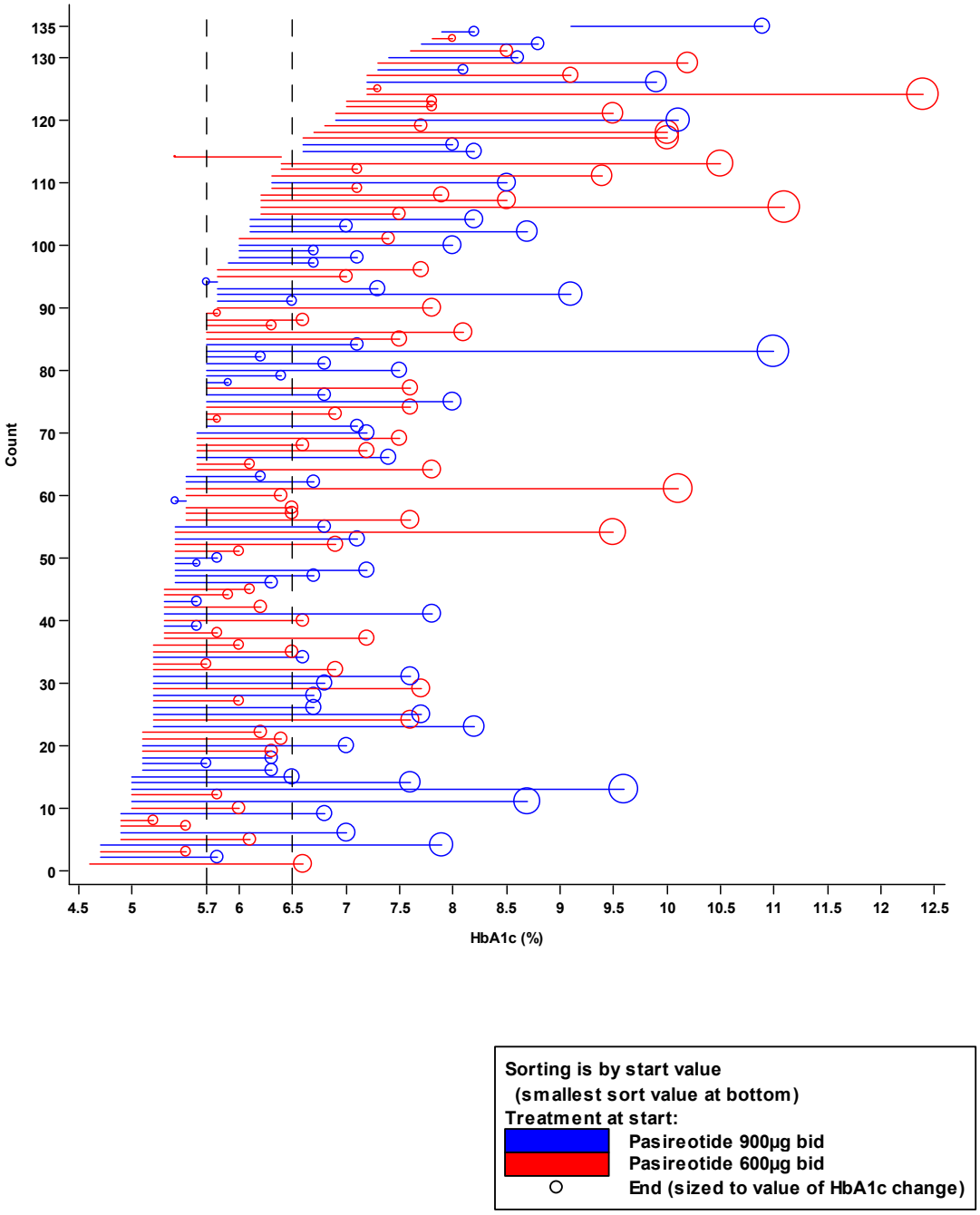
The data provided in the table above is graphically displayed in the figure here. The "missing" categories are excluded from the figure.

Figure 10: Shift in HbA1c from baseline to last value up to Month 6 by randomized dose group



Individual changes in HbA1c from baseline to Month 6 are displayed in the figure below. This graph includes paired HbA1c data from 70 subjects from the 600 µg group and 65 subjects for the 900 µg group. The data are presented in ascending order of baseline HbA1c. Shifts to the right indicate elevations in HbA1c relative to baseline and changes to the left point to reductions. It is important to note that very few subjects had a decrease in HbA1c during the trial. Graphs similar to the one below but separated by dose group are provided in Appendix 2.

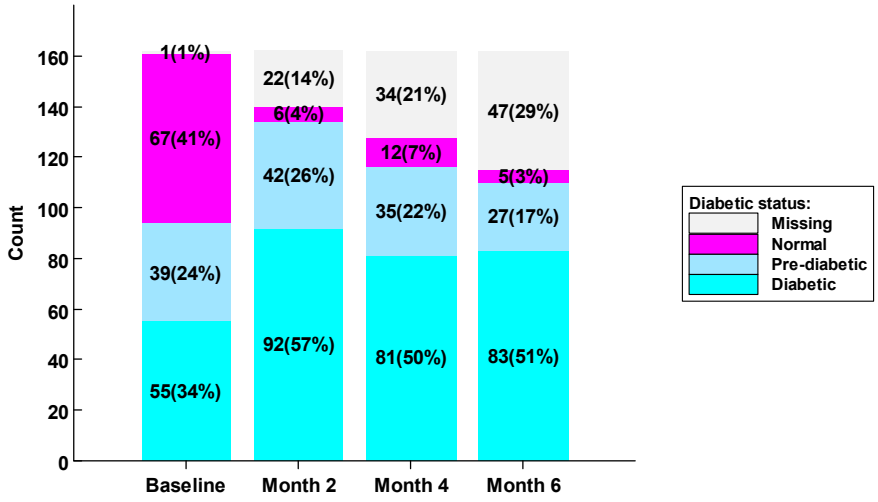
Figure 11: Individual changes in HbA1c from baseline to Month 6



3.7.3 Shifts in diabetes status during the trial

To assess changes in diabetes status, the Applicant used a variant of the American Diabetes Association (ADA) definition of diabetes. Specifically, all subjects enrolled in the trial that used antidiabetic medications, or had fasting plasma glucose (FPG) ≥126 mg/dL, or had a HbA1c ≥ 6.5% were classified as having diabetes. Patients with FPG greater or equal to 100 mg/dL but less than 126 mg/dL or with a HbA1c greater or equal to 5.7% but less than 6.5% were classified as having pre-diabetes. Patients were considered normal if FPG was < 100 mg/dL and/or HbA1c <5.7%. According to this definition, 41% of patients enrolled in trial 2305 had normal glucose status at baseline, 24% had pre-diabetes, and 34% had diabetes. It is evident that at Months 2 and 6, the percentage of subjects with normal glucose decreased and the percentage of subjects with diabetes increased.

Figure 12: Changes in pre-diabetes and diabetes status

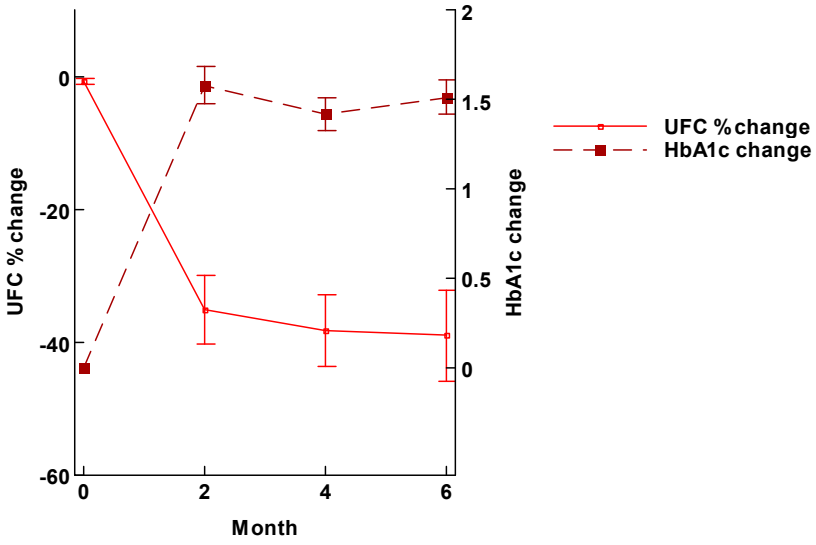


Additional results for analyses of shifts in diabetic status are provided in Appendix 4.

Temporal Relationship between Changes in Hemoglobin A1c and Mean Urinary Free Cortisol

The graph below displays the concomitant changes for mUFC and HbA1c to Month 6 for all subjects with available data. The percent change in mUFC and the absolute HbA1c values followed a similar temporal pattern of change but quantitatively moved in opposite directions: HbA1c increased as mUFC decreased. Changes appear to peak by Month 2.

Figure 13: mUFC and HbA1c changes from Baseline (Completers)



3.7.4 Changes in antidiabetic medications

Usage of antihyperglyemic medication before and during the trial is summarized in the table below. The use of antihyperglycemic therapy dramatically increased during the trial. For instance antihyperglycemic use increased from 6.2% to 22.8% for insulin, from 0.6% to 9.3% for glinides, from 1.9% to 21.6% for sulphonamides, and from 15.4% to 43% for metformin.

Table 23: Concomitant antidiabetic medication use prior to and following pasireotide dosing

	Prior to pasireotide dosing			Following pasireotide dosing		
ATC class Preferred Term	**Pasi 600 µg bid N=82 n (%)**	**Pasi 900 µg bid N=80 n (%)**	**Overall N=162 n (%)**	**Pasi 600 µg bid N=82 n (%)**	**Pasi 900 µg bid N=80 n (%)**	**Overall N=162 n (%)**
Biguanides						
Metformin	15 (18.3)	10 (12.5)	25 (15.4)	37 (45.1)	33 (41.3)	70 (43.2)
Insulins	6 (7.3)	4 (5.0)	10 (6.2)	19 (23.2)	18 (22.5)	37 (22.8)
Glinides	1 (1.2)	0 (0.0)	1 (0.6)	9 (11.0)	6 (7.5)	15 (9.3)
Nateglinide	1 (1.2)	0 (0.0)	1 (0.6)	1 (1.2)	0 (0.0)	1 (0.6)
Rapeglinide	0 (0.0)	0 (0.0)	0 (0.0)	8 (9.8)	6 (7.5)	14 (8.6)
Sulfonamides	3 (3.7)	0 (0.0)	3 (1.9)	15 (18.3)	20 (25.0)	25 (21.6)
Thiazolodinediones	1 (1.2)	0 (0.0)	1 (0.6)	4 (4.9)	1 (1.3)	5 (3.1)
Rosiglitazone	1 (1.2)	0 (0.0)	1 (0.6)	3 (3.7)	0 (0.0)	3 (1.9)
Pioglitazone	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.3)	2 (1.2)

ATC= Anatomical Therapeutic Chemical (ATC) Classification System
Pasi=pasireotide
Extracted from Sponsor's Full Clinical Study Report (2305), Tables 14.23-1.2 and 14.3-1.5

It should be noted that one Phase 1 trial (Study 2124, in Appendix) looked at the effect of concomitant administration of anti-hyperglycemic drugs and pasireotide compared to

pasireotide alone in healthy volunteers. No antihyperglycemic effect was seen with metformin. In this trial, liraglutide had the greatest antihyperglycemic effect.

3.7.5 Measures of glycemia after treatment discontinuation

The Applicant attempted to examine the reversibility of the hyperglycemia following drug discontinuation. The table below summarizes the changes in HbA1c and FPG at baseline, at the time when the last on-treatment value was available, and off treatment at approximately 1 month after the last dose of study drug. Values for both parameters did not return entirely to baseline levels (not unexpected for HbA1c given the short period of follow-up), although the mean values for FPG came close to normalizing.

Table 24: Mean FPG and HbA1c after discontinuation of treatment in Study 2305

	Pasireotide 600 µg bid		Pasireotide 900 µg bid	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Fasting plasma glucose				
Baseline	27	97.8 (20.51)	30	98.6 (21.33)
Last value prior to discontinuation	27	126.1 (36.92)	30	133.7 (55.05)
Safety follow-up	27	102.2 (23.00)	30	104.5 (22.02)
HbA1c				
Baseline	25	6.0 (0.83)	29	5.8 (0.90)
Last value prior to discontinuation	25	7.7 (1.20)	29	7.6 (1.59)
Safety follow-up	25	6.9 (1.00)	29	6.8 (1.60)

Sponsor's Response to FDA Information Request September 21, 2012, Table 2-2

3.8 Liver and Gallbladder Events

This section of the review focuses on changes in liver tests and gallbladder abnormalities. Cholestasis and cholelithiasis are well-recognized (and labeled) class effects of somatostatin analogues. Liver test elevations that are unrelated to cholelithiais are less understood, although the package inserts for other somatostatin analogues do mention their occurrence in registration clinical trials and the post-marketing setting.

3.8.1 Elevations in liver enzymes

Patients enrolled in Study 2305 had normal mean liver tests at baseline. Although mean ALT and AST values increased relative to baseline at Month 1 and at other timepoints during the trial, they remained below the upper limit of normal. For instance, the mean ALT at baseline, months 1, 2, 3, 4, 5 and 6 was 30.1, 39.4, 35.7, 34.4, 32.7, 28.8 and 29.9 U/L, respectively. Similarly, the mean AST at baseline, and the same post-baseline timepoints was 19.8, 26.3, 23.7, 22.7, 23.0, 21.1 and 22.1 U/L, respectively. Mean bilirubin levels also stayed within normal limits for the duration of the trial. No differences were noticeable between the two dose groups (600 mcg b.i.d. and 900 mcg b.i.d.) for the above mentioned analytes.

Categorical analyses of liver enzyme elevations were conducted for the 162 patients enrolled in Study 2305. Eight patients (5.1%) had elevations of ALT or AST>3x upper limit of normal (ULN); 6 of them were in the 600 µg group and 2 were in the 900 µg group. One subject was found to have an ALT 6 x ULN. This subject, in the 600 µg group, had baseline elevations of ALT (1.5xULN) and GGT (1.7xULN). On Day 30, this subject's AST was 3.3xULN, ALT was 6xULN, GGT was 8.5xULN and ALP 1.4xULN and study drug was stopped. On Day 46, after the noted events had improved, study drug was restarted at a reduced dose. On Day 93, GGT was elevated again to 7.6xULN. Study drug was permanently discontinued. This event was ongoing at the time of the last report.

No patient in Study 2305 experienced concomitant ALT/AST and bilirubin elevations. Despite this apparently reassuring observation made during the pivotal trial, it should be mentioned that the issue of hepatic safety of pasireotide was raised in 2010, when a patient receiving pasireotide in a compassionate use program was found to have increased liver enzymes in association with elevated bilirubin, suggestive of liver toxicity. The Applicant conducted a comprehensive review of the pasireotide safety database and identified 3 additional healthy volunteers with concomitant elevations of ALT>3xULN and total bilirubin>2xULN. The 3 healthy volunteer cases were asymptomatic; the one Cushing's patient developed jaundice. None of the cases required clinical intervention other than drug discontinuation.

The narratives for the 4 subjects (3 healthy volunteers and one compassionate use patient) follow:

Subject B2124-0001/10116 is a 47 year old man with no baseline laboratory abnormalities who received pasireotide 600 µg for 7 days in a study on the effect of anti-diabetic medications on pasireotide-induced hyperglycemia. On Day 7, he presented with elevated liver tests (shown below). He completed the study and remained asymptomatic. ALT decreased and total bilirubin normalized 8 days after the last dose of study drug. ALT returned to normal 18 days after the last dose.

Table 25: Liver laboratory values--Subject 2124-001/10116

Study Day	Total Bilirubin 0-17.1 µmol/L	ALT 10-50 U/L	AST 10-50 U/L	ALP 40-129 U/L	GGT 0-59.9 U/L
Baseline	11.7	21.8	21.0	73.0	46.0
Day 7	48.4 (x2.83)	149.4 (x2.99)	78.1 (x1.56)	93.0	105.0 (x1.75)
Day 11	19.0 (x1.11)	173.8 (x3.48)	67.9 (x1.36)	ND	128.0 (x2.14)
Day 15	10.4	97.6 (x1.95)	33.5	ND	104.0 (x1.74)
Day 21	5.3	50.9 (x1.02)	27.7	83.0	78.0 (x1.30)
Day 30	ND	ND	ND	ND	61.0 (x1.02)

From Sponsor's Hepatic Report, Table 4-3
ND=not done

Subject B2125-0001/10132 is a 44 year healthy male volunteer who participated in a thorough QT study. He received the following sequence of study drugs:

- Day 1-5: placebo
- Day 6-15: washout period
- Day 16-20: pasireotide 600 µg s.c. bid
- Day 21-34: washout period
- Day 35: moxifloxacin 400 mg
- Day 36-45: washout
- Day 46-50: pasireotide 1950 µg s.c. bid[11]

He completed the study, receiving the last dose of pasireotide on Day 50. Day 51 tests showed liver test elevations and a follow-up ultrasound showed extra-hepatic bile duct dilatation. Follow-up showed normalization of values.

Table 26: Live laboratory values—Subject B2125-0001/10132

Study Day	Total Bilirubin 0-17.1 µmol/L	ALT 10-50 U/L	AST 10-50 U/L	ALP 40-129 U/L	GGT 0-59.9 U/L
Baseline	7.5	17.2	17.9	52.0	19.0
Day 46	8.1	14.1	14.5	51.0	33.0
Day 51	68.9 (x4.03)	157.6 (x3.15)	147.1 (x2.94)	68.0	130.0 (x2.17)
Day 55	12.6	165.9 (x3.32)	32.3	ND	227.0 (x3.79)
Day 68	ND	39.2	ND	73.0	97.0 (x1.62)

From Sponsor's Hepatic Report, Table 4-4
ND=not done

Subject B2124-0001-10113 is a 46 year old healthy volunteer who participated in a study that evaluated the effect of anti-diabetic medications on pasireotide-induced hyperglycemia. He received the first dose of pasireotide 600 µg bid on Day 1 and the first dose of vildagliptin 50 mg bid on Day 2. Both drugs were continued until Day 7 when ALT and TB were elevated. Four days after the last dose of study drug total bilirubin normalized and ALT was decreasing. Of note, vildagliptin has been associated with marked elevated liver tests.

Table 27: Liver laboratory values—Subject B2124-0001-10113

Study Day	Total Bilirubin 0-17.1 µmol/L	ALT 10-50 U/L	AST 10-50 U/L	ALP 40-129 U/L	GGT 0-59.9 U/L
Baseline	12.6	22.5	18.1	47.0	37.0
Day 8	38.5 (x2.25)	156.3 (x3.13)	78.4 (x1.57)	ND	140.0 (x2.34)
Day 11	6.2	107.2 (x2.14)	38.2	ND	166.0 (x2.77)
Day 21	7.1	32.3	22.4	62.0	85.0 (x1.42)

From Sponsor's Hepatic Report, Table 4-5
ND=not done

Subject PHHO2010AU13717 is a 37 year old woman with Cushing's disease who was receiving pasireotide in a compassionate use study. Baseline labs were notable for ALT 1.8xULN and ALP 1.3xULN. Nine days following the start of therapy ALT was 10.3xULN. She developed nausea, vomiting, and jaundice. Pasireotide was discontinued on Day 10. All liver tests were normal 45 days after pasireotide discontinuation.

[11] This dose exceeds the Applicant's proposed range of doses for the treatment of Cushing's disease.

Table 28: Liver laboratory values—Subject PHHO2010AU13717

Visit date	Total Bilirubin 2-24 µmol/L (xULN)	ALT 0-55 U/L (xULN)	AST 0-45 U/L (xULN)	ALP 30-110 U/L (xULN)	GGT 0-60 U/L (xULN)
Baseline	13 (0.54)	99 (1.80)	41 (0.91)	145 (1.32)	24 (0.40)
Day 4 of pasireotide	80 (3.33)	131 (2.38)	70 (1.56)	128 (1.16)	27 (0.45)
Day 10 and last day of pasireotide	94 (3.92)	568 (10.33)	251 (5.58)	157 (1.43)	22 (0.37)
Day 1 off pasireotide	91 (3.79)	564 (10.25)	228 (5.07)	145 (1.32)	24 (0.40)
Day 3 off pasireotide	88 (3.67)	637 (11.58)	236 (5.24)	180 (1.64)	30 (0.50)
Day 7 off pasireotide	55 (2.29)	366 (6.65)	88 (1.96)	157 (1.43)	25 (0.42)
Day 22 off pasireotide	25 (1.04)	185 (3.36)	55 (1.22)	117 (1.06)	25 (0.42)
Day 46 off pasireotide	14 (0.58)	44 (0.80)	24 (0.53)	89 (0.81)	25 (0.42)

From Sponsor's Response to FDA Information Request of June 20, 2012
ND=not done

Interestingly, in these cases the bilirubin elevations either preceded or were concomitant with the transaminase elevations. Alkaline phosphatase elevations were either absent or minimal. Of note, there was only a limited hepatologic work-up of these patients and therefore a full and satisfactory explanation about the cause of the liver enzyme elevation was not submitted to the Agency to date. Overall, the mechanism of these liver test elevations is not understood and is not typical of changes observed in drug-induced liver injury.

At the request of the Agency, the Applicant provided safety data from the pasireotide clinical program for acromegaly. In a pivotal trial of long-acting pasireotide (pasireotide LAR), subjects with acromegaly were randomized to treatment with either pasireotide LAR or octreotide LAR. The results, presented below, showed similar elevations in liver tests in the two groups.

Table 29: Categorical Elevations in Liver Tests by randomized group in Study C2305

Randomized group	N	ULN<AxT[1] ≤3xULN n (%)	AxT >3x ULN n (%)	AxT >5x ULN n (%)	AxT >10x ULN n (%)	AxT >20x ULN n (%)	Tbili >ULN to <2xULN n (%)	Tbili ≥2x ULN n (%)	AxT>3x ULN, Tbili≥2xULN AP <2xULN n (%)
Pasireotide LAR	178	62 (34.8)	9 (5.1)	1 (0.6)	1 (0.6)	0	37 (20.8)	4 (2.2)	0
Octreotide	180	71 (39.4)	6 (3.3)	1 (0.6)	0	0	45 (25.0)	5 (2.8)	0

[1=]AST or ALT
From Sponsor's Response to FDA Information Request, August 24, 2012

In addition, the Applicant provided analyses of liver tests for all clinical trials in this development program. While it is outside the scope of this document, these analyses are provided in Appendix 4.

3.8.2 Gallbladder and biliary-related adverse events

Cholelithiasis is known to occur in association with somatostatin analogue use. In Study 2305, cholelithiasis (as a pre-defined clinical term) was reported in 30.2% of all subjects. This comprised the vast majority of cases included in this AE category of interest. Other events included in the category are summarized here:

Table 30: Gallbladder and biliary related AEs, by PT and dose group up to data cut-off

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Total	27 (32.9)	29 (36.3)	56 (34.6)
Biliary colic	0 (0.0)	2 (2.5)	2 (1.2)
Blood ALP increased	4 (4.9)	1 (1.3)	5 (3.1)
Cholecystitis	3 (3.7)	1 (1.3)	4 (2.5)
Cholecystitis acute	1 (1.2)	0 (0.0)	1 (0.6)
Cholelithiasis	25 (30.5)	24 (30.0)	49 (30.2)
Cholestasis	2 (2.4)	3 (3.8)	5 (3.1)
Gallbladder disorder	1 (1.2)	1 (1.3)	2 (1.2)
Ultrasound biliary tract abnormal	0 (0.0)	1 (1.3)	1 (0.6)

From Sponsor's Clinical Study Report, Table 14.3.1-1.37
ALP=alkaline phosphatase

Gallbladder ultrasound was performed at screening and Study Day 90 (start of partially blind period). It was also repeated at the end of the 6 month period and periodically during the open-label period.

The majority (84.6%) of subjects had normal ultrasound findings at baseline. For the analysis to the most extreme value (below), the percentage of subjects with normal findings decreased to 46.9%. Of the 137 subjects with normal findings at baseline, 32 developed gallstones.

Table 31: Shifts in gallbladder ultrasound results from baseline to extreme level up to data cut-off, Study 2305

Baseline value			Extreme value			
Dose group		**n (%)**	**Normal n (%)**	**Sludge detected n (%)**	**Gallstones n (%)**	**Missing n (%)**
600 µg bid	Normal	68 (82.9)	39 (47.6)	5 (6.1)	16 (19.5)	8 (9.8)
	Sludge detected	0	0	0	0	0
	Gallstones	8 (9.8)	0	0	8 (9.8)	0
	Missing	6 (7.3)	3 (3.7)	1 (1.2)	2 (2.4)	0
	Total	82 (100.0)	42 (51.2)	6 (7.3)	26 (31.7)	8 (9.8)
900 µg bid	Normal	69 (86.3)	37 (46.3)	6 (7.5)	16 (20.0)	10 (12.5)

	Sludge detected	3 (3.8)	0	0	1 (1.3)	2 (2.5)
	Gallstones	4 (5.0)	0	0	4 (5.0)	0
	Missing	4 (5.0)	2 (2.5)	0	1 (1.3)	1 (1.3)
	Total	80 (100.0)	39 (48.8)	6 (7.5)	22 (27.5)	13 (16.3)
Overall	Normal	137 (84.6)	76 (46.9)	11 (6.8)	32 (19.8)	18 (11.1)
	Sludge detected	3 (1.9)	0	0	1 (0.6)	2 (1.2)
	Gallstones	12 (7.4)	0	0	12 (7.4)	0
	Missing	10 (6.2)	5 (3.1)	1 (0.6)	3 (1.9)	1 (0.6)
	Total	162 (100.0)	81 (50.0)	12 (7.4)	48 (29.6)	21 (13.0)

From Sponsor's Clinical Study Report, Table 12-18

3.9 Gastrointestinal adverse events

Gastrointestinal side effects—particularly diarrhea, nausea, constipation--are known adverse effects of somatostatin analogues. Diarrhea was reported for 58% of subjects overall. For the category of nausea, 52% of subjects receiving pasireotide were reported. Finally, constipation was reported in 6.8% of pasireotide-treated subjects.

3.10 Hypocortisolism

Although hypocortisolism-related events were an AE of special interest, interestingly for this drug, hypocortisolism can also be seen as a sign of efficacy. The Sponsor identified preferred terms to capture these events which included adrenal insufficiency, secondary adrenocortical insufficiency, blood cortisol decreased and cortisol free urine decreased. Not all cases were biochemically confirmed.

Overall, 13 (8.0%) of subjects had such an event: 7 in the 600 µg group and 6 in the 900 µg group. Two of the subjects had a hypocortisolism-related SAE, and both of these subjects (one in each dose group) withdrew from the trial. The other cases resolved with a reduction or temporary interruption in the dose of pasireotide. Only three of the 13 subjects required a short-term course of exogenous steroid treatment. The fact that not all subjects were treated with exogenous steroids should question whether these events were related to true hypocortisolemia.

Of the 7 subjects in the 600 µg group discussed above who had a hypocortisolism-related event (6 that completed the trial), 2 were considered responders at Month 6, while of the 6 subjects in the 900 µg group (5 that completed the trial), 4 were responders at Month 6.

3.11 Bradycardia and QT prolongation

Considered a class effect for somatostatin analogues, AEs related to bradycardia were observed in 14.2% of subjects of the pivotal trial. The preferred terms comprising this

category are summarized here. QT prolongation and sinus bradycardia made up the majority of events.

Table 32: Bradycardia related AEs, by PT and dose group up to data cut-off

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Total	15 (18.3)	8 (10.0)	23 (14.2)
AV block second degree	0 (0.0)	1 (1.3)	1 (0.6)
Bradycardia	2 (2.4)	1 (1.3)	3 (1.9)
PR interval shortened	1 (1.2)	0 (0.0)	1 (0.6)
QT interval prolonged	5 (6.1)	5 (6.3)	10 (6.2)
Sinus bradycardia	8 (9.8)	2 (2.5)	10 (6.2)

From Sponsor's Clinical Study Report, Table 14.3.1-1.37

The QT prolongation category included the "QT interval prolonged" cases as well as 3 cases of syncope.

For this Application, the Sponsor conducted two thorough QT studies. Testing was conducted with one of the therapeutic doses (600 µg) and with a supratherapeutic dose of 1950 µg (to simulate a possible "worst case scenario" of hepatic impairment). In both studies an effect of pasireotide on the QTc interval was observed with the maximum placebo-subtracted mean change from baseline occurring at two-hour post dose. In one study investigating a 1950 µg b.i.d. dose, the maximum mean placebo-subtracted QTcF change from baseline was 17.5 ms (90% CI: 15.53; 19.38). In the other study, investigating doses of 600 µg b.i.d. and 1950 µg b.i.d., the maximum mean placebo-subtracted QTcI change from baseline was 13.19 ms (90% CI: 11.38; 15.01) and 16.12 ms (90% CI: 14.30; 17.95 ms), respectively. Both pasireotide doses decreased heart rate, with a maximal difference to placebo observed at 1 hour for pasireotide 600 µg bid (-10.39 bpm), and at 0.5 hours for pasireotide 1950 µg bid (-14.91 bpm). No episodes of torsade de pointes (transient or sustained) were observed. In clinical studies in Cushing's disease patients, QTcF of >500 msec was observed in two patients (out of 201 patients) with no clinical consequence observed. Episodes of torsade de pointes were not observed either in those studies or in other patient populations.

3.12 Changes in coagulation parameters

The Applicant observed increased PT and PTT in the nonclinical program in one of two animal species (in rodents but not in monkeys). Because of these findings, coagulation-related AEs were considered an AE of special interest. The most frequent hematological abnormalities were increased PTT and INR. In the pivotal trial, approximately 52% of subjects overall had a post-baseline elevation of PTT or PT-INR during the trial. The majority were CTC grade 1 elevations. Comparing baseline to final values, 74.7% of subjects overall had a normal PTT at baseline. By the last value, 61.7% of subjects had a normal PTT; the majority of the remaining subjects had a Grade 1 elevation. For PT-INR, 95.1% of subjects overall had a normal value at baseline, while this decreased to

82.7% by the final value. Once again, the majority of the remaining subjects had a Grade 1 elevation. For PTT and PT-INR, there were 3 subjects with a Grade 3 elevation for both parameters. All 3 were in the 600µg group and all 3 discontinued the trial before 12 months for reasons unrelated to the PTT and PT-INR elevations. It would appear that concomitant medications could not account for the abnormalities. In order to clinically correlate these laboratory abnormalities with bleeding events, the Applicant performed a search for coagulation-related AEs that would reflect bleeding; none was identified.

No subjects had concomitant elevations of PT/PTT-INR and total bilirubin, suggesting that the abnormal coagulation parameters were not a result of liver damage resulting in decreased hepatic function. Overall, the clinical significance of these laboratory abnormalities is unclear.

3.13 Safety Conclusions

The pasireotide clinical program has provided important safety information derived from a variety of clinical sources that included not only the Phase 3 clinical trial described above in detail but also mechanistic and safety studies such as studies that evaluated the drug's effect on hepatic function, cardiac conduction (dedicated QT studies) and glucose metabolism.

In final analysis, the safety issues that are of immediate relevance in establishing a favorable benefit-to-risk ratio for this application are: 1) the development of hyperglycemia and 2) the elevations in liver enzymes. All other adverse events such as cholelithiasis, gastrointestinal tolerability, hypocortisolism, bradycardia, QT prolongation, pancreatitis, and changes in coagulation parameters represent safety findings that, we believe, can be communicated to health care providers via adequate labeling.

The development or worsening of hyperglycemia and diabetes is of particular concern in patients with Cushing's disease since they already have insulin resistance as a manifestation of the underlying hypercortisolism. Although by reducing endogenous cortisol production pasireotide is expected to ameliorate the clinical signs and symptoms related to hypercortisolemia (including glucose impairment/diabetes and its long-term complications), multiple observations made in the clinical program indicate that pasireotide treatment is also responsible for a concomitant reduction in insulin production which by itself results in the development and/or worsening of hyperglycemia. In the pivotal study B2305 marked increases in fasting plasma glucose were observed as early as 2 weeks after pasireotide treatment initiation, and HbA1c increases (approximately 1.5% mean absolute change on treatment relative to baseline) were seen in both dose groups by Month 2, which this led to an increase in the use of antihyperglycemic medications during the trial. This degree of deterioration in glycemic status poses challenges in establishing a clear favorable benefit/risk profile. In this context an answer needs to be provided as to whether the cortisol-lowering effect of the drug outweighs the

risks associated with pasireotide-induced hyperglycemia. It should be mentioned that this magnitude of HbA1c change is out of proportion to what has been observed with other somatostatin analogs approved to date for non-Cushing's disease indications.

Additional observations of potential concern which require further discussion and scrutiny are those related to liver enzyme elevations. Although mean liver enzyme levels remained within normal limits in the pivotal trial, 5.1% of all patients had ALT or AST elevations >3x upper limit of normal without concomitant bilirubin elevations. Across the clinical program there were 4 subjects - 3 healthy volunteers and one patient in a compassionate use study - with concomitant elevations of ALT and total bilirubin. Even though, as opposed to cases typical of drug-induced liver injury, the bilirubin elevations preceded or were concomitant with the transaminase elevations, in the absence of a complete hepatological work up, the mechanism and etiology of the liver test elevations remain unclear and require further discussion.

Finally, it should be noted that there were no striking safety differences between the 600 μg bid and the 900 μg bid dose regimens (although some analyses indicated a slightly higher incidence of AEs - including those related to hyperglycemia - in the 900 μg bid arm). With this in mind, exposure-response analyses provided in the pharmacometric review indicate a higher risk of developing hyperglycemia or of experiencing a worsening in hyperglycemia in association with higher exposure to pasireotide. This observation, along with the clinical trial data need to be considered in selecting a starting dose for pasireotide.

Appendix 1: Listing of Clinical Trials

Table 33: Clinical trials of pasireotide in non-Cushing's disease indications

Study	Study objective	# of patients	Treatment duration	Dosage
Acromegaly				
B2103	Double-blind randomized 3-way crossover to compare efficacy of single doses of SOM230 and sandostatin	12	Single doses with 6 day washout	octreotide 100 µg pasireotide 100 µg and 250 µg
B2201	Open-label, randomized, crossover study in acromegalic patients to assess efficacy, safety, PK/PD	60	16 weeks	octreotide 100 µg tid for 28 days followed by pasireotide
B2201E1	Open-label extension to assess long-term safety, efficacy and PK	30	Dependent on clinical benefit	Pasireotide 600 µg bid 900 µg bid
Carcinoid syndrome				
B2202	Open-label, non-randomized study in inadequately controlled carcinoid patients to assess safety, efficacy, QoL and PK	45	Dependent on clinical benefit	Pasireotide 300 µg bid 600 µg bid 900 µg bid 1200 µg bid

From Sponsor's Summary of Clinical Safety, Table 1-2

Table 34: Clinical studies in healthy volunteers used in evaluation of hepatic safety

Study	Study objective	# of patients	Treatment duration	Dosage
Single day studies				
B2102	Randomized, double-blind, placebo controlled ascending dose study	72 (18 placebo, 54 pasireotide)	1 day	Single dose pasireotide: 1µg, 2.5µg, 10µg, 30µg, 100µg, 200µg, 300µg, 600µg, or 1200µg
B2106	Open-label, ascending dose	17	1 day	Ascending dose Pasireotide 900µg, 1200µg, 1500 µg qd OR pasireotide 450 µg, 600 µg, 750 µg bid
B2112	Human ADME study	4	1 day	Single dose pasireotide 600 µg ^{14}C
C2101	Open-label, ascending single LAR dose	78	1 day	Single dose pasireotide 300 µg

Multiple Day Studies				
B2102	Randomized, double-blind, placebo-controlled crossover study	33	Crossover: 14 days placebo and 14 days pasireotide with 2-week washout	Screening and baseline of periods 1 and 2
B2107	Open-label ascending dose	66	8 days	Dose escalation: 150, 300, 600, 900, 1200, 1500µg qd 150µg, 300µg, 450µg, 600µg, 750µg bid
B2108	Open-label, ascending dose	44	7 days	s.c. continuous infusion: 450µg, 900µg, 1350µg, 1800µg, 2025µg, 2250µg
B2113	Part 1: ascending dose to assess MTD Part 2: Thorough QT study, randomized, double-blind	Part 1: 37 subjects on pasireotide Part 2: 88 subjects on pasireotide	Part 1: 7 days Part 2: 38 days	Part 1: Pasireotide ascending dose (MTD) 900µg, 1200µg, 1500µg, 1800µg, 1950µg, 2100µg bid Part 2: Pasireotide MTD with active and placebo-controlled crossover 1950µg bid, moxifloxacin (active control) and placebo
B2124	Randomized, open-label Phase 1 study of the effects of antihyperglycemic drugs and pasireotide on glucose metabolism in healthy males	90	7 days	Pasireotide monotherapy: 600 µg bid Pasireotide combination therapy: 600 µg bid + one of the following: metformin, nateglinide, vildagliptin, liraglutide
B2125	Randomized, placebo and active controlled, blinded QT study	107 subjects received pasireotide	51 days	4-way crossover with pasireotide (2 doses), moxifloxacin, and placebo 4 treatment periods of 5 days separated by 10 day washout period
Hepatic Impairment				
B2114	Open-label study	15 healthy volunteers, 19 subjects with hepatic insufficiency	Liver test monitoring at screening, Study Day 2, and Completion Day 7	Pasireotide 600 µg single dose
Investigator-initiated Trial (IIT)				
B2116	Randomized, double-blind looking at the effects of pasireotide on insulin secretion and glucose metabolism	45	8 days	Pasireotide 600 µg bid, 900 µg bid, 1200 µg bid

From Sponsor's Summary of Clinical Safety

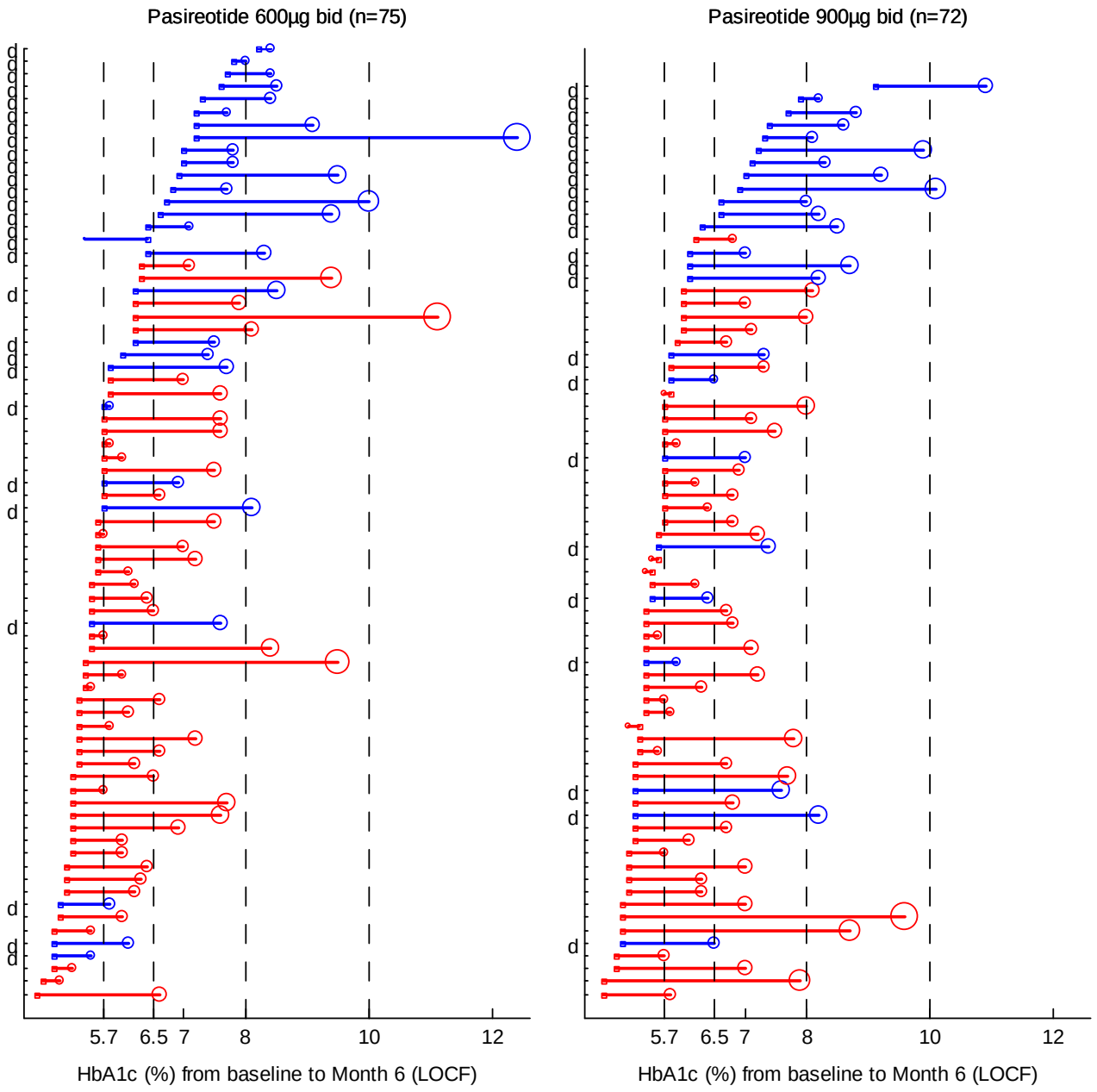
Table 35: Clinical studies in other indications used in evaluation of hepatic safety

Study	Study objective	# of patients	Treatment duration	Dosage
Acromegaly				
B2103	Double-blind randomized 3-way crossover to compare efficacy of single doses of SOM230 and sandostatin	12	Single doses with 6 day washout	octreotide 100 µg pasireotide 100 µg and 250 µg
B2201	Open-label, randomized, crossover study in acromegalic patients to assess efficacy, safety, PK/PD	60	16 weeks	octreotide 100 µg tid for 28 days followed by pasireotide
B2201E1	Open-label extension to assess long-term safety, efficacy and PK	30	Dependent on clinical benefit	pasireotide 600 µg bid 900 µg bid
Carcinoid syndrome				
B2202	Open-label, non-randomized study in inadequately controlled carcinoid patients to assess safety, efficacy, QoL and PK	45	Dependent on clinical benefit	pasireotide 300 µg bid 600 µg bid 900 µg bid 1200 µg bid

From Sponsor's Summary of Clinical Safety, Table 1-2

Appendix 2: Individual HbA1c changes

Figure 14: Individual HbA1 c changes from baseline to Month 6 for the 600 µg bid and 900 µg bid dose groups; d=subject was diabetic at baseline



Appendix 3: Additional Efficacy Analyses

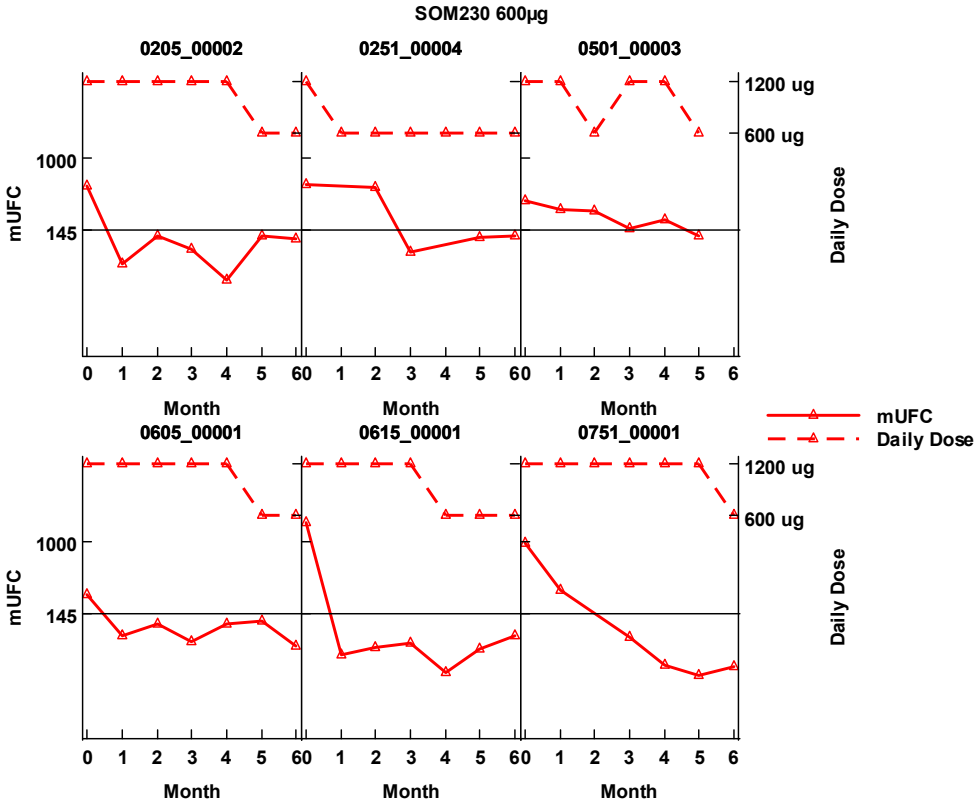
Dose reduction in responders

It should be noted that although the primary endpoint results are presented according to the randomized dose group, there were subjects--including "controlled" subjects--who were actually taking lower doses than their original randomized doses. Doses were allowed to be lowered for tolerability issues. Specifically, at Month 6, of the 13 controlled subjects in the 600 µg bid group, there were 6 subjects taking 300 µg bid. In the 900 µg bid group, there were 5 subjects who achieved mUFC normalization at a lower dose. For these 11 subjects, the figures below concomitantly display the mUFC (subjects with at least 2 samples) and total daily dose prior to each monthly study visit over time.

One of the 6 patients normalized in the 600 µg bid group was down titrated in the first month (Subject 0251-00004). The other 5 subjects were on the randomized dose for 3 to 5 months.

Overall, in these subjects, it appears that down-titration did not affect the drug's efficacy.

Figure 15: mUFC (left y-axis) and daily dose (right axis) over monthly visits by responders with dose decrease



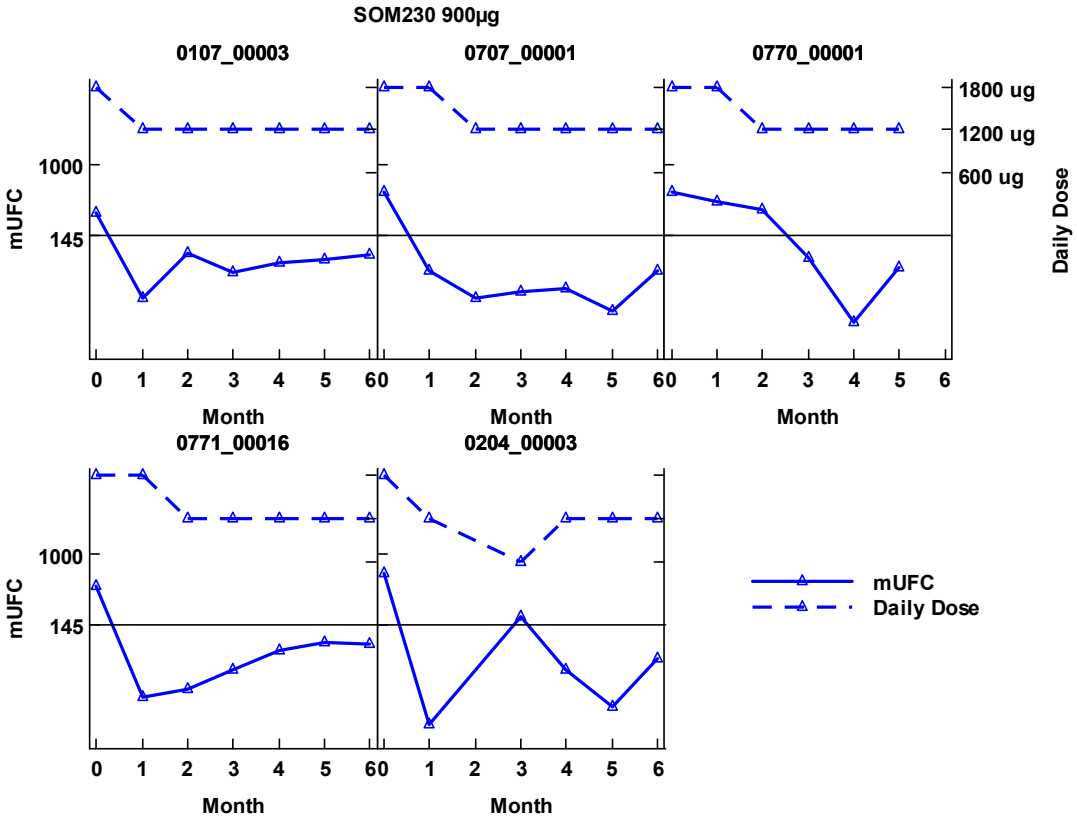

SOM230 900µg
0107_00003
0707_00001
0770_00001
0771_00016
0204_00003
mUFC
1000
145
Month
1800 ug
1200 ug
600 ug
Daily Dose
mUFC
Daily Dose

Table 36: Mean change from baseline in other clinical signs and symptoms of Cushing's disease by randomized dose group at Month 6

Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80		
n	**Baseline mean (SD)**	**Mean (SD)**	**n**	**Baseline mean (SD)**	**Mean (SD)**
BMI, kg/m^2					
59	30.3 (6.5)	-1.2 (1.6)	57	30.4 (7.0)	-2.1 (1.7)
Waist circumference, cm					
53	103 (18)	-1.9 (8.3)	54	102 (18)	-3.4 (5.4)
Total cholesterol, mmol/L					
59	6.1 (1.3)	-0.4 (1.2)	55	5.5 (1.2)	-0.4 (1.0)
Triglycerides, mmol/L					
59	1.8 (0.9)	0.0 (0.9)	55	1.7 (0.9)	0.1 (1.00)
Beck depression inventory (BDI-II score)					
56	19.3 (11)	-4.6 (9.5)	55	18.2 (10.7)	-5.5 (8.8)
Ferriman-Galway hirsutism score					
44	7.6 (5.5)	-0.9 (2.9)	47	8.7 (8.1)	-2.4 (4.7)
Lumbar vertebrae (L1-L4) bone mineral density, mg/cm^3					
47	0.98 (0.16)	-0.0 (0.06)	39	1.03 (0.16)	-0.01 (0.04)
Proximal femur (total hip) bone mineral density, mg/cm^3					
46	0.91 (0.16)	-0.0 (0.07)	38	0.94 (0.15)	-0.02 (0.05)
Proximal femur (femur neck) bone mineral density, mg/cm^3					
46	0.82 (0.14)	-0.0 (0.03)	38	0.86 (0.15)	-0.01 (0.05)
Body composition: Region (% fat)					
39	41.3 (8.1)	-0.43 (3.77)	32	41.5 (6.9)	-0.95 (4.06)

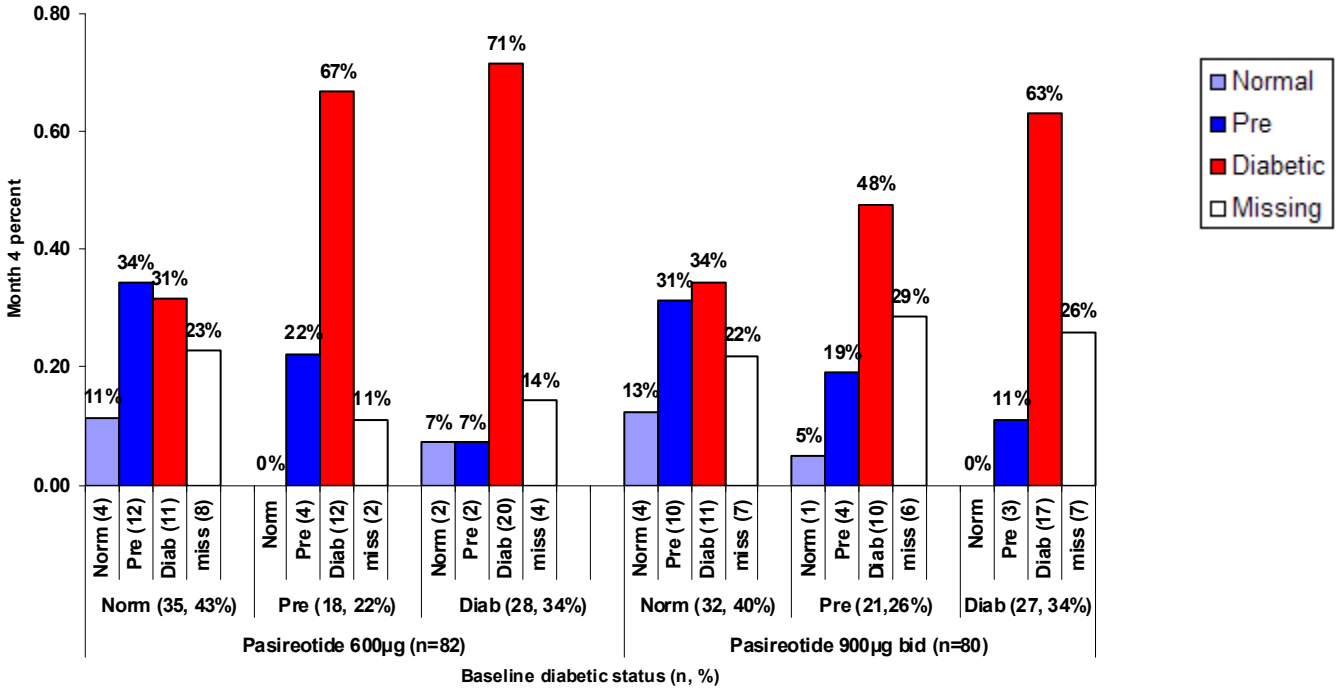
From Sponsor's Clinical Study Report

Appendix 4: Shift tables for diabetic status at Month 4

Table 37: Shift in diabetic status from baseline to Month 4 by randomized dose group (Study 2305)

Baseline status	Pasireotide 600 µg s.c. bid					Pasireotide 900 µg s.c. bid				
		Month 4					Month 4			
	Baseline	Normal	Pre-Diabetic	Diabetic	Missing	Baseline	Normal	Pre-Diabetic	Diabetic	Missing
Normal	35 (43%)	4 (11%)	12 (34%)	11 (31%)	8 (23%)	32 (40%)	4 (13%)	10 (31%)	11 (34%)	7 (22%)
Pre-Diabetic	18 (22%)	0 (0.0%)	4 (22%)	12 (67%)	2 (11%)	21 (26%)	1 (5%)	4 (19%)	10 (48%)	6 (29%)
Diabetic	28 (34%)	2 (7%)	2 (7%)	20 (71%)	4 (14%)	27 (34%)	0	3 (11%)	17 (63%)	7 (26%)
Missing	1 (1%)	1 (100%)	0	0	0	0	0	0	0	0
Total	82 (100%)	7 (9%)	18 (22%)	43 (52%)	14 (17%)	80 (100%)	5 (6%)	17 (21%)	38 (48%)	20 (25%)

Figure 16: Shift in diabetic status from baseline to Month 4 by randomized dose group (Study 2305)



Sponsor's Glucose Metabolism Report, Table 5-35

Appendix 5: Additional Hepatic Safety Analyses

For this Application, the Sponsor prepared a dedicated "Hepatic Report" to specifically address the hepatic safety of pasireotide and focuses on the safety data from 19 Phase 1, 2, and 3 clinical trials in both healthy volunteers and patients treated with the s.c. formulation. The patient data includes those treated with Cushing's disease, acromegaly, and carcinoid syndrome.

The analysis includes a number of different populations—including healthy volunteers and patients with Cushing's disease, acromegaly, and carcinoid. The complete list and descriptions of studies used in the evaluation of hepatic safety are in the Appendix.

Results for studies in healthy volunteers are presented first.

Healthy volunteer studies

The table below is a summary of liver test outliers for studies in healthy volunteers. Overall, elevations in total bilirubin (particularly >ULN to <2xULN) were the most commonly observed parameter. There were 3 subjects who had concomitant elevations of ALT>3xULN and TB≥2xULN, and 2 of these (bolded in table below), from a strictly biochemical perspective, met criteria for Hy's Law. Hy's law cases have the following three components[1]:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such ALT elevations, often with ALTs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

It should be noted that a full diagnostic work-up (including testing for hepatitis) was not done in subjects with liver test elevations. It is only with the thorough and thoughtful exclusion of other causes of liver test elevations that one can employ Hy's law criteria in diagnosing drug-induced liver injury (DILI). The third did not have an alkaline phosphatase measured and was therefore not included in the table below (and not technically included in the count of Hy's law subjects).

Table 38: Liver enzyme and total bilirubin outlier summary—healthy volunteers (single & multiple day dosing) and hepatic impairment study

Study	N	AxT[1] >3xULN n (%)	AxT >5xULN n (%)	AxT >10xULN n (%)	AxT >20xULN n (%)	Tbili >ULN to <2xULN n (%)	Tbili ≥2xULN n (%)	ULNs>3x AxT, ≥2x Tbili, <2x AP n (%)
Healthy volunteers single day studies								
B2101								
<300 µg/d	36	0	0	0	0	3 (8.3)	0	0
≥300 µg/d	18	0	0	0	0	1 (5.6)	0	0
Placebo	18	0	0	0	0	1 (5.6)	0	0
B2106								
≥300 µg/d	17	0	0	0	0	7 (41.2)	1 (5.9)	0
B2112								
≥300 µg/d	4	0	0	0	0	0	0	0
C2101								
≥300 µg/d	78	0	0	0	0	0	0	0
Healthy volunteers multiple day studies								
B2102								
<300 µg/d	22	0	0	0	0	0	1 (4.5)	0
≥300 µg/d	11	0	0	0	0	1 (9.1)	0	0
Placebo	30	0	0	0	0	2 (6.7)	0	0
B2107								
<300 µg/d	6	0	0	0	0	0	0	0
≥300 µg/d	60	0	0	0	0	6 (10.0)	0	0
B2113 Part1								
≥300 µg/d	37	0	0	0	0	0	0	0
Placebo	18	1 (5.6)	0	0	0	1 (5.6)	0	0
B2213 Part2								
1950 µg/bid	103	1 (1.0)	0	0	0	3 (2.9)	0	0
Placebo	83	0	0	0	0	0	0	0
Mox[2]	84	1 (1.2)	1 (1.2)	0	0	3 (3.6)	0	0
B2124								
600 µg/bid	90	8 (8.9)	2 (2.2)	0	0	28 (31.1)	8 (8.9)	**1 (1.1)[3]**
B2125								
600 µg/bid	105	0	0	0	0	10 (12.7)	0	0
1950 µg/bid	105	3 (3.8)	1 (1.3)	0	0	9 (11.4)	1 (1.3)	**1 (1.3)**
Placebo	108	0	0	0	0	2 (1.9)	1 (0.9)	0
mox[2]	107	0	0	0	0	3 (2.8)	0	0
Hepatic Impairment Study								
B2114								
600 µg/d	34	0	0	0	0	18 (52.9)	6 (17.6)	0
Continuous s.c. infusion study								
B2108								
≥300 µg/d	43	3 (7.0)	0	0	0	5 (11.6)	0	0

From Sponsor's Hepatic Report, Table 4-1

[1]AxT=AST or ALT

[2]=moxifloxacin (active control used in B2113 and B2125 thorough QT studies)

[3]=One additional subject had a concomitant elevation of ALT>3xULN and TB≥2xULN, but the ALP was not measured and therefore this subjects is not captured in this table.

The following are specific observations for some of the healthy volunteer and hepatic impairment studies above:

- Study 2124, designed to evaluate the effect of several anti-diabetic medications on pasireotide-induced hyperglycemia, had a notably high percentage of subjects with bilirubin elevations. Two subjects had concomitant elevations of ALT>3xULN and TB≥2xULN (discussed above). One was treated with pasireotide alone and one was treated with pasireotide + vildagliptin. Both had normal liver tests at baseline. There was one subject treated with pasireotide + liraglutide who became clinically jaundiced at Day 7 with a total bilirubin 4.9xULN. ALT and AST were normal and GGT was 1.5xULN. Over 2 weeks after the last dose of pasireotide, total bilirubin remained elevated (2.7xULN). Liver biopsy did not indicate drug-induced toxic cholestasis.
- Study 2125, a second thorough QT study, had a notable percentage of subjects with bilirubin elevations. Also included was another subject who met Hy's law criteria.
- Study 2114 looked at the pharmacokinetics of a single injection of pasireotide in healthy volunteers and patients with varying degrees of hepatic insufficiency. In most of the cases of bilirubin≥2xULN there was baseline hyperbilirubinemia.
- Study 2108 looked at the safety of 7 days of continuous subcutaneous infusion of pasireotide. Four subjects in the 1800 µg/d had elevated liver tests (mostly Grade 1 ALT increases). Therefore a second 1800 µg/d cohort was recruited, and one subject in this cohort had elevated liver tests. The increases were mostly transient and not clinically notable. These 5 subjects with elevated liver tests were all re-challenged at the same dose: 3 of these subjects had increases in ALT and AST and 2 had increase in GGT. Of all the subjects in this study with liver test elevations, there was no clear dose dependency.

Patient trials

Interestingly, there were no cases meeting biochemical Hy's law criteria in the patient trials. In the pivotal trial 2305, of 162 subjects there were 8 (5.1%) with elevations of ALT or AST>3xULN. Six of these 8 were in the 600 µg group.

Table 39: Liver enzyme and total bilirubin in patient trials

Study	**N**	**AxT[1] >3xULN n (%)**	**AxT >5xULN n (%)**	**AxT >10xULN N (%)**	**AxT >20xULN n (%)**	**Tbili >ULN to <2xULN n (%)**	**Tbili ≥2xULN n (%)**	**ULNs>3x AxT, ≥2x Tbili, <2x AP n (%)**
Cushing's disease								
B2208 Pasireotide	39	2 (5.1)	0	0	0	2 (5.1)	0	0
B2208E Pasireotide	19	1 (5.3)	1 (5.3)	1 (5.3)	0	5 (26.3)	0	0
B2305[2] Pasireotide	162	8 (5.1)	1 (0.6)	0	0	8 (5.1)	0	0
Acromegaly								
B2103 pasireotide	12	0	0	0	0	0	0	0
octreotide	12	0	0	0	0	0	0	0
B2201 pasireotide	60	1 (1.7)	0	0	0	10 (15.9)	0	0

octreotide	60	1 (1.7)	0	0	0	8 (13.3)	0	0
B2201E Pasireotide	30	1 (3.3)	1 (3.3)	0	0	8 (26.7)	0	0
Carcinoid Syndrome								
B2202 Pasireotide	45	2 (4.4)	2 (4.4)	2 (4.4)	1 (2.2)	2 (4.4)	2 (4.4)	0

From Sponsor's Hepatic Report, Table 4-2

[1]=AST or ALT

[2]Percentages based on number of patients who had a non-missing post-baseline assessment.

Study 2305: In this pivotal trial of 162 subjects (156 with evaluable liver tests), 8 (5.1%) had elevations of ALT or AST>3xULN; 6 were in the 600 µg group and 2 were in the 900 µg group. One subject from the 600 µg group was found to have an ALT 6 x ULN (and GGT 8.5 x ULN) on Day 30. This subject's narrative is included below.

Study 2208 and 2008E: All 39 subjects in this trial received pasireotide 600 µg bid for 15 days. There were 2 subjects with ALT or AST >3xULN. One of these subjects had a baseline elevated ALT (8.1xULN), GGT 11.2xULN and AST 2.1xULN; TB and ALP were normal. During the 15 day trial the ALT remained between 3x and 5xULN. In the extension phase the ALT peaked at 12.6xULN. This subject's narrative is included below.

Study 2201: Sixty subjects with acromegaly were treated with octreotide for 30 days followed by a 3 month period with pasireotide at doses of 200, 300, and 600 µg bid (each dose for 30 days). Both groups had notable mild elevations in total bilirubin.

Study 2202: There were 45 subjects with carcinoid treated with doses ranging from 300 to 1200 µg bid. There were 2 subjects with AST or ALT>10xULN and 1 subject had a one-rime elevation of AST 58.2xULN on Day 339. There were 2 subjects with total bilirubin≥2xULN: one had a value of 4.1xULN and the other had an elevated baseline value of 4.3xULN but the highest value on pasireotide was 3.8xULN. No patients had concomitant notable elevations of AST/ALT and bilirubin.

Mean changes in liver tests: For the healthy volunteer studies, the Sponsor calculated mean changes for Studies 2124 and 2125, based on a sufficiently large sample size and drug exposure. Overall, in Study 2124 changes in ALT were notable at Day 7. Pasireotide alone was associated with mean increases in ALT and total bilirubin but still remained within the upper limits of normal. There was no consistent effect on liver tests when adding anti-hyperglycemic medications to pasireotide. For ALT at Day 7, the steepest increases were observed in the metformin and vildagliptin groups, although the pasireotide 600 µg only group nearly doubled ALT at Day 7. The greatest increases for total bilirubin at Day 7 were seen in the vildagliptin and liraglutide groups. Detailed data are included in the Appendix.

In Study 2125, the second through QT study, 2 different doses of pasireotide in addition to moxifloxacin and placebo were studied. Most of the remarkable changes were limited to the pasireotide 1950 µg group: ALT and bilirubin nearly doubled (although still

remained below the ULN). The pasireotide 600 µg group had slight decreases in AST and ALT, and a modest median increase in total bilirubin.

During the 15-day Study 2008, changes in ALT and total bilirubin were minimal. There were slight mean increases in AST. From a strictly biochemical perspective, the changes were not remarkable.

In the pivotal trial 2305, mean changes in liver tests were mostly unremarkable. There were some increases in AST and ALT at Month 1, but values returned to normal by Month 4 and beyond. Mean total bilirubin did not increase.

Liver safety-related/gallbladder and biliary-related SAEs and discontinuations due to AEs:
In all the healthy volunteer studies, there were only 2 subjects with an SAE or discontinuation due to an AE:

- One subject in 2124 treated with pasireotide 600 µg had mild cholestasis that was deemed to be drug-related.
- One subject in 2114 had baseline severe hepatic insufficiency and was hospitalized for worsening hepatic encephalopathy 16 days after the single dose of pasireotide 600 µg

The table below summarizes liver-related AEs and SAEs in the patient studies leading to discontinuation.

Table 40: Liver safety-related and biliary-related SAEs and AEs leading to discontinuation—Cushing's disease, acromegaly, carcinoid syndrome for patients treated with pasireotide

		Serious Adverse Events		Discontinuations due to AEs	
	N	Hepatic n (%)	Biliary n (%)	Hepatic n (%)	Biliary n (%)
Cushing's Disease					
B2305	162	0	6	6	1
B2208	39	0	0	0	0
B2208E	19	0	0	0	0
Acromegaly					
B2103	12	0	0	0	0
B2201	60	0	0	0	0
B2201E	30	0	1	0	1
Carcinoid Syndrome					
B2202	45	2	0	0	0

From Sponsor's Hepatic Report, Table 4-17

The pivotal trial 2305 had the most events, with 6 SAEs and 7 discontinuations due to an AE. All of the SAEs were related to cholelithiasis. The discontinuations due to liver-related AEs were as follows:

- Subject 361/00003 (900 µg bid) was noted to have elevated GGT and ALT on Day 196, which resolved or improved without stopping study drug. On Day 252,

the elevations were noted again and were resolved without stopping study drug. On Day 301, AST, ALT and GGT were elevated. Study dug was discontinued. All three events resolved 47 days after receiving the last lose of study drug.

- Subject 0904/00009 (600 µg bid) was noted to have increased liver tests (ALT=46 U/L) on Day 34. Study drug was unchanged. On Day 93, the liver tests worsened (ALT=139 U/L, AST=57 /L, GGT=291 U/L, ALP=68 U/L, TB=10 µmol/L). Study drug was discontinued. Approximately 30 days after receiving the last dose of study drug, liver tests were still improving.
- Subject 0382/00003 (was diagnosed with an elevated GGT on Day 85; other liver tests were normal. On Day 171, the GGT worsened. Study drug was discontinued. The event was noted to be resolved on Day 211.
- Subject 0711/0002 (900 µg bid) had an elevated ALT at baseline (72 U/L). On Day 29 the ALT was noted to be 121 U/L and GGT was 147 U/L. Study drug was discontinued and the events worsened on Day 57 (ALT=165 U/L and GT=190 U/L). Study drug was discontinued. On Day 72 events were ongoing.
- Subject 0501/00007 had a history of diabetes which required increasing doses of both glipizide and metformin and eventually insulin. On Day 32. GGT was noted to be elevated at 998 U/L. Study drug was discontinued.
- Subject 0501/00003 (600 µg bid) had baseline elevations of ALT (1.5xULN) and GGT (1.7xULN). On Day 30, this subject's AST was 3.3xULN, ALT was 6xULN, GGT was 8.5xULN and ALP 1.4xULN. On Day 46, after the noted events had improved, study drug was restarted at a reduced dose. On Day 93, GGT was elevated again to 7.6xULN. Study drug was permanently discontinued. This event was ongoing at the time of the last report.

In the acromegaly studies, 1 subject had a biliary-related SAE (Study 2201E). This was a case of chronic cholecystitis which also resulted in study discontinuation.

In the carcinoid studies, there were 2 subjects with lever-related SAEs. Both had hepatic artery embolism and both were likely unrelated to study drug.

Table 41: Hyperglycemia-related adverse events by preferred term, up to data cut-off

	Pasireotide 600 µg b.i.d. N = 82		Pasireotide 900 µg b.i.d. N = 80		Overall N = 162	
	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	19 (23.2)	61 (74.4)	21 (26.3)	57 (71.3)	40 (24.7)	118 (72.8)
Blood glucose increased	0 (0.0)	6 (7.3)	0 (0.0)	3 (3.8)	0 (0.0)	9 (5.6)
Blood insulin decreased	0 (0.0)	1 (1.2)	0 (0.0)	4 (5.0)	0 (0.0)	5 (3.1)
Diabetes mellitus	6 (7.3)	13 (15.9)	6 (7.6)	16 (20.0)	12 (7.4)	29 (17.9)
Glucose tolerance impaired	0 (0.0)	2 (2.4)	0 (0.0)	2 (2.5)	0 (0.0)	4 (2.5)
Glycosuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.6)
Glycosylated hemoglobin increased	1 (1.2)	10 (12.2)	0 (0.0)	8 (10.0)	1 (0.6)	18 (11.1)
Hyperglycemia	8 (9.8)	31 (37.8)	13 (16.3)	34 (42.5)	21 (13.0)	65 (40.1)
Hypoglycemia	3 (3.7)	12 (14.6)	0 (0.0)	3 (3.8)	3 (1.9)	15 (9.3)
Type 2 diabetes mellitus	4 (4.9)	10 (12.2)	3 (3.8)	5 (6.3)	7 (4.3)	15 (9.3)

Applicant's Glucose Metabolism Report

Study 2124

Another Phase 1 study (2124) entitled "A randomized, open-label, single center, phase I study to evaluate the effects of the co-administration of anti-hyperglycemic drugs and pasireotide s.c. compared to pasireotide s.c. alone on glucose metabolism in healthy male volunteers" was initiated to understand the effects of anti-hyperglycemic agents when used in combination with pasireotide. The primary objective was to evaluate the effect of concomitant administration of pasireotide s.c. and metformin, nateglinide, vildagliptin or liraglutide, on glucose levels, after 1 week of pasireotide treatment, assessed by AUC during a 4-hour OGTT. There were 5 treatment arms, each treated for 7 days:

- Treatment arm 1: Pasireotide 600 µg s.c. bid + metformin 500 mg immediate release (IR) p.o. b.i.d
- Treatment arm 2: Pasireotide 600 µg s.c. bid + nateglinide 60 mg p.o. t.i.d.
- Treatment arm 3: Pasireotide 600 µg s.c. b.i.d. + vildagliptin 50 mg p.o. t.i.d.
- Treatment arm 4: Pasireotide 600 µg s.c. b.i.d. + liraglutide 0.6 mg s.c. q.d.
- Treatment arm 5: Pasireotide 600 µg s.c. b.i.d.

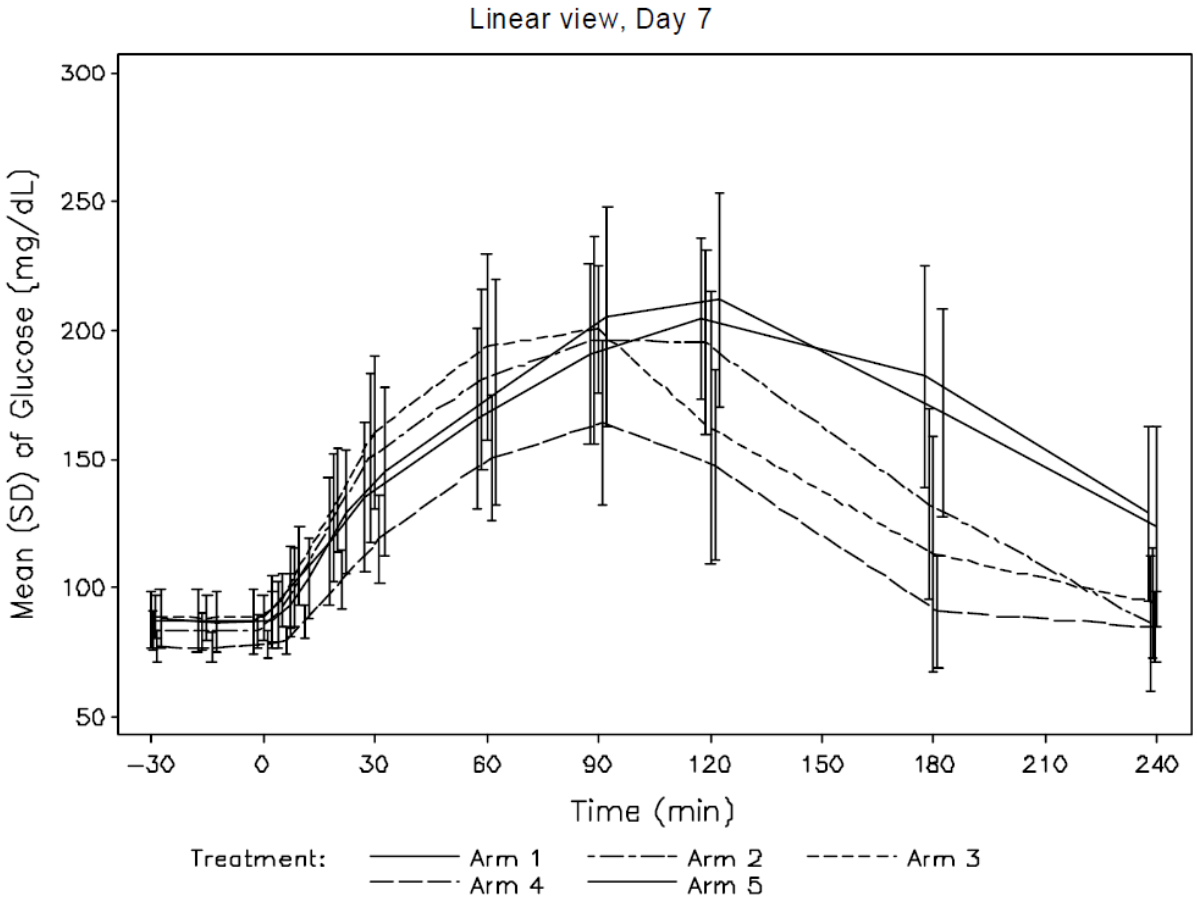
As an overall trend, mean postprandial plasma glucose levels on Day 7 were lower when pasireotide was co-administered with nateglinide, vildagliptin and liraglutide. During an OGTT, reductions in plasma glucose $AUC_{0\text{-}4hr}$ were 10%, 15% and 29%, respectively, when compared to pasireotide alone. The results are depicted in the figure below.

The reductions seem to be consistent with studies in which these drugs were administered to patients with type 2 diabetes or healthy subjects.[12] The greatest effect was seen with

[12] He YL et al 2007, Hirose et al 2002, Kalbag et al 2001, Vilsboll et al 2008.

liraglutide. No antihyperglycemic effect was observed with metformin. However, the Sponsor hypothesizes that the lack of effect is consistent with metformin's mechanism of action to decrease hepatic glucose production and to improve insulin sensitivity by increasing peripheral glucose uptake, which are not effected by pasireotide.

Figure 17: Arithmetic mean (SD) plasma concentration-time profiles for glucose (mg/dL) on Day 7 (PD set—Study SOM230B2124)



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.
Time relative to OGTT

From Applicant's Glucose Metabolism Report

Changes in fasting glucose levels did not appear to be clinically significant at Day 7, with the exception of the liraglutide arm, which had an approximately 10% decrease.

After 7 days of treatment, serum insulin $AUC_{0\text{-}4h}$ was increased by 71% and 34% for the vildagliptin and liraglutide groups, respectively, compared to pasireotide alone. In

contrast, the increases were minor for the metformin and nateglinide groups (6% and 3% respectively). The Sponsor believes the minor effect from nateglinide is related to its short-acting profile.

On Day 7, there were 11-21% lower pasireotide OK exposures in combination with nateglinide and liraglutide. The Sponsor asserts that this decrease, however, would have a minimal effect of the PD effects when combining these drugs with pasireotide.

From as safety perspective, the co-administration of pasireotide with liraglutide appeared to the most problematic. Specifically, abdominal pain and vomiting were increased compared to pasireotide alone. Also, this combination of drugs, compared to the other treatment arms, had an overall greater frequency of more common AEs, CTCAE Grade 3 clinically significant AEs, and laboratory abnormalities.

The majority of hypoglycemic events (12 of 14 total events) were experienced after the noon dose of nateglinide.

Table 42: Mean and median changes in liver enzymes and total bilirubin over time –Study 2124 (healthy volunteers)

Visit		Pasireotide 600 µg Metformin 500 mg IR po bid N=18	Pasireotide 600 µg Nateglinide 60 mg po tid N=18	Pasireotide 600 µg vildagliptin 50 mg po bid N=18	Pasireotide 600 µg liraglutide 0.6 mg s.c. qd N=18	Pasireotide 600 µg N=18
ALT (U/L)		n=17	n=18	n=18	n=17	n=17
baseline	Mean (SD) Median	25.5 (7.4) 23.6	20.8 (7.6) 19.1	2.24 (6.7) 21.7	20.2 (9.9) 18.8	21.2 (5.9) 21.8
Day 7 change from baseline	Mean (SD) Median	n=17 47.6 (82.0) 17.5	n=18 17.56 (41.7) 2.1	n=18 35.2 (46.3) 16.8	n=17 11.6 (27.7) 1.1	n=17 19.8 (46.1) -0.2
FU change from baseline	Mean (SD) Median	n=18 3.14 (7.7) 3.7	n=18 0.7 (4.7) 1.9	n=18 4.8 (7.7) 3.7	n=17 2.5 (10.6) 1.1	n=18 2.7 (7.9) 0.1
AST (U/L)		n=17	n=18	n=18	n=17	n=17
baseline	Mean (SD) Median	24.7 (6.2) 24.4	21.9 (4.7) 20.9	23.6 (4.9) 22.4	21.6 (4.6) 21.3	23.2 (3.4) 22.5
Day 7 change from baseline	Mean (SD) Median	n=17 21.0 (39.7) 8.2	n=18 7.2 (21.1) -0.6	n=18 16.4 (25.9) 6.0	n=17 6.7 (14.8) 1.1	n=17 5.2 (18.9) -0.1
FU change from baseline	Mean (SD) Median	n=18 1.8 (9.3) 0.5	n=18 1.6 (3.3) 2.2	n=18 2.0 (4.8) 1.25	n=17 2.8 (4.3) 1.9	n=18 0.8 (3.5) 1.3
Total bilirubin (umol/L) baseline	Mean (SD) Median	n=17 11.7 (5.4) 10.9	n=18 12.5 (4.5) 11.9	n=18 12.6 (5.0) 11.1	n=17 11.1 (3.2) 10.4	n=17 12.5 (4.0) 11.7
Day 7 change from baseline	Mean (SD) Median	n=17 4.45 (4.7) 5.2	n=18 2.8 (7.9) 1.5	n=18 7.5 (11.7) 4.1	n=17 9.54 (18.4) 4.2	n=17 6.7 (12.2) 2.5
FU change from baseline	Mean (SD) Median	n=18 -3.3 (4.3) 2.2	n=18 -3.9 (4.3) -2.7	n=18 -2.5 (4.0) -2.1	n=17 -0.2 (10.4) -3.2	n=18 -3.4 (4.3) -3.2

Adapted from Sponsor's Hepatic Report, Table 4-10
FU=follow-up (14 days after last dose of study medication)

bilirubin (umol/L) baseline	Mean (SD) Median	11.7 (5.4) 10.9	12.5 (4.5) 11.9	12.6 (5.0) 11.1	11.1 (3.2) 10.4	12.5 (4.0) 11.7
Day 7 change from baseline	Mean (SD) Median	n=17 4.45 (4.7) 5.2	n=18 2.8 (7.9) 1.5	n=18 7.5 (11.7) 4.1	n=17 9.54 (18.4) 4.2	n=17 6.7 (12.2) 2.5
FU change from baseline	Mean (SD) Median	n=18 -3.3 (4.3) 2.2	n=18 -3.9 (4.3) -2.7	n=18 -2.5 (4.0) -2.1	n=17 -0.2 (10.4) -3.2	n=18 -3.4 (4.3) -3.2

Adapted from Sponsor's Hepatic Report, Table 4-10
FU=follow-up (14 days after last dose of study medication)

Exposure-Response Analysis

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Exposure-Response Analysis to Support Lower Starting Dose

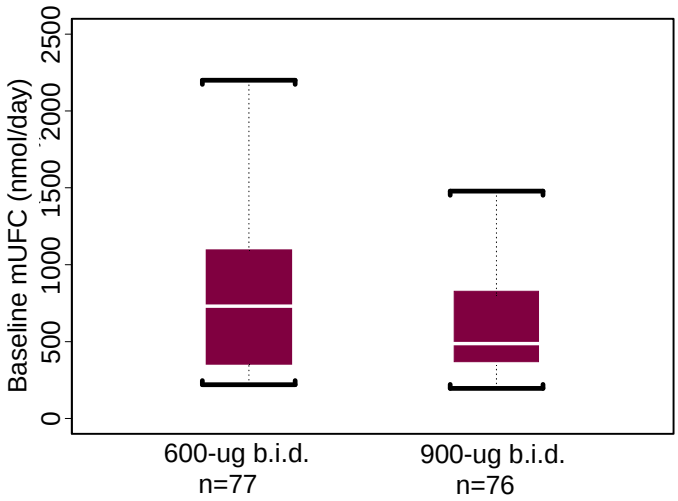
The objective of the present analysis was to explore the adequate starting dose from an exposure-response perspective. Both exposure-response analysis for efficacy and safety were performed on the pivotal trial data (study B2035). The data from phase 2 trial (study B2208) was not utilized in the exposure-response analysis because the duration of the trial was 15 days and the mUFC response does not reach its steady state by Day 15.

1. Introduction

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.

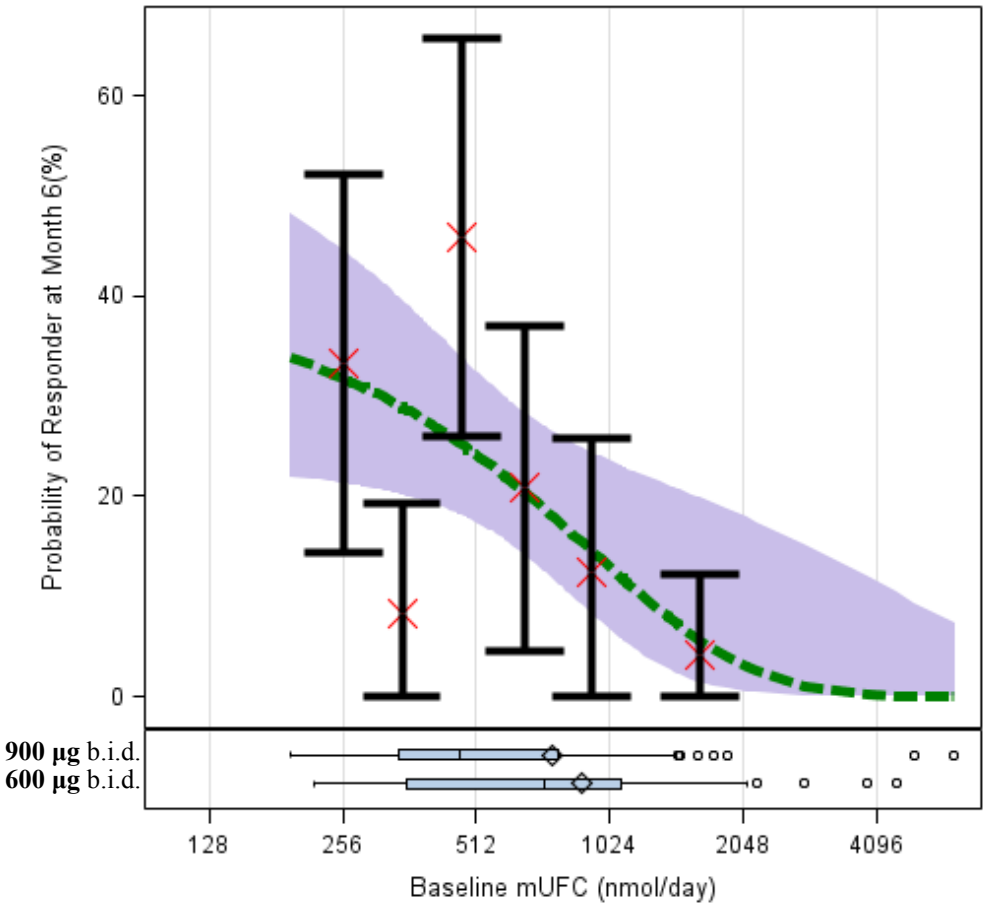
It is important to note that although the pivotal trial (Study B2305) was randomized, the baseline mUFC of patients in 600 µg b.i.d. dose group was 50% higher than in the 900 µg b.i.d. dose group (**Figure 1**). Furthermore, it was observed that the probability of responding to pasireotide decreases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



Note: The above figure is based on FDA's Pharmacometric analysis of the data from the B2305 trial

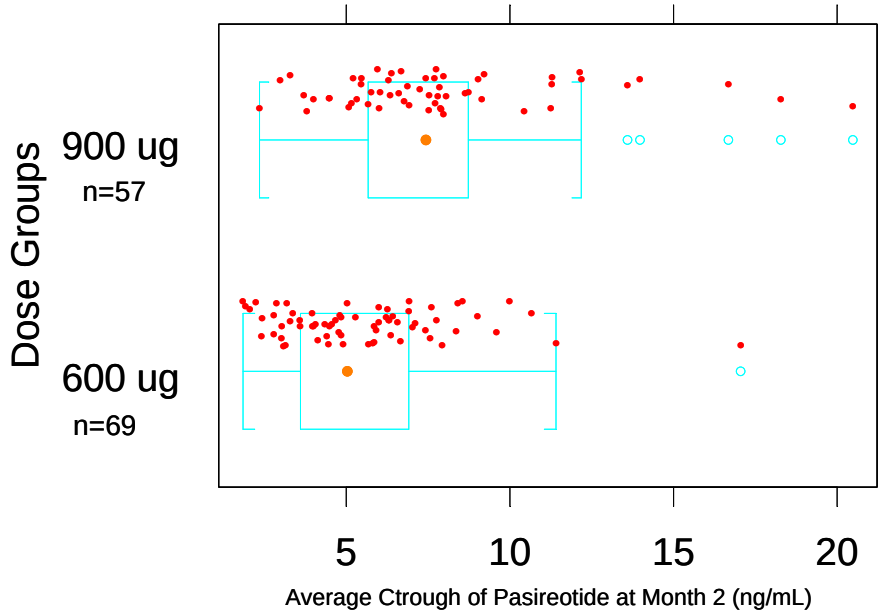
Figure 2: Responder Status is associated with baseline mUFC. Logistic regression model includes the probability of responder at month 6 as a function of baseline mUFC. The mean and 95% CI of the observed response rate versus the mean observed baseline mUFC is represented by black bars while dashed green 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.



Note: The above figure is based on FDA's Pharmacometric analysis of the data from the B2305 trial

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.

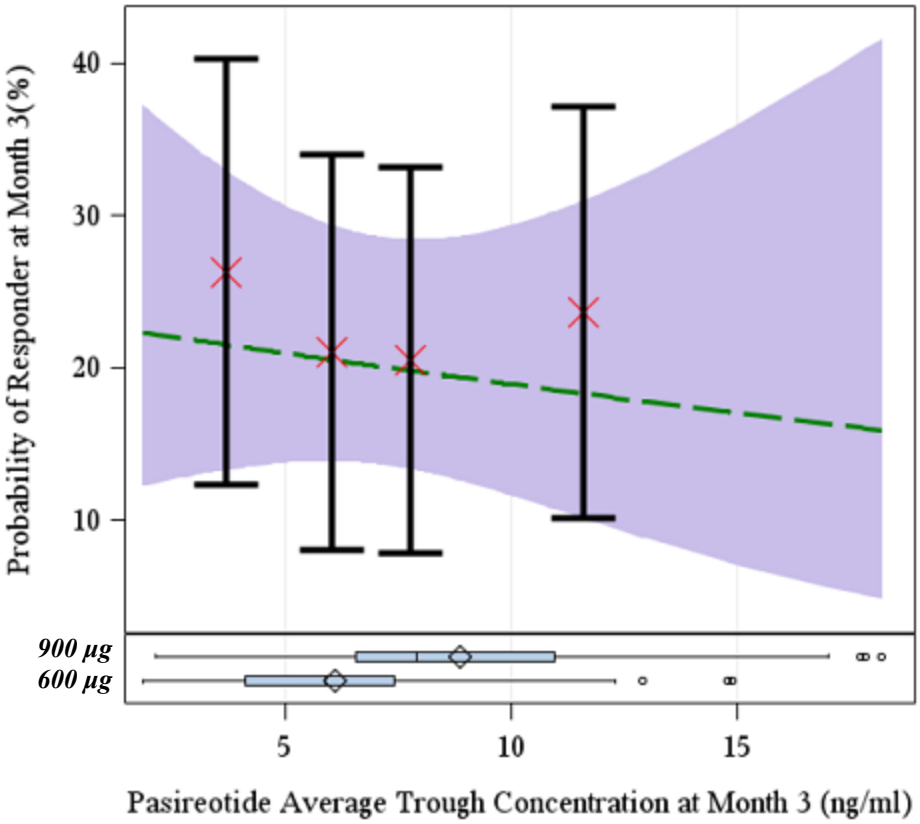


Note: The above figure is based on FDA's Pharmacometric analysis of the data from the B2305 trial

2. Exposure-Response Analysis for Efficacy

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.

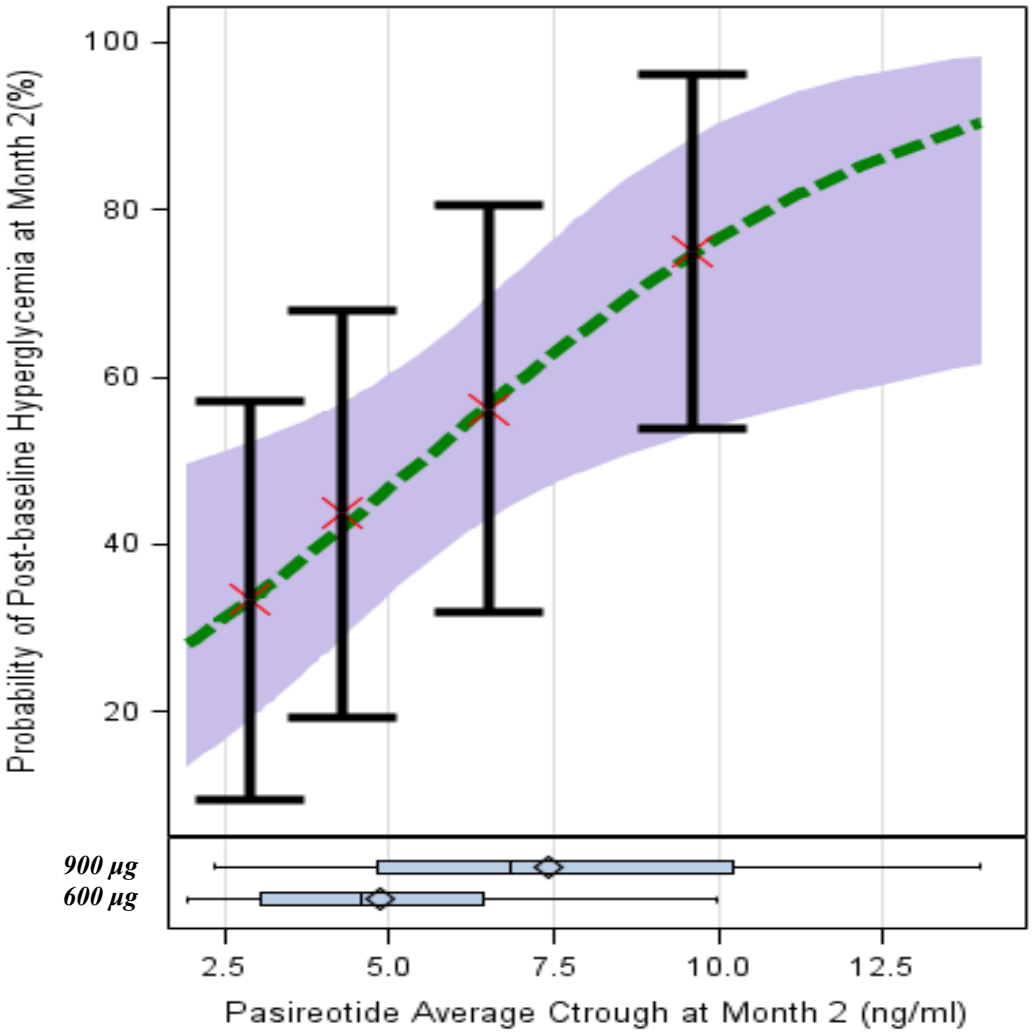


Note: The above figure is based on FDA's Pharmacometric analysis of the data from the B2305 trial

3. Exposure-Response Analysis 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.

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.

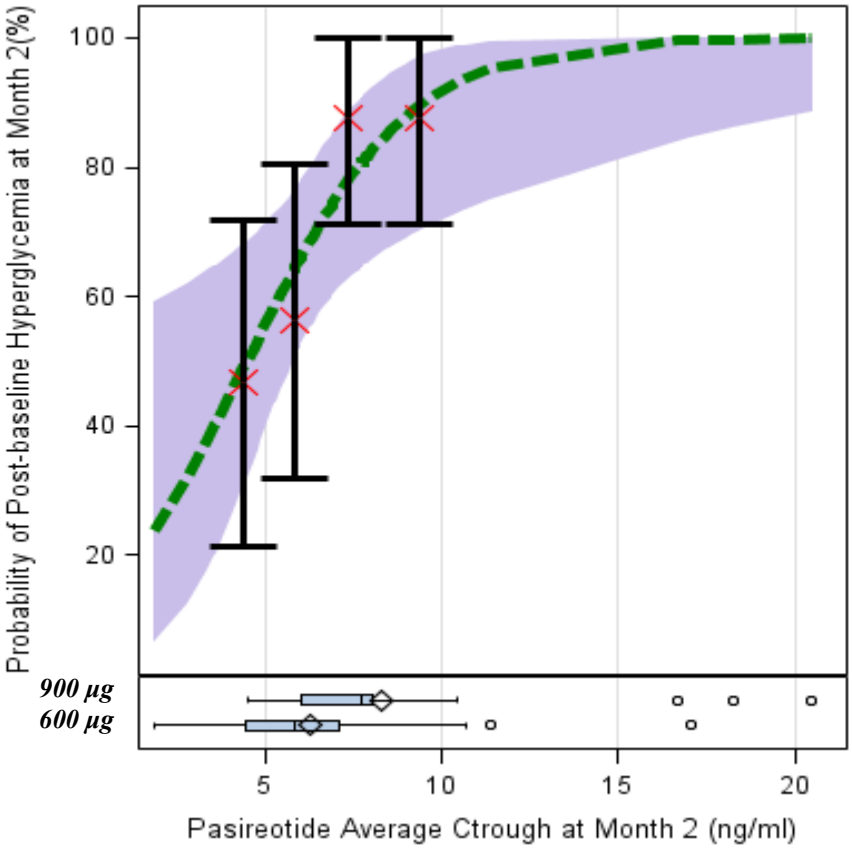


Note: The above figure is based on FDA's Pharmacometric analysis of the data from the B2305 trial

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 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.

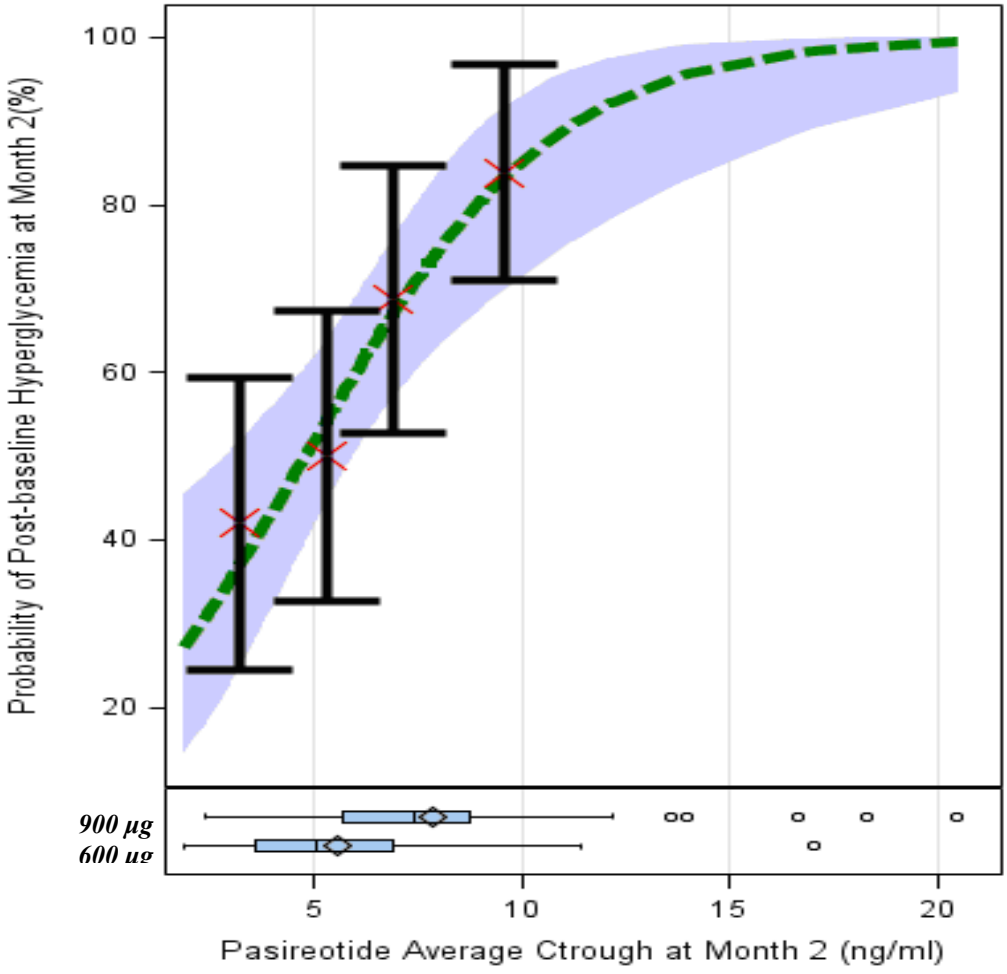


Note: The above figure is based on FDA's Pharmacometric analysis of the data from the B2305 trial

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.



Note: The above figure is based on FDA's Pharmacometric analysis of the data from the B2305 trial

4. Summary

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.

STUDY ENDPOINT REVIEW

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

A. EXECUTIVE SUMMARY

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

The review concludes that the evidence submitted by the sponsor does not demonstrate a clear measurable benefit in HRQL despite the sponsor's assertion of "improvement in the patients' perception of their health status." No dossier for the CushingQoL was submitted in line with FDA guidance. As a result, content validity for the CushingQoL remains in doubt.

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

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

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

B. PRELIMINARY RESPONSES TO DIVISION QUESTIONS

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

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

Yes, the questionnaire likely measures some concerns of importance to Cushing's disease patients. However, we cannot determine if these items are a comprehensive elaboration of Cushing's HRQL concerns, or if they include elements that are most important in measuring quality-of-life for these patients.

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

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

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

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

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

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

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

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

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

C. STUDY ENDPOINT REVIEW

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

1 CONTEXT OF USE

1.1 Target Population

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

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

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

1.2 Target Product Profile

No TPP was part of the material reviewed here. Although a claim related to HRQL may have been intended originally, the failure to establish content validity for the instrument, the failure to demonstrate benefit in core signs and symptoms, and the inconsistent and inconclusive results for HRQL as measured do not support labeling claims.

1.3 Endpoint Model

The endpoint structure for Trial CSOM230B2305 is as follows:

Primary efficacy endpoint:

Month 6 responders defined as the proportion of responders in each of the pasireotide dose groups at Month 6. A Month 6 responder was defined as a patient with Month 6 mUFC $\leq$ULN and no dose increase (relative to the randomized dose) prior to Month 6

UFC assessment. If Month 6 mUFC was missing then it was imputed by the last available mUFC (of at least 3 specimens) between (and including) Month 3 and Month 6. Primary analysis of this endpoint was performed on the full analysis set.

Secondary efficacy endpoints:

- Proportion of patients with mUFC ≤ ULN at Months 3, 6 and 12 (mUFC based on 4 UFC samples) and at intermediate visits (mUFC based on 2 UFC samples).
- Time to first UFC response
- Plasma ACTH and serum cortisol
- UFC responders at Month6 based on median UFC response
- Clinical signs
- Clinical symptoms
- Tumor volume
- Response rates at Month 6 after pooling dose groups
- Quality of Life

2 CONCEPT OF MEASUREMENT AND CONCEPTUAL FRAMEWORK

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

3 CLINICAL OUTCOME ASSESSMENT MEASURE(S)

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

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

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

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

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

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

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

4 CONTENT VALIDITY

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

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

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

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

- Some of the items of the instrument may be confusing to the patient, e.g., "I bruise easily," has the response options of "always, often, sometimes, rarely, never." Do patients pick "never" because they avoid getting bruises effectively or because they observe that they don't bruise easily, understanding the item in the way it was intended?

Cognitive debriefing was not performed to answer this concern about how items are understood.

- The CushingQoL uses a four-week time frame for assessing HRQL status. This is typical of HRQL instruments designed for use in clinical practice conditions or apt for observational health services studies. More frequently, FDA Divisions prefer the use of 24-hour recalls of specific symptoms and impacts for drug development trials when appropriate.

- We also have concerns when patients are asked to summarize their experience over time. Do patients pick "sometimes" because their bruising experience varies over the course of a month or because they are not sure when or how many times they have bruised over the last month (i.e. does long recall encourage satisficing that is inaccurate)?

- The questionnaire has at least two items that reflect more distal affective or social patient characteristics. These items may not clearly reflect treatment benefit or be expected to respond to changing health status.
    - 6. I have less self-confidence, I feel more insecure.
    - 8. I feel less like going out or seeing relatives or friends.

  The latter question also 'double-barrels' different kinds of relationships, in turn combining these with "going out," which could create considerable ambiguity in the item.

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

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

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

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

Longitudinal validation tests were to have been demonstrated in Trial CSOM230B2305. In particular, the protocol suggested that the ability to detect change would be reviewed. However, there is no data presented that clarifies the clinical meaning of changes in the CushingQoL in the Final Report. Demonstrations of test-retest reliability seem not to have been conducted in this study or elsewhere.

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

6 INTERPRETATION OF SCORES

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

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

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

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

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

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

* Wild D, Eremenco S, Mear I, Martin M, Houchin C, Gawlicki M, Hareendran A, Wiklund I, Chong LY, von Maltzahn R, Cohen L, Molsen E. Multinational trials—recommendations on the translations required, approaches to using the same language in in different countries, and the approaches to support pooling the data: The ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force Report. Value in Health 2009; 12(4):430-40.

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

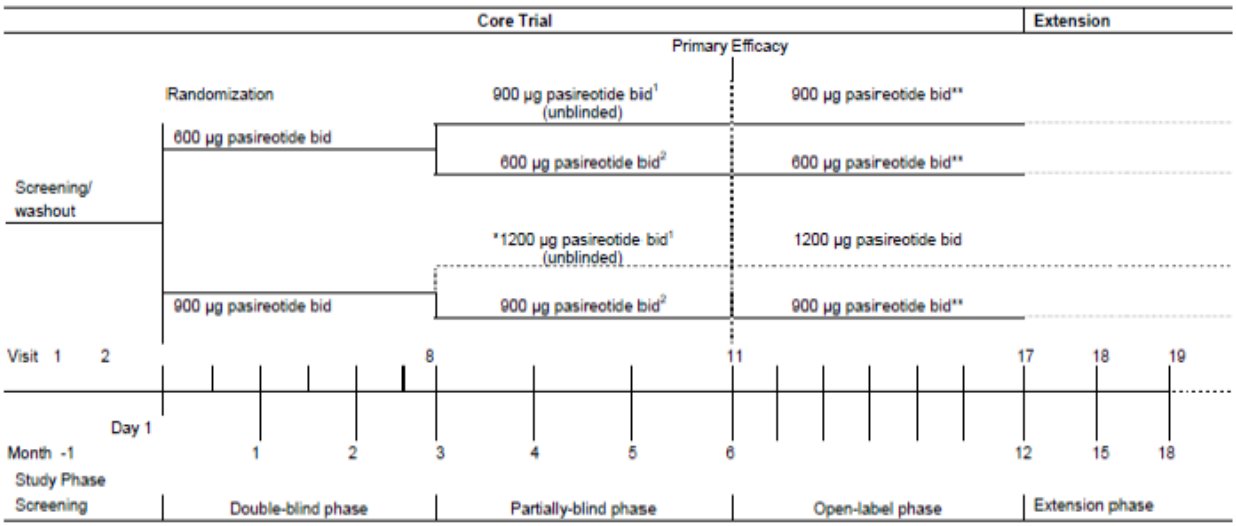
8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

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

9 PROTOCOL AND ANALYSIS PLAN

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

Figure 9-1 Study design



[1] For patients who had a baseline mUFC ≥ 2 x ULN with a Month 3 mUFC > 2 x ULN or who had a baseline mUFC < 2 x ULN with a Month 3 mUFC > baseline mUFC
[2] For patients who had a baseline mean UFC ≥ 2 x ULN with a Month 3 mUFC ≤ 2 x ULN or who had a baseline mUFC < 2 x ULN with a Month 3 mUFC ≤ baseline mUFC
* Permitted dose increase only if patient had tolerated 900 µg
** During open-label phase doses could be increased by 300 µg at any time during the study if response was lost
All doses were allowed to be reduced by 300 µg at any time during the study if the doses were not tolerated
China only: patients did not receive doses higher than 900 µg s.c. b.i.d. at anytime during the study

Source: NDA 200677. Full Clinical Study Report. Novartis, 2010, p. 55.

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

morbidity associated with extended hypercortisolism and the clinical symptoms associated with Cushing's disease.

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

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

Reviewer note: Although the HRQL was placed correctly in the hierarchy of secondary endpoints following symptoms measures, efficacy for the symptoms was not demonstrated. Thus, an HRQL claim could not be made even if the HRQL results had been significant.

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

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

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

10 KEY REFERENCE FOR MEASURE

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

D. APPENDICES

Appendix A

Demographic and Clinical Characteristics of Patient Population

Trial CSOM230B2305

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

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

Note: % for the first three rows based on N. % for the remaining rows based on randomized and treated subjects. *Patients who completed Month 12 and did not enter extension phase are not counted as discontinuations.
Source: Table 14.1-1.3.

Source: NDA 200677. Full Clinical Study Report. Novartis, 2010, p. 96.

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

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

Source: Table 14.1-3.1.

Source: NDA 200677. Full Clinical Study Report. Novartis, 2010, p. 100.

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

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

Time to first pasireotide dose since diagnosis = (First pasireotide dose date – date of diagnosis of Cushing's disease +1)*12/365.25.
Source: Table 14.1-3.2.

Source: NDA 200677. Full Clinical Study Report. Novartis, 2010, p. 101.

Appendix B

The Cushings Syndrome Quality of Life (CushingsQoL) Questionnaire

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SOM230B CSOM230B2305	ID ⌊⌊⌊⌊⌋⌊⌊⌊⌊⌊⌊⌋ (Center No. / Subject No.) Subject's initials ⌊⌊⌋ (1. 2. fam.) Visit Date ⌊⌊⌋⌊⌊⌋⌊⌊⌊⌊⌋ (day / month / year)	Visit #____

CUSHING'S SYNDROME QUALITY OF LIFE QUESTIONNAIRE (CUSHING'S QOL QUESTIONNAIRE)

The following sentences refer to what you may think or feel about your Cushing's syndrome. Your answers will help us to know how you feel and how much your illness has interfered in your usual activities in **the past 4 weeks.**

Below each sentence you will find several response choices. Please read each sentence carefully. After reading each sentence, check the box next to the answer that best describes what you think is happening to you.

There are **NO** right or wrong answers. We are simply interested in what is happening to you because of your Cushing's syndrome.

1. I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.).
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

2. I have pain that keeps me from leading a normal life.
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

3. My wounds take a long time to heal.
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

4. I bruise easily.
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

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SOM230B CSOM230B2305	ID Center No. Subject No. Subject's initials 1. 2. fam.	Visit #____

5. I am more irritable, I have sudden mood swings and angry outbursts.
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

6. I have less self-confidence, I feel more insecure.
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

7. I'm worried about the changes in my physical appearance due to my illness.
   - ☐ Very much
   - ☐ Quite a bit
   - ☐ Somewhat
   - ☐ Very little
   - ☐ Not at all

8. I feel less like going out or seeing relatives or friends.
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

9. I have had to give up my social or leisure activities due to my illness.
   - ☐ Always
   - ☐ Often
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

10. My illness affects my everyday activities such as working or studying.
    - ☐ Always
    - ☐ Often
    - ☐ Sometimes
    - ☐ Rarely
    - ☐ Never

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Page 4003

SOM230B CSOM230B2305	ID Center No. Subject No. Subject's initials 1. 2. fam.	Visit #____

11. It's difficult for me to remember things.
    - ☐ Always
    - ☐ Often
    - ☐ Sometimes
    - ☐ Rarely
    - ☐ Never

12. I'm worried about my health in the future.
    - ☐ Very much
    - ☐ Quite a bit
    - ☐ Somewhat
    - ☐ Very little
    - ☐ Not at all

qol.S054_1 Cushing's QoL-English/US 3 of 3 ©2006, **IMS Health®** - Health Economics and Outcomes Research

Source: NDA 200677. Full Clinical Study Report. Novartis, 2010, p. 4767-9.

Appendix C

Analysis of Changes in HRQL Score

By Time of Instrument Completion

Trial CSOM230B2305

CSOM230B2305 Month 12

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

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

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

/report/pgm_eff/techgm4.sas@@/main/2 15JUL10:16:32 (Production version)

CSOM230B2305 Month 12

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

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

Source: NDA 200677. Full Clinical Study Report. Novartis, 2010, p. 535-536.