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RESEARCH**

APPLICATION NUMBER:

200677Orig1s000

MEDICAL REVIEW(S)

Addendum

This is a brief addendum to the Medical Officer for Review for NDA 200,677. This document serves to clarify or correct two issues:

- 1) On page 82 of the review, it is stated “This shows paired data for individual subjects and yields a weak positive correlation ($r=0.23$, $r^2=0.05$, $p=0.02$) suggesting that for any one subject a larger decrease in mUFC correlates with a larger decrease in mUFC.” The sentence should read “...a larger decrease in mUFC correlates with a smaller increase in HbA1c”.
- 2) In Section 3.2, it states that exclusion of blood pressure data from the problematic Chinese site did not change the overall BP results and that this issue would be covered in greater detail under Efficacy, which it is not. Therefore, the details are provided here. Below is a table which summarizes mean BP values for the 4 site with lowest BP variability, the other sites (excluding the 4 sites), and all sites combined. While the 4 sites had somewhat greater decreases in BP changes, the mean BP excluding these sites’ was similar to all sites combined.

Sites	N	Label	Mean	Median	SD	Min	Max
4 low variability sites	16	Mean of sitting SBP at baseline	128.6	128.8	15	98	160
		Mean of sitting SBP chg. from baseline	-12.5	-12.8	10.7	-30	10
		Mean of sitting DBP at baseline	89.6	89.7	11.2	70	115
		Mean of sitting DBP chg. from baseline	-10.2	-10	9.2	-28.7	5
Other sites	100	Mean of sitting SBP at baseline	135.5	133.3	20.4	99.7	213
		Mean of sitting SBP chg. from baseline	-8.5	-7.2	18.7	-68.3	49
		Mean of sitting DBP at baseline	87.1	84.7	12.3	54.7	128.3
		Mean of sitting DBP chg. from baseline	-3.7	-3.3	12.8	-38.3	42.7
All sites	116	Mean of sitting SBP at baseline	134.5	132.3	19.8	98	213
		Mean of sitting SBP chg. from baseline	-9.1	-8.2	17.8	-68.3	49
		Mean of sitting DBP at baseline	87.4	85	12.2	54.7	128.3
		Mean of sitting DBP chg. from baseline	-4.6	-4.8	12.6	-38.3	42.7

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/s/

NAOMI N LOWY
12/05/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	200,677
Priority or Standard	Standard
Submit Date(s)	February 17, 2012
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Division / Office	DMEP
Reviewer Name(s)	Naomi Lowy, M.D.
Review Completion Date	October 17, 2012
Established Name	Pasireotide/SOM230
(Proposed) Trade Name	Signifor
Therapeutic Class	Somatropin release-inhibiting factor
Applicant	Novartis
Formulation(s)	Subcutaneous injection
Dosing Regimen	600 to 900 micrograms (μg) twice daily (bid)
Indication(s)	Patients with Cushing's disease who require medical therapeutic intervention
Intended Population(s)	Adults

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.2	Risk Benefit Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	13
1.4	Recommendations for Postmarket Requirements and Commitments	13
2	INTRODUCTION AND REGULATORY BACKGROUND	13
2.1	Product Information	13
2.2	Tables of Currently Available Treatments for Proposed Indications	14
2.3	Availability of Proposed Active Ingredient in the United States	15
2.4	Important Safety Issues With Consideration to Related Drugs.....	15
2.5	Summary of Presubmission Regulatory Activity Related to Submission	16
2.6	Other Relevant Background Information	16
3	ETHICS AND GOOD CLINICAL PRACTICES.....	17
3.1	Submission Quality and Integrity	17
3.2	Compliance with Good Clinical Practices	17
3.3	Financial Disclosures.....	17
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	18
4.1	Chemistry Manufacturing and Controls	18
4.2	Clinical Microbiology.....	18
4.3	Preclinical Pharmacology/Toxicology	18
4.4	Clinical Pharmacology	18
4.4.1	Mechanism of Action.....	20
4.4.2	Pharmacodynamics.....	20
4.4.3	Pharmacokinetics.....	20
5	SOURCES OF CLINICAL DATA.....	21
5.1	Tables of Studies/Clinical Trials	21
5.2	Review Strategy	23
5.3	Discussion of Individual Studies/Clinical Trials.....	23
6	REVIEW OF EFFICACY	30
	Efficacy Summary.....	30
6.1	Indication	31
6.1.1	Methods	32
6.1.2	Demographics	33
6.1.3	Subject Disposition.....	37
6.1.4	Analysis of Primary Endpoint(s)	39
6.1.5	Analysis of Secondary Endpoints.....	50

6.1.6	Other Endpoints	57
6.1.7	Subpopulations	58
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ...	58
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	59
6.1.10	Additional Efficacy Issues/Analyses	60
7	REVIEW OF SAFETY.....	60
	Safety Summary	60
7.1	Methods.....	62
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	62
7.1.2	Categorization of Adverse Events	62
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	62
7.2	Adequacy of Safety Assessments	63
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	63
7.2.2	Explorations for Dose Response.....	64
7.2.3	Special Animal and/or In Vitro Testing	64
7.2.4	Routine Clinical Testing	64
7.2.5	Metabolic, Clearance, and Interaction Workup	64
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	64
7.3	Major Safety Results	65
7.3.1	Deaths.....	65
7.3.2	Nonfatal Serious Adverse Events	65
7.3.3	Dropouts and/or Discontinuations	71
7.3.4	Significant Adverse Events	73
7.3.5	Submission Specific Primary Safety Concerns	73
7.4	Supportive Safety Results	111
7.4.1	Common Adverse Events	111
7.4.2	Laboratory Findings	112
7.4.3	Vital Signs	115
7.4.4	Electrocardiograms (ECGs)	116
7.4.5	Special Safety Studies/Clinical Trials	117
7.4.6	Immunogenicity	117
7.5	Other Safety Explorations.....	117
7.5.1	Dose Dependency for Adverse Events	117
7.5.2	Time Dependency for Adverse Events.....	117
7.5.3	Drug-Demographic Interactions	117
7.5.4	Drug-Disease Interactions.....	117
7.5.5	Drug-Drug Interactions.....	117
7.6	Additional Safety Evaluations	117
7.6.1	Human Carcinogenicity	118
7.6.2	Human Reproduction and Pregnancy Data.....	118
7.6.3	Pediatrics and Assessment of Effects on Growth	118

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	118
7.7	Additional Submissions / Safety Issues	119
8	POSTMARKET EXPERIENCE.....	122
9	APPENDICES	123
9.1	Literature Review/References	123
9.2	Labeling Recommendations	123
9.3	Advisory Committee Meeting.....	123
	Appendix 1: Review of Study 2208	123
	Appendix 2 Individual Plot of mUFC for subjects whose dose was increased at Month 3	133
	Appendix 3 Shifts in mUFC category during treatment to Month 6	136
	Appendix 4 Individual HbA1c changes by dose group.....	137
	Appendix 5 Summary of Trials used in Safety Review	138
	Appendix 6: Summary of Antihypertensive Use Before and During Pasireotide Treatment.....	142

Table of Tables

Table 1 Medical therapies used off-label for Cushing's Disease	15
Table 2 Overview of trials	21
Table 3 Clinical studies in other indications.....	22
Table 4 Study 2305: Visit and Evaluation Schedule	28
Table 5 Comparison of Studies B2208 and B2305	32
Table 6 Baseline demographics by randomized dose group.....	33
Table 7 Disease history and baseline characteristics by randomized dose group	34
Table 8 Number of enrolled subjects by baseline UFC	35
Table 9 Medical histories and continuing medical conditions by system organ class and preferred term*	36
Table 10 Subject disposition by randomized dose group	38
Table 11 Major protocol deviations up to Month 6, leading to exclusion from per-protocol analyses, by randomized dose group.....	38
Table 12 Analysis set by randomized dose group.....	39
Table 13 Primary responder's analysis at Month 6	40
Table 14 Statistical Reviewer Responder's analysis at Month 6	40
Table 15 Efficacy Analysis excluding subjects who were responders with insufficient urine collections at Month 6.....	41
Table 16 Percentage of subjects with mUFC \leq ULN or \geq 50% reduction from baseline at Month 6	41
Table 17 Descriptive statistics for mUFC Values by Randomization Group through Month 6	42
Table 18 Percentages of mUFC primary responders at Month 6 by baseline mUFC category (at least 2 samples) - FAS	45
Table 19 Mean total daily dose (SD) for both dose group through Month 6	47
Table 20 Mean change from baseline in blood pressure by randomized dose group at Month 6	51
Table 21 Mean change from baseline in other clinical signs and symptoms of Cushing's disease by randomized dose group at Month 6.....	53
Table 22: Change in HRQL score from baseline to Month 6 by randomized dose group	54
Table 23 Change in pituitary volume (cm ³) by randomized dose group	55
Table 24 Proportion of UFC responders at Month 6 by randomized dose group and subgroup factors	56
Table 25 Responders by prior medication (medical therapy for Cushing's) at baseline	57
Table 26 General and Specific Reasons for Discontinuation in Subjects who were Responders at Month 6 but Dropped Out at or Prior to Month 12	59
Table 27 Duration of exposure to study drug by randomized dose group, up to data cut-off for Study 2305.....	63
Table 28 Serious Adverse Events (SAEs) by randomized dose group, up to data cut-off (Safety analysis set).....	65
Table 29 SAEs, by SOC and randomized dose group, up to data cut-off.....	65

Table 30 Frequent serious adverse events (> 2% in any group) by preferred term and randomized dose group, up to data cut-off (Safety analysis set)	67
Table 31 AEs causing study drug discontinuation by SOC and PT up to data cut-off (Safety Analysis Set)	71
Table 32 Summary of mean fasting plasma glucose by randomized group and visit—Study 2305 (Safety analysis set)	75
Table 33: Shift in fasting glucose from baseline to Month 6 (LOCF) by randomized dose group—Study 2305 (safety analysis set).....	75
Table 34: Summary of mean HbA1c (%) by randomized group and visit (Safety analysis set)	76
Table 35: Shift in HbA1c from baseline to last value up to Month 6 by randomized dose group (safety analysis set, LOCF).....	76
Table 36 Summary of baseline diabetic status by randomized dose group (Study 2305)	80
Table 37 Summary of responders by baseline diabetic status (Full analysis set-Study 2305).....	81
Table 38 Summary of anti-diabetic medication at baseline and post-baseline	83
Table 39: Concomitant antidiabetic medication use prior to and following pasireotide dosing.....	83
Table 40: Mean FPG and HbA1c after discontinuation of treatment in Study 2305	84
Table 41 Percent change in mUFC from baseline to End of Treatment (EOT) by subjects' diabetic status at baseline and EOT	84
Table 42 Hyperglycemia-related adverse events by preferred term, up to data cut-off ..	85
Table 43 Hyperglycemia-related SAEs by PT and randomized dose group in Study 2305	86
Table 44 Mean total daily dose (µg) over time in Cushing's Phase 2 trials	90
Table 45 Liver enzyme and total bilirubin outlier summary—healthy volunteers (single & multiple day dosing) and hepatic impairment study.....	92
Table 46 Liver enzyme and total bilirubin outlier summary—Cushing's disease, acromegaly and carcinoid syndrome studies	94
Table 47 Liver laboratory values--Subject 2124-001/10116	95
Table 48 Live laboratory values—Subject B2125-0001/10132.....	96
Table 49 Liver laboratory values—Subject B2124-0001-10113	96
Table 50 Liver laboratory values—Subject PHHO2010AU13717	97
Table 51 Mean and median changes in liver enzymes and total bilirubin over time – Study 2124 (healthy volunteers).....	100
Table 52 Mean changes in liver enzymes and total bilirubin over time—Study 2305..	101
Table 53 Liver safety-related and biliary-related SAEs and AEs leading to discontinuation—Cushing's disease, acromegaly, carcinoid syndrome for patients treated with pasireotide	102
Table 54 Adverse events of special interest by category and randomized dose group, up to data cut-off	104
Table 55 Gallbladder and biliary related AEs, by PT and dose group up to data cut-off	105

Table 56 Shifts in gallbladder ultrasound results from baseline to extreme level up to data cut-off, Study 2305	106
Table 57 Liver safety related AEs, by PT and dose group up to data cut-off.....	106
Table 58 Bradycardia related AEs, by PT and dose group up to data cut-off.....	108
Table 59 Pancreatitis related AEs, by PT and dose group up to data cut-off	109
Table 60 PTT Shift table by dose group—baseline versus extreme lab value up to data cut-off based on CTC grades	110
Table 61 PT Shift table by dose group—baseline versus extreme lab value up to data cut-off based on CTC grades	110
Table 62 Most frequently reported AEs (>10% in any group) by preferred term (PT), up to data cut-off (Safety Analysis Set)	112
Table 63 Newly occurring or worsening CTC hematology abnormalities up to data cut-off by randomized dose group (safety analysis set)	113
Table 64 Mean hemoglobin (g/dL) over time.....	113
Table 65 Newly occurring or worsening CTC biochemistry abnormalities up to data cut-off by randomized dose group (safety analysis set)	114
Table 66 Newly occurring or worsening CTC hepatobiliary and pancreatic biochemistry abnormalities up to data cut-off by randomized dose group (safety analysis set)	115
Table 67 Number (%) of subjects with past-baseline abnormality in vital signs up to data cut-off by randomized dose group (Safety analysis set).....	116
Table 68 Mean fasting plasma glucose by randomized group for Study 2305	121
Table 69 Mean HbA1c (%) by randomized group for Study 2305	122
Table 70 Major protocol deviations (safety population)	125
Table 71 Summary of responders based on mean UFC levels (Efficacy population)..	125
Table 72 Individual patient % change in mean UFC at End of Study (Day 15) (Primary Efficacy population).....	126
Table 73 Most common (≥5%) adverse events regardless of study drug relationship by preferred term (Safety population)	127
Table 74 Serious or Significant Events in Trial 2208.....	129
Table 75 Liver tests: shift tables of baseline versus highest CTC grade post baseline—Liver function tests	129
Table 76 Use of antihypertensive medications at baseline and after start of pasireotide in Trial 2305 (FAS)	142

Table of Figures

Figure 2 Study Design: 2305.....	25
Figure 3 Mean (\pm SE) Urinary Free Cortisol (nmol/24h) at all Time Points up to Month 12 by Randomized Dose Group (Completers, n=39/group)	43
Figure 8 Mean ACTH plasma concentrations.....	50
Figure 10 Change in midnight salivary cortisol (nmol/L) from baseline to time points up to Month12 by randomized dose group	57
Figure 11: Shift in HbA1c from baseline to last value up to Month 6 by randomized dose group	77
Figure 12: Individual changes in HbA1c from baseline to Month 6.....	79
Figure 13: Changes in pre-diabetes and diabetes status	80
Figure 14: mUFC and HbA1c changes from Baseline (Completers)	81
Figure 15 Change in HbA1c as UFC changes from baseline (Completers at Month 6). 82	
Figure 16 Arithmetic mean (SD) plasma concentration-time profiles for glucose (mg/dL) on Day 7 (PD set—Study SOM230B2124).....	88
Figure 17 Mean (SD) blood glucose versus time profiles after pasireotide s.c. dosing by study day (Safety Population 2208)	90
Figure 18 Mean (SD) pasireotide plasma concentration versus time profiles.....	127
Figure 19 Mean (SD) blood glucose versus time profiles by day following pasireotide dosing (Safety population).....	131
Figure 20 Mean (SD) insulin versus time profile by day following pasireotide dosing (Safety population)	132
Figure 21 Mean (SD) glucagon versus time profile by day following pasireotide dosing (Safety population)	132
Figure 22 Individual plots of mUFC for subjects whose dose was increased	133
Figure 23 Shifts on treatment from baseline UFC categories (1-2, 2-5, 5-10, > 10x ULN) to Month 6 (LOCF)	136
Figure 24: Individual HbA1 c changes from baseline to Month 6 for the 600 μ g bid and 900 μ g bid dose groups; d=subject was diabetic at baseline	137

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend approval of pasireotide injection because: 1) the drug has an indisputable cortisol-lowering effect in most patients, 2) serious risks have been identified and can likely be managed with labeling and more data in the post-marketing setting, and 3) with a strengthening of the proposed indication, this drug will be intended only for those patients with Cushing's disease who failed surgery or cannot undergo surgery. The input from an upcoming Advisory Committee meeting may modify these recommendations.

The overwhelming safety concerns pertain to the development and worsening of hyperglycemia and diabetes in this population of insulin-resistant patients. In the pivotal trial, the Sponsor failed to adequately anticipate and manage the dramatic levels of pasireotide-induced hyperglycemia. Although one can argue that this may negate the cortisol-lowering effect of the drug, it is reasonable to believe that labeling and a post-market study addressing this issue could ease the impact of this adverse event. Elevated liver tests—mechanistically unexplained—are also a major safety concern that I believe can be addressed in labeling.

1.2 Risk Benefit Assessment

Cushing's disease is associated with high morbidity and mortality. Although surgery is first-line therapy, remission rates are high and until recently, no medical therapy addressing this population has been approved.¹ Earlier this year, Korlym (mifepristone) was specifically “for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.”²

The pivotal trial was small and did not include a comparator arm, which would be considered unethical in this population. There were high numbers of drop-outs in the trial with approximately one-third discontinuing at or before the primary efficacy time point. The most common reason for discontinuing was lack of efficacy. Finally, there was a large numerical imbalance in the baseline mean urinary free cortisol (mUFC) between the dose groups, with the 600 µg dose group having a higher baseline mean

¹ Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2008;93:2454-2462

² Korlym Approval Letter, February 17, 2012

value. Although found to be not statistically different, efficacy results should be viewed in the context of these numerical differences.

Without a proper dose-ranging study, the Sponsor studied two doses (600 µg bid and 900 µg bid, herein referred to as “600 µg group” and “900 µg group”) in the pivotal trial. Subjects only met the primary efficacy endpoint (and were therefore considered “responders” if their mUFC was normalized at Month 6 and they did not require dose titration to achieve the normalization. Only the 900 µg group met the stringent primary efficacy criterion, with a 26% responder rate (lower bound of the two-sided 95% CI equal to 17% and greater than the non-inferiority margin of 15%). Apart from the primary efficacy endpoint itself, majority of subjects in both dose groups had some degree of cortisol-lowering. Still, the responder rate in the 600 µg bid group (“600 µg group”) is clinically important for the following reasons: 1) decreases in cortisol levels were seen across dose groups and across subjects with varying levels of baseline mUFC and 2) when applying an alternative definition of responder (normalization of MUFC or more than 50% reduction from baseline at Month 6), both dose groups achieved important biochemical reductions in mUFC). It should be noted that in general dose increases had little effect on normalization or further percentage decreases in mUFC. There were some subjects who achieved normalization of mUFC with even lower doses (300 µg bid). Finally, the highest percentage of responders generally had lower baseline mUFC values. Only one subject with a baseline mUFC value over 10 times the upper limit of normal was a responder.

There were a number of secondary endpoints in this trial. Although some mean improvements were observed in blood pressure, BMI, waist circumference, and quality of life, the methodological limitations imposed by the uncontrolled design of the clinical study limit the ability to draw firm conclusions.

This Review has identified a number of safety issues. Many of the adverse events, including gastrointestinal disorders, are consistent with that of other somatostatin analogues (SSAs). The safety profile of pasireotide, however, is not identical to other SSAs and important issues include the following:

- **Dysglycemia:** Of most concern in this insulin-resistant patient population is the development and worsening of hyperglycemia and diabetes observed in the pivotal trial. Although somatostatin analogues are known to impair insulin secretion and lead to hyperglycemia, the extent of hyperglycemia and diabetes observed in this trial was unexpected. Nearly all subjects developed hyperglycemia. Unfortunately, it was not aggressively treated in the trial and despite cortisol-lowering, FPG and HbA1c sharply increased immediately and stayed elevated with pasireotide treatment. Few subjects had normal glycemic status at the primary efficacy time point. One needs to question how decreasing cortisol translates into a clinical benefit in the setting of increasing glucose. Theoretically, pasireotide-induced hyperglycemia can be managed and needs to

be studied further in the post-marketing setting. It is likely than insulin may be required. However, given that pasireotide is a twice-daily injection, it remains to be seen whether patients will be willing to undergo additional, multiple daily injections.

- Elevated liver tests: There were four subjects—3 healthy volunteers and 1 patient in a compassionate use study-- with concomitant elevations of ALT and total bilirubin. These elevations resolved with discontinuation of pasireotide. These cases do not have a clearly defined mechanism of action. However, the data do not suggest a mechanism of drug-induced liver injury. Adequate labeling should warn of these findings.
- Gastrointestinal events: Diarrhea and nausea frequently occurred in the pivotal trial.
- Cholelithiasis: Cholelithiasis is known to occur in association with somatostatin analogue use. In the pivotal trial, cholelithiasis was reported in 30.2% of all subjects. This risk can be managed with adequate labeling.
- Hypocortisolism: Although a clinically important adverse event, the occurrence of hypocortisolism is also a sign of efficacy in this population. Overall, 8% of subjects in the pivotal trial had an event related to hypocortisolism, although not all were suggestive of true, clinically important hypocortisolism. Patients should be adequately warned of the possibility of hypocortisolism.
- QT prolongation: QT prolongation is considered class effects of somatostatin analogues. In a thorough ST study, pasireotide was found to have a significant QTc prolongation effect. In the trial, 10% of subjects were reported to have QT prolongation. Once again, this AE can be managed adequately through labeling.
- Increased PTT/PT and decreased hemoglobin: Both of these abnormal laboratory parameters were observed in the pivotal trial. However, they did not appear to have clinical relevance. These events should be adequately labeled.

It is important to note that subjects who responded did so in the first two months of treatment. Given the safety issues, it is reasonable to discontinue the drug after 2 months in subjects who are not biochemically improving.

The issue of the appropriate starting dose must take into account efficacy and safety data. From a statistical perspective, only the 900 µg dose achieved efficacy by the primary efficacy endpoint. On the other hand, both doses achieved important percentage reductions in mUFC. From a pharmacometrics perspective, the two doses appear similar from an efficacy standpoint but hyperglycemia increases with increasing dose. From a clinical and statistical perspective, the adverse event profiles—particularly hyperglycemia—do not sufficiently discriminate the two doses. Given these complicated perspectives, it is reasonable to propose a starting dose of either 600 µg bid or 900 µg bid. A 300 µg dose should be available for down titration for those with tolerability reasons. The dose should be adjusted down for subjects with hepatic impairment. These dosing recommendations may be modified following input from the advisory committee members.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The Company should be required to conduct the following studies post-marketing:

- The Applicant will be required to conduct a post-marketing trial of pasireotide in Cushing's disease patients to study the optimal treatment for pasireotide-induced hyperglycemia.

Recommendations for post-marketing activities may be modified with the input of the advisory committee.

2 Introduction and Regulatory Background

2.1 Product Information

Pasireotide (Signifor®) injection, a new molecular entity (NME), is an immediate-release somatostatin analog for subcutaneous injection developed for the treatment of patients with Cushing's disease. Specifically, the Applicant is seeking the following indication: for the treatment of patients with Cushing's disease for whom medical therapy is appropriate.

The Sponsor is proposing 600 µg bid as a starting dose [REDACTED] (b) (4) [REDACTED] as the option to up-titrate to 900 µg bid (maximum).

Pasireotide, a somatostatin analog, is a peptide hormone known as somatropin release-inhibiting factor. It exerts its pharmacological activity by binding to four of the five known somatostatin receptors (SSTR): sst1, sst2, sst3, and sst5. In general, somatostatin analogs activate these receptors with different potencies, leading to inhibition of hormone secretion, including ACTH and growth hormone. In general, the role of somatostatin and the currently available somatostatin analogs in the treatment of Cushing's disease has been shown to be limited.³

³ Hofland LJ. Somatostatin and somatostatin receptors in Cushing's disease. *Molecular Cell Endocrinology* May 2008.

In vitro studies demonstrate a high level of expression of sst5 in corticotroph tumor cells from Cushing's disease patients. The Sponsor touts pasireotide's broad binding profile as well as its high affinity to sst5 in explaining its efficacy in treating Cushing's disease.

The IND was submitted in 2006 and orphan drug designation was granted in 2009.

In April 2012 the European Medicines Association (EMA) granted approval of pasireotide in patients who cannot have surgery or for whom surgery has not been successful. The EMA approved it with a starting dose of 0.6 mg twice a day (0.3 mg twice a day in patients with moderate liver problems).

2.2 Tables of Currently Available Treatments for Proposed Indications

Cushing's disease (CD) results from a chronic excess of cortisol secretion caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma. Transsphenoidal pituitary adenomectomy, with the goal of complete removal of the tumor, is the treatment of choice. However, long-term cure rates, even in the hands of expert neurosurgeons however, are suboptimal. Immediate remission rates range from 65-90%, but the recurrence rate is approximately 25% at 10 years.⁴ Unfortunately, there is no uniformly accepted definition of cure.

Medical therapy is considered a second-line treatment in patients with persistent or recurrent disease, as well as in patients treated with radiotherapy (for whom treatment effect is delayed), prior to adrenalectomy and in patients generally not suitable for surgery.⁵

There are no drugs specifically approved for the treatment of Cushing's disease, and surgery is considered first-line treatment. Recently, Korlym™ (mifepristone), a cortisol receptor blocker, was approved "to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery."⁶ Notable adverse events include mineralocorticoid excess resulting in severe hypokalemia and endometrial hyperplasia/vaginal bleeding.

In addition, there are drugs used off-label in patients for whom surgery is not curative. They are summarized below.⁷

⁴ Arnaldi G et al. New Treatment Guidelines on Cushing's Disease. Medicine Reports 2009.

⁵ Biller et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. Journal of Clinical Endocrinology and Metabolism 2008.

⁶ Korlym™ Full Prescribing Information, approved February 17, 2012

⁷ Adapted from Nieman LK. Medical Therapy of Cushing's Disease. Pituitary 5: 77-82, 2002

Table 1 Medical therapies used off-label for Cushing's Disease

Name	Mechanism of action	Major side effects	Comments
Agents that inhibit steroidogenesis			
Ketoconazole	Inhibits cortisol synthesis by inhibiting 11 β -hydroxylase and 17 α -hydroxylase	Hepatic toxicity, gastrointestinal disturbance, gynecomastia	Best tolerated of steroidogenesis inhibitors. Potent inhibitor of P450 enzymes, thereby limiting its use due to potential drug-drug interactions
Metyrapone	Inhibits cortisol and aldosterone synthesis by blocking 11 β -hydroxylase	Hypertension, acne, hirsutism, nausea	Not commercially available in many countries
Mitotane	Inhibits 11 β -hydroxylase, 18-hydroxylase and 3 β -hydroxysteroid dehydrogenase	Gastrointestinal disturbance, neurologic complaints	Prolonged half-life with slow onset of action
Aminoglutethimide	Blocks conversion of cholesterol to pregnenolone	Neurologic complaints, rash, sedation	Must be given in combination

In contrast to the agents above that act at the adrenal level or at the peripheral level, pasireotide acts at the hypothalamic-pituitary level.

2.3 Availability of Proposed Active Ingredient in the United States

Pasireotide is not marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Pasireotide is a somatostatin analog and therefore some of the safety concerns are consistent with the side effect profile of approved somatostatin analogs. These safety issues include:

- Gastrointestinal AEs, such as nausea, diarrhea, and abdominal pain
- Gallbladder related AEs, such as cholelithiasis
- Hyperglycemia, which is more concerning in treating patients with Cushing's disease as this is a serious manifestation of the disease itself
- QT prolongation

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Application submitted on February 17, 2012 is a resubmission of an Application initially submitted on May 21, 2011. That Application, which proposed the drug to be marketed in pre-filled syringes, was withdrawn by the Sponsor on August 19, 2011, following an Amendment alerting the Division that (b) (4) particulates were discovered in historical and intended commercial drug batches for the to-be-marketed presentation of pre-filled syringes. A root cause analysis was performed and the Sponsor believes that the source of the particulates in the pre-filled syringes originated from (b) (4). Since there is no (b) (4) in the ampoule, the now intended presentation, one would not expect to see particulate matter. It should be noted that all completed and ongoing clinical trials with pasireotide solution for injection were and are being conducted with the ampoule form of the drug product.

On May 15, 2006, the Sponsor and the Division met for an End-of-Phase 2 (EOP2) meeting for guidance on the Phase III clinical development program. Key discussion points included:

- (b) (4)
- In the discussion of appropriate doses, the Division noted that the Sponsor had not conducted a dose-ranging study. For the pivotal trial, the Sponsor proposed (b) (4). The Sponsor stated that this would be part of their dose-ranging data. The Division stated that results from the proposed study design, specifically in regards to responder status, results would be difficult to interpret. The Sponsor revised the study design so that subjects were randomized to the 600 µg or 900 µg doses.
- The Division and the Sponsor agreed that (a mean of) four 24-hour baseline UFC measurements over a 2-week period would be acceptable as a baseline UFC value.
- The Division stated that a single registration trial could be sufficient to support the efficacy of pasireotide, provided that there is adequate data to support the proposed dosing and that there is convincing evidence that the decreases in UFC did not occur spontaneously.

2.6 Other Relevant Background Information

Pasireotide is also being developed also for the treatment of acromegaly and gastroenteropancreatic neuroendocrine tumors. There is also a long-acting (LAR formulation) being developed, but not yet studied in Cushing's patients.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no major issues with the overall quality of the application. There were several narratives that, upon review, were clearly written with errors, and the Applicant corrected it with the Division's request.

3.2 Compliance with Good Clinical Practices

In the Phase 3 trial, changes in blood pressure (BP) were a clinically important secondary endpoint. Upon routine inspection at a Chinese investigational site, issues related to reliability of blood pressure measurements were discovered. Blood pressure measured at this site did not likely follow the Protocol-specified procedure for measuring BP and therefore recorded measurements do not reflect subjects' true blood pressure. Nevertheless, exclusion of this site's blood pressure results does not change the overall results for analyses of blood pressure changes. Upon statistical analyses, there were other sites that were similarly problematic. Still, excluding the blood pressure data from these sites provided similar overall mean changes in blood pressure compared to analyses including all sites' data. This issue is discussed in greater detail under Secondary Efficacy Endpoints.

3.3 Financial Disclosures

Financial disclosure forms were provided by all Investigators. For Study B2208/B2208E, a total of 4 Investigators (b) (4) (b) (6) disclosed significant payments, described as educational grants, which exclude the costs of conducting the trial that exceed \$25,000. For Study B2305, three Investigators (b) (4) (b) (6) disclosed the same type of payment exceeding \$25,000.

(b) (4)

(b) (4)

These Investigators randomized a small proportion of overall subjects in the pivotal trial. Overall, potential bias from these Investigators would have a minimal effect on the safety and efficacy data of pasireotide.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to Dr. Olen Stephens' Review for full details. Approval is recommended.

4.2 Clinical Microbiology

Refer to Dr. Bryan Riley's Review for full details. Pasireotide is a sterile aqueous solution that is provided in a single-dose, 1 ml glass ampoule. There were no Microbiology deficiencies identified and Approval is recommended.

4.3 Preclinical Pharmacology/Toxicology

Refer to Dr. Miyun Tsai-Turton's Review for full details. There were no unexpected findings and Approval is recommended. The toxicological profile is consistent with other somatostatin analogues.

4.4 Clinical Pharmacology

Refer to the separate Clinical Pharmacology and Pharmacometrics Review for details.

Pharmacometrics

The Pharmacometrics Review explores whether the starting dose is appropriate from an exposure-response perspective.

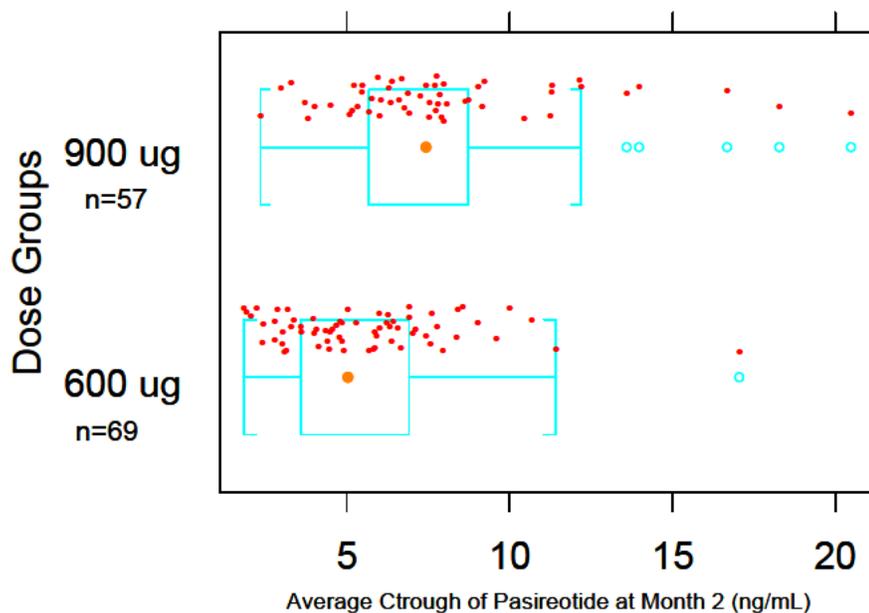
The conclusion of the Pharmacometrics Reviewer is that from an exposure-response analysis, 600 µg bid may be as effective as 900 µg bid and could provide better hyperglycemia-related safety profile compared to the 900 µg dose. Although their recommendation is 600 µg bid as a starting dose, they acknowledge that because of

high unexplained variability in response, 900 µg bid may be a preferred starting dose in some patients.

Specifically, the Reviewer notes that the probability of responding to pasireotide decreases with the increase in baseline mUFC, and therefore direct comparison of the primary efficacy endpoint between dose groups may not be appropriate.

The Review also discusses that there were substantial overlap in exposure between the two dose groups. This is graphically displayed below. The red dots are observed data for individual subjects.

Figure 1 Distribution of average trough concentration at Month 2 for the dose groups in Study 2305



From Pharmacometrics Review

An exposure-response analysis was performed which showed no relationship between exposure and response rate after adjusting for baseline. This suggests no difference in efficacy between the two doses.

The Review focuses on hyperglycemia as the primary safety issue. Here, there is a clear exposure-response relationship between increasing exposures (measured as

trough levels at Month 2) and increasing probability of developing post-baseline hyperglycemia (defined as a more than 1% increase in HbA1c) in subjects who had normal HbA1c at baseline. Similar relationships were seen in analyses looking at subjects with pre-diabetes and diabetes. Furthermore, the possibility of developing post-baseline hyperglycemia was correlated with baseline HbA1c. The Reviewer therefore agrees with the Sponsor's proposal of a starting dose of [REDACTED] (b) (4)

4.4.1 Mechanism of Action

The pharmacological activity of pasireotide is through binding to four somatostatin receptors (sst1, sst2, sst3, and sst5). In vitro studies supported by the Sponsor show that corticotroph tumor cells from Cushing's disease patients express high levels of sst5, compared to the other subtypes which are either not expressed or expressed at lower levels.⁸ Other Sponsor-supported studies report that sst2 receptors are down-regulated in the presence of high levels of glucocorticoids, while sst5 are not.⁹

4.4.2 Pharmacodynamics

The Clinical Pharmacology Reviewer concludes that the proposed initial dose of 900 µg bid is not supported by exposure-response relationship for efficacy. There is no clear relationship between exposure (trough) and probability of response, suggesting no additional benefit of 900 µg over 600 µg. Also, the proposed initial dose of 900 µg for patients with normal baseline HbA1c is not supported by exposure-response relationship for safety. In those normal baseline HbA1c, there is a clear trend toward increasing probability of experiencing more than 1% HbA1c with increasing exposure., suggesting that 900 µg will result in a higher probability of post-baseline hyperglycemia than 600 µg. Clinical Pharmacology recommends a lower starting dose of 600 µg bid. Similar relationships are observed for patients with pre-diabetic or diabetic status at baseline.

4.4.3 Pharmacokinetics

Absorption

Absolute bioavailability of pasireotide was not evaluated in humans and is predicted to be low from in vitro studies. Maximum concentrations (C_{max}) were reached between 0.25 and 0.5 hour after s.c injection. Pasireotide exposure measured using the

⁸ Batista DL et al. The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas. J Clin Endocrinol Metab; 91(11): 4482-8.

⁹ Hofland LJ et al. The multi-ligand somatostatin analog SOM230 inhibits ACTH secretion by cultured human corticotroph adenomas via somatostatin receptor type 5. Eur J Endocrinol; 152: 645-54.

maximum concentration and area under the curve (AUC) showed apparent proportionality to dose up to 1.5 mg.

Distribution

Pasireotide plasma protein binding was 88%.

Metabolism

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

Elimination

Fecal excretion is the major route of elimination with 48% total radioactivity recovered in feces. Hepatic impairment increased pasireotide exposure and indicated that biliary excretion may significantly contribute to pasireotide hepatic clearance. The population analysis indicates that pasireotide clearance in patients with Cushing's disease is lower compared to that of healthy volunteers. Effective half life was about 12 hours. Steady state is reached within 3 days following daily dosing.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

To support safety and efficacy, the Sponsor submits data from B2305 ("pivotal trial") and Study B2208 with its extension B2208E1. These are summarized below:

Table 2 Overview of 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 in Cushing's disease patients to assess efficacy, safety,	162	Extension is ongoing

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

	QoL, PK, and PK/PD relationship. Primary efficacy analysis done at Month 6.		
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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

To support the safety profile, the Sponsor also submits data from trials in other indications:

Table 3 Clinical studies in other 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 Summary of Clinical Safety, Table 1-2

In addition, there were other clinical studies that contributed to understanding the safety profile of pasireotide, particularly its glycemic, hepatic, and cardiovascular effects. These included 7 Phase 1 studies and 5 special safety clinical studies. These are detailed in the Appendix and are discussed throughout this Review. Also, the Sponsor

submitted safety reports for patients receiving pasireotide in a compassionate use basis.¹⁰

The Sponsor submitted Clinical Efficacy and Safety Updates which included data through the extension phase.

Finally, a large source of data is the Applicant's responses to FDA requests for information, which were many during the Review process.

5.2 Review Strategy

In the efficacy evaluation, the Phase 3 trial data was used.

In the safety evaluation, although the Phase 3 data were emphasized, data from all trials in which pasireotide has been tested was used to make broader conclusions regarding the drug's complicated safety profile. Specifically, certain safety issues—such as hyperglycemia and liver tests elevations—required review of Phase 1 and Phase 2 trials in the development program as well as trials conducted in other indications. The Safety section of the review discusses which trials were used in specific analyses.

The extension data provided in the Clinical Safety and Efficacy Update were reviewed. The Safety Update was reviewed to ensure that no new safety signals emerged. The Efficacy Update was reviewed to make observations regarding efficacy in the setting of more prolonged use of pasireotide.

Aside from the trials, data from patients enrolled in compassionate use studies was used as specific safety issues arose.

5.3 Discussion of Individual Studies/Clinical Trials

Study 2305

The primary objective was to assess efficacy of pasireotide in the treatment of Cushing's disease in terms of response to pasireotide 600 µg s.c. bid and 900 µg s.c. bid independently in patients with Cushing's disease as measured by mean urine free cortisol (mUFC) ≤ upper limit of normal (ULN) after 6 months of treatment.

The primary efficacy variable was defined as the proportion of responders to pasireotide 600 µg bid or 900 µg bid. A responder was defined as a subject who attained

¹⁰ A total of 365 patients worldwide received pasireotide for compassionate use. This includes 170 with Cushing's syndrome.

mUFC ≤ ULN at Month 6 *and* whose dose was not increased relative to the randomized dose prior to Month 6.

The trial did not use a comparator or placebo.

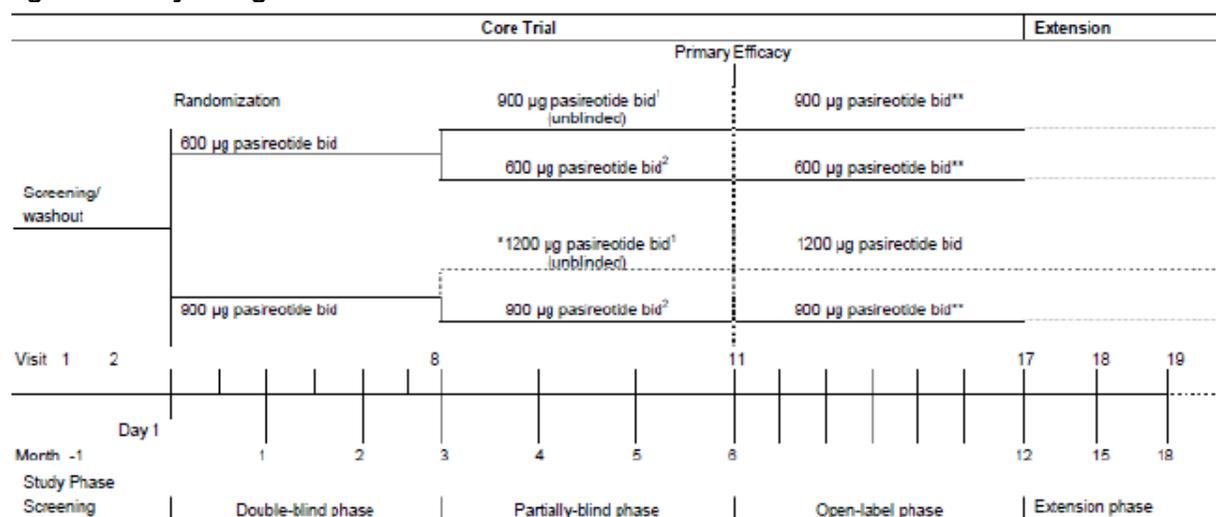
There are a combined total of 16 secondary and exploratory objectives. The secondary endpoints were:

- Assess reduction of mUFC to \leq ULN at Month 3 and 12
- Assess time to first response
- Assess the effect of pasireotide s.c. on plasma ACTH and serum cortisol as measured by the percent of change from baseline by treatment group.
- Assess median UFC response
- Assess improvement in clinical signs and symptoms of Cushing's disease
- Assess the effect of pasireotide s.c. on tumor volume as evaluated with MRI scanning.
- Assess censored-adjusted response
- Assess pooled dose response
- Assess the response by dose group at intermediate visits
- Assess the effect of pasireotide s.c. on Quality of Life
- Determine the pharmacokinetics of pasireotide after s.c. b.i.d. administration
- Identify any patient-related factors that may affect the pharmacokinetics of pasireotide after s.c. b.i.d. dosing
- Explore potential relationships between pharmacokinetics and pharmacodynamics of pasireotide after s.c. b.i.d. dosing
- Evaluate the safety and tolerability of pasireotide s.c. in patients with Cushing's disease

Evaluating midnight salivary cortisol levels in relation to serum cortisol and UFC levels were an exploratory endpoint.

The design of the trial is depicted below.

Figure 2 Study Design: 2305



¹ For patients who had a baseline mUFC $\geq 2 \times$ ULN with a Month 3 mUFC $> 2 \times$ ULN or who had a baseline mUFC $< 2 \times$ ULN with a Month 3 mUFC $>$ baseline mUFC

² For patients who had a baseline mean UFC $\geq 2 \times$ ULN with a Month 3 mUFC $\leq 2 \times$ ULN or who had a baseline mUFC $< 2 \times$ ULN with a Month 3 mUFC \leq 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
 From 2305 Clinical Study Report, Figure 9-1

After the screening period, subjects were randomized 1:1 to the 2 treatment arms. At Month 3, a decision on the continuation of the randomized dose and blinding was made as follows:

1. For subjects in the 600 µg bid treatment arm:
 - Subjects continued at this dose until Month 6 if their Month 3 mUFC was a) $\leq 2 \times$ ULN and b) below or equal to their baseline mUFC.
 - Subjects not meeting these mUFC criteria at Month 3 were unblinded and were required to increase their dose to 900 µg bid, given open-label. These subjects were classified as non-responders for the primary analysis. Subjects who did not escalate to the 900 µg bid dose were discontinued from the trial.
2. For subjects in the 900 µg bid treatment arm:
 - Subjects continued at this dose until Month 6 if their Month 3 mUFC was a) $\leq 2 \times$ ULN and b) below or equal to their baseline mUFC.
 - Subjects not meeting these mUFC criteria at Month 3 were unblinded and were offered to increase their dose to 1200 µg bid, given open-label. These subjects were classified as non-responders for the primary analysis. Subjects who did not escalate to the 1200 µg bid dose were discontinued from the trial.

(In China only, subjects in the 900 µg bid group were not offered to have their dose increased to 1200 µg bid and were discontinued).

After the initial 6 months, subjects entered an open-label treatment period in which they continued on the same dose if response was achieved. If response was not achieved or maintained during the open-label period, dose could be increased by 300 µg bid up to a maximum of 1200 µg bid (except China, which had a maximum of 900 µg bid).

In order to enter the extension phase, the following criteria had to be met:

- The subject achieved $mUFC \leq ULN$ at Month 12 or the investigator believed the patient was receiving significant clinical benefit (improvement in signs and symptoms) from treatment
- The subject showed acceptable tolerability of treatment
- The subject agreed to use contraception

The total core study treatment was 12 months after which subjects had the option to continue treatment.

Study Population

Subjects were 18 years of age and 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.

Subjects with *de novo* Cushing's disease were included if they were not considered candidates for pituitary surgery because of any of the following:

- Poor surgical candidates
- Surgically unapproachable tumors
- Refused to have surgery in favor of medical treatment

Subjects who were surgical candidates were not eligible for the trial.

Inclusion Criteria

- Confirmed diagnosis of ACTH-dependent Cushing's disease as evidenced by:
 - Mean urinary free cortisol of four 24-hour urine samples collected within 2 weeks, at least 1.5 times the upper limit of normal
 - Morning plasma ACTH within normal or above normal range (≥ 5 ng/L)
 - Either MRI confirmation of pituitary macroadenoma, or inferior petrosal sinus gradient >3 after corticotrophin-releasing hormone (CRH) stimulation for those patients with a microadenoma, or for subjects who have had prior pituitary surgery, histopathology confirming an ACTH staining adenoma
 - If inferior petrosal sinus sampling had been performed without CRH, than a central to peripheral pre-stimulation gradient >2 was required.
- Subjects with *de novo* Cushing's disease could be included only if they were not considered candidates for pituitary surgery
- Confirmatory testing prior to IPSS had to be performed for subjects with $UFC \leq 3 \times ULN$ and a pituitary microadenoma in order to exclude possible pseudo-Cushing's syndrome

- Karnofsky performance status ≥ 60
- For subjects on medical treatment for Cushing's disease the following washout periods must have been completed before baseline efficacy assessments were performed:
 - Inhibitors of steroidogenesis: 1 week
 - Dopamine agonists: 4 weeks
 - Rosiglitazone: 1 week
 - Octreotide LAR and Lanreotide autogel: 8 weeks
 - Lanreotide SR: 4 weeks
 - Octreotide (immediate release): 1 week
- Subjects with a known history of impaired fasting glucose or diabetes mellitus could be included, however blood glucose and antidiabetic treatment was monitored closely throughout the trial and adjusted as necessary

Exclusion Criteria

Major criteria included:

- Subjects who received pituitary irradiation within the last ten years
- Subjects treated with mitotane during the last 6 months
- Subjects with compression of the optic chiasm causing any visual field defect
- Subjects with a known inherited syndrome as the cause for hypercortisolism
- Subjects with a diagnosis of glucocorticoid-remedial aldosteronism (GRA)
- Subjects who are hypothyroid and not on adequate replacement therapy
- Major surgery within 1 month prior to starting trial
- Symptomatic cholelithiasis
- Diabetic patients on antidiabetic medications whose fasting blood glucose as poorly controlled as evidenced by $HbA1c > 8\%$
- Abnormal coagulation parameters
- Receiving anticoagulants that effect PT or PTT
- Congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry of clinically significant impairment in cardiovascular function
- Risk factors for torsades de pointes
- Liver disease
- Pregnant or lactating
- History of immunocompromise

Withdrawal of Drug

Subjects would be with withdrawn from the trial for multiple reasons, including:

- a confirmed $ATc \geq 500$ ms at any time during the trial
- uncontrolled DM
- evidence of hypoadrenalism
- lack of efficacy: during the open-label period, sustained elevated UFC levels $\geq 2 \times$ ULN after 3 months of treatment with the higher dose of pasireotide (900-1200 μ g bid)

Monitoring of Glucose Metabolism

According to the Protocol, subjects with a history of impaired fasting glucose or DM had daily fasting blood glucose by fingerstick. If glucose was poorly controlled and/or two consecutive $HbA1c$ measurements were $> 8\%$, subjects were referred to a diabetes specialist. Any subject with $HbA1c > 10\%$ at any time was referred to a specialist.

Diabetic subjects monitored their fasting blood glucose by fingerstick twice daily during the first week following initiation of study drug or dose increase.

Visit Schedule

The following summarizes the visit schedule for 2305. EKGs were performed at every visit and gallbladder ultrasound was performed at baseline and at the conclusion of the double-blind period.

Table 4 Study 2305: Visit and Evaluation Schedule

Visit no ¹	Screen phase	Double-blind period						Partially-blind period				Open-label period		Safety FU ¹⁴
	1	2	3	4	5	6	7	8	9	10	11	12-16	17	
Study Day ¹⁰	-30 to -1	1	15	30	45	60	75	90	120	150	180	Month 7-11	Month 12	Last dose + 1 month
Informed consent ² (S) ³	X													
Demography (D)	-30 to 1													
Inclusion/exclusion criteria (S)	X	X												
Relevant medical history/current medical conditions (D)	X	X												
Randomization		X												
Physical examination ⁴ (S)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR and temperature) (D)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (D)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (D)	X													
Weight (D)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky performance status (D)	-15 to 1										X	X	X	X
Serum pregnancy test ⁵ (D)	-15 to 1							X			X	X ⁰	X	X
Gallbladder ultrasound (D)	-30 to 1							[G:X] ¹³			X	[G:X] ¹³	X	
Hematology (D)	-15 to 1 ¹⁶			X		X		X	X	X	X	X	X	X
CBG (D)	-15 to 1 ¹⁶							X			X		X	
Free T4, TSH (D)	-15 to 1 ¹⁶			X				X			X		X	X
Blood chemistry (including electrolytes, LFT, amylase, lipase, TC, LDL-C, triglycerides) (D)	-15 to 1 ¹⁶			X		X		X	X	X	X	X	X	X
Coagulation parameters (PT and PTT) (D)	-15 to 1 ¹⁶		X	X				X			X		X	X
Fasting blood glucose (D)	-15 to 1 ¹⁶		X	X	X	X	X	X	X	X	X	X	X	X

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

Visit no ¹	Screen phase	Double-blind period						Partially-blind period				Open-label period		Safety FU ¹⁴
	1	2	3	4	5	6	7	8	9	10	11	12-16	17	
Study Day ¹⁰	-30 to -1	1	15	30	45	60	75	90	120	150	180	Month 7-11	Month 12	Last dose + 1 month
Fasting insulin (D)	-15 to 1 ¹⁶		X	X		X		X	X	X	X	X	X	X
HbA1c ⁶ (D)	-15 to 1 ¹⁶					X			X			X ⁶	X	X
Vitamin B12 (D)	-15 to 1 ¹⁶							X			X		X	
Midnight salivary cortisol ¹⁵ (D)	-21 to 1 ¹⁶							X			X	X ⁹	X	
Urinary free cortisol ⁷ (D)	-21 to 1 ¹⁶			X		X		X	X	X	X	X ⁹	X	
Serum creatinine, urine volume and creatinine clearance (D)	-21 to 1 ¹⁶			X		X		X	X	X	X	X	X	
Serum cortisol (D)	-15 to 1 ¹⁶		X	X	X	X	X	X	X	X	X	X	X	
Plasma ACTH (D)	-15 to 1 ¹⁶		X	X	X	X	X	X	X	X	X	X	X	
Signs and symptoms of Cushing's disease ⁸ (D) (Photographs, muscular strength evaluation, depression scale, hirsutism scale, waist circumf.)		X						X			X		X	
Bone mineral density / body composition (D) ¹²	-30 to 1										X ¹²		X ¹²	
MRI (D)	-30 to 1										X		X	
Quality of life assessment (D)		X						X			X		X	
PK sample (D)		X ¹¹	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis (D)	-15 to 1 ¹⁶							X			X		X	
Drug administration record (D)		X	X	X	X	X	X	X	X	X	X	X	X	
Study completion information (D)													X	
Concomitant medications (D)	As required													
Adverse events (D)	As required													

From Clinical Study Report, Table 9-3

Calculation of mUFC

Multiple 24-hour urine collections were done in order to calculate a mUFC at various time points for each subject. The number of collections required varied by the study visit. In addition, a Protocol Amendment changed the number of collections required at baseline.

During the baseline and at Months 3, 6, and 12, subjects were to collect four 24 hour urine samples collected within 2 weeks. At least 3 were required to calculate mUFC for those timepoints. The results from the samples per timepoint were averaged to obtain the baseline, Month 3, Month 6 and Month 12 mUFC levels, respectively.

For Months 1, 2, 4, 5, and 9, at least two UFC specimens were required at each of those months.

A Protocol Amendment (Amendment 6) changed the specification for *two* specimens for *four* specimens for the screening period only.

Issues related to urine collections

The assessment of the primary efficacy endpoint was 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. The Sponsor pre-defined an extremely low 24-hour urine creatinine by a value that is 15% lower than the lower limit of normal. Although collections associated with an extremely low 24-hour urine creatinine were not excluded, the Division noted and analyzed them to ensure that overall efficacy results were not impacted. This is further discussed in the Efficacy discussion.

Protocol Amendments

There were a total of 9 amendments implemented prior to database lock. Notable ones are discussed here:

- Amendment 4 changed the criteria for dose escalation at Month 3 from mUFC>1.5xULN or ≤50% reduction compared to baseline to mUFC>2xULN. It also changed the definition of responders at Month 6 so that any subject who was dose escalated and unblinded at Month 3 would be automatically counted as a non-responder in the primary efficacy analysis.
- Amendment 6 lowered the UFC entry criterion from ≤2xULN to ≤1.5xULN. As a result, the Month 3 dose-determination criteria were adapted. The response criteria at Month 6 were amended from mean UFC≤1.5xULN and a >50% reduction in mUFC to mUFC≤1xULN. Midnight salivary cortisol measurements were added. An extension treatment phase added for subjects benefiting from study treatment. Amendment included prolongation of the exclusion criteria of pituitary irradiation from 2 to 10 years prior to study start.
- Amendment 9 was a local amendment for China sites only that set the maximum dose a subject could to receive to 900 µg bid. This was requested by the Chinese Health Authorities.

6 Review of Efficacy

Efficacy Summary

Efficacy was demonstrated from the pivotal trial 2305. Limitations of this study were small sample size and lack of a comparator. Both of these limitations were considered acceptable given the patient population.

The primary efficacy endpoint was a stringent one, with a response defined by normalization of mUFC without a dose increase needed to achieve that at Month 6. 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.

Although the 600 µg dose did not meet the primary efficacy criterion, one can not declare that the two doses are different statistically. This is because Study 2305 was not powered to differentiate between doses and there was no plan to formally test for statistical differences in mUFC between dose groups.

Beyond from the primary efficacy endpoint, we pursued exploratory efficacy analyses. These showed consistent reductions in mUFC from baseline. Specifically, we constructed an alternate definition of 'responder' defined as: percentage of subjects who achieved 50% reduction in mUFC from baseline and/or normalization of mUFC at Month 6. In this analysis, 34% of subjects in the 600 µg group and 41% of subjects in the 900 µg group met this definition. This suggests a substantial biochemical benefit short of achieving normalization. Furthermore, analyses of individual responses indicate that the vast majority of subjects, in both dose groups and regardless of baseline mUFC, exhibited reduction in mUFC from baseline.

There was a large numerical imbalance in baseline mUFC values between the two dose groups. Statistically, there was no evidence pointing to a difference in baseline values. When adjusting for baseline values, the analyses were similar to the unadjusted analysis.

It was an important observation that mUFC levels appear to reach a nadir by about Month 2. Therefore, it seems prudent to assess overall clinical benefit by that time point. Given the safety issues to be discussed, practitioners should consider stopping pasireotide on patients who do not exhibit a reasonable response by Month 2.

Also, it was an interesting and perhaps unexpected observation that increasing dose in patients who have not achieved normalization does not confer much additional benefit.

Finally, given the strictly biochemical criteria for the primary efficacy endpoint, clinical benefit as evidenced by improvement in secondary endpoints would have been ideal. Overall, there was a suggestion that these clinical endpoints improved. However, because of limitations of the measurements and analysis of the secondary endpoints, these data do not overwhelmingly lend support to the overall efficacy profile.

6.1 Indication

The Applicant proposes pasireotide injection for the treatment of patients with Cushing's disease for whom medical therapy is appropriate.

6.1.1 Methods

The Applicant seeks to prove their claim of efficacy by one pivotal trial, B2305. Study 2208 and its extension are considered supportive.

Data from Phase II and Phase III were not pooled for either efficacy or safety analyses because of differences in study design, summarized here:

Table 5 Comparison of Studies B2208 and B2305

Characteristic	B2208	B2305
Type of study	Phase II proof of concept, open label, single arm study	Phase III double-blind, randomized, 2-arm registration study
Number of subjects	39	162
Duration of core phase	15 days	12 months
Inclusion of patients eligible for surgery	Yes	No
Primary efficacy measure	Mean of 2 24-hour UFC collections after 15 days of treatment	Mean of 4 24-hour UFC collections after 6 months of treatment
Assay to measure UFC (normal range)	Electrochemiluminescence immunoassay	High-pressure liquid chromatography
Dose interruption between end-core-phase and start of extension phase	Allowed (some patients with up to 6 month gap)	Not allowed

From Sponsor's Clinical Overview, Table 4-1

Statistical Analysis Plan

Dr. Lee Ping Pian's Statistical Review (included as part of the Advisory Committee Joint Clinical /Statistics briefing document) for details of the Statistical Analysis Plan (SAP). A general overview is provided here.

In Study B2305, the pre-specified primary efficacy endpoint was the proportion of responders at Month 6 by an individual dose group (pasireotide 600 µg s.c. b.i.d. or 900 µg s.c. b.i.d) 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/L) 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.

If the Month 6 mUFC was unavailable for a subject, the results of the last available mUFC based on at least 3 samples (from Month 3 to Month 6) were imputed to Month

6. If no suitable sample could be imputed the subjects was considered a non-responder.

Estimated response rates and corresponding 95% confidence intervals 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 Amendment 6, the sponsor removed the Hochberg procedure in favor of nominal statistical tests and 95% CIs for each dose. The Agency calculated results for both 95% and 97.5% CIs, the latter for the purpose of controlling type 1 error across the two doses.

The Sponsor also pre-specified a statistical model for the purpose of analyzing mUFC as a continuous variable. This is further explained in the Statistical Review.

6.1.2 Demographics

There were 162 randomized subjects in Study 2305. A summary of baseline demographic characteristics is presented below. Overall, characteristics were comparable between the 2 groups.

The mean age of subjects was 40.2 years and the majority of subjects were female (77.8%) and Caucasian (78.4%). Very few black (1.9%) and elderly subjects were enrolled.

Table 6 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)

Clinical Study Report, Table 11-2

The following table summarizes disease characteristics for all randomized subjects. With the exception of baseline mean UFC and previous medications for Cushing's disease, characteristics were generally similar in the 2 groups. Overall, subjects had been diagnosed with Cushing's disease for a mean of 54.03 months. The overwhelming majority of subjects had persistent or recurrent Cushing's disease (83.3%) and had previous surgery (79%). A minority of subjects had pituitary irradiation (4.3%).

As noted in the table below, not all subjects had a baseline mUFC value. Such values were available only for 77 of the 82 subjects in the 600 µg bid group and for 76 of the 80 subjects in the 900 µg bid group. Nine subjects did not have the minimum of three 24-hour urine specimens required in order to compute mUFC at baseline. However, all 9 subjects did have a set of two baseline mUFC values prior to the first pasireotide dose. The baseline mUFC values for these subjects were all greater than 2xULN, ranging from 2 to 11xULN. The mUFC calculated from 2 samples for these 9 subjects was used to assess the inclusion criteria. Therefore, there was biochemical (and historical) evidence to support the diagnosis of Cushing's disease. Since the primary endpoint did not specifically rely on the baseline mUFC value, their inclusion in the trial was considered to be acceptable.

The mean baseline mUFC was higher in the 600 µg bid group than in the 900 µg bid group. The significance of this is further discussed below.

Table 7 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)	1155.94 (2629.78)	781.90 (926.384)	970.14 (1979.020)
Median	730.00	487.00	564.50
Minimum, maximum	219.50-22943.75	195.00-6122.75	195.00-22943.75

Clinical Study Report, Table 11-3

There was a clear numerical difference in baseline mUFC in the two groups. Median mUFC values were 730 nmol/24 hours in the 600 µg group and 487 nmol/24 hours in the 900 µg group. Dr. Pian assessed the statistical significance of this difference by comparing the baseline MUFC values in the 2 groups using tests that accounted for the non-normality of the distributions. Baseline MUFC values were found to be not statistically significant.

The table below, which summarizes subjects in both dose groups by baseline mUFC categories, is helpful in understanding the baseline mUFC imbalance. Because the inclusion criteria allowed for enrollment of subjects with mUFC > 1.5xULN, baseline values spanned a large range of values. As such, normalization of UFC 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.

While the majority of subjects (41%) of subjects 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 mcg bid group had mUFC > 5XULN (48% vs. 28%), which contributed to the numerical imbalance in baseline mUFC levels between the 600 µg and the 900 µg groups.

Table 8 Number of enrolled subjects by baseline UFC

Baseline mUFC category	Pasireotide 600 µg bid	Pasireotide 900 µg bid	Overall
------------------------	------------------------	------------------------	---------

	N=82 n (%)	N=80 n (%)	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 Deficiency Responses, 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.

Most randomized subjects listed a medical history/continuing condition at baseline (96.3% in the 600 µg group and 100% in the 900 µg group). An exhaustive list of these conditions is beyond the scope of this Review. However, the conditions considered clinically important and relevant to this Application, are mentioned here. This includes conditions with particularly high prevalence among patients with Cushing's disease as well as those with relevance to the known safety profile of somatostatin analogues.

The high prevalence of certain diseases, summarized in the table below, is consistent with the complications associated with Cushing's disease: hypertension, impaired glucose tolerance and diabetes, obesity, hyperlipidemia, coagulopathy, osteoporosis, and psychiatric disorders. Overall, hypertension was the most frequent term (62% and 66% in the 600 and 900 µg groups, respectively). Disorders of glucose metabolism—captured among various terms including diabetes mellitus, type 2 diabetes mellitus and hyperglycemia--were prevalent in the study population.

Cardiac disorders were more prevalent in the 900 µg group. Although the conditions leading to the higher prevalence were spread out over a number of different terms, subjects in the 900 µg group had a higher number of reported conduction defects and cardiac rhythm disorders.

Table 9 Medical histories and continuing medical conditions by system organ class and preferred term*

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)
Cardiac Disorders	6 (7.3%)	18 (22.5%)
Endocrine Disorders	32 (39.0%)	38 (47.5%)
Hypothyroidism	16 (19.5%)	17 (21.3%)
Hepatobiliary Disorders	18 (22.0%)	19 (23.8%)
Cholelithiasis	5 (6.1%)	6 (7.5%)
Metabolism and Nutrition Disorders	54 (65.9%)	42 (52.5%)
Diabetes Mellitus	6 (7.3%)	11 (13.8%)
Hypercholesterolemia	14 (17.1%)	15 (18.8%)

Hyperglycemia	2 (2.4%)	2 (2.5%)
Type 2 Diabetes Mellitus	12 (14.6%)	8 (10.0%)
Musculoskeletal and Connective Tissue Disorders	44 (53.7%)	40 (50.0%)
Osteoporosis	17 (20.7%)	19 (23.8%)
Nervous System Disorders	22 (26.8%)	25 (31.3%)
Headache	13 (15.9%)	13 (16.3%)
Psychiatric Disorders	23 (28.0%)	33 (41.3%)
Anxiety	9 (11.0%)	9 (11.3%)
Depression	12 (14.6%)	14 (17.5%)
Insomnia	11 (13.4%)	14 (17.5%)
Renal and Urinary Disorders	19 (23.2%)	16 (20.0%)
Nephrolithiasis	10 (12.2%)	5 (6.3%)
Vascular Disorders	54 (65.9%)	57 (71.3%)
Hypertension	51 (62.2%)	53 (66.3%)

Clinical Study Report, Table 14.1-3.3

*table does not include all SOCs and PTs submitted

Medications taken at baseline were reviewed and important issues related to baseline drugs are discussed (not in detailed tabular form) here. 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%). Further and more detailed analysis of the use of antihyperglycemic medication before and during pasireotide use is in the Safety discussion.

Prohibited Concomitant Medications

Prohibited medications were taken by 17.1% and 17.5% of subjects in the 600 and 900 µg groups respectively. The most common prohibited medications were corticosteroids (dexamethasone and hydrocortisone), which were taken by 8.5% and 7.5% of subjects. Imidazole derivatives (ketoconazole) were taken short-term by 7.3% and 7.5% of subjects. Although use of any of these prohibited medications could have potentially influenced the response analysis, these treatments were short-term and were generally stopped prior to urine collections (washout period is one week for ketoconazole). Although none of these were considered protocol deviations, one should have been. This was a subject in the 600 µg group who was under ketoconazole treatment at the time of the UFC measurement for the primary efficacy analysis. This subject had also discontinued pasireotide 4 weeks prior to these UFC measurements. Given that the 600 µg group did not meet the primary efficacy endpoint, this would not have changed the primary efficacy results.

6.1.3 Subject Disposition

The following table summarizes subject disposition for Study 2305. At or prior to Month 6, a total of 55 subjects (34%) discontinued the trial. A total of 78 subjects (48.1%)

completed the core study (Month 12). At the time of data cut-off, 44 subjects (27.2%) were ongoing in the extension.

Table 10 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)
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)
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)

*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 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. In most of the remaining subjects there was biochemical evidence of efficacy but the subjects still chose to discontinue treatment.

Protocol Deviations

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.

The following table summarizes only the protocol deviations up to Month 6 that led to these subjects’ exclusion from the per-protocol analysis.

Table 11 Major protocol deviations up to Month 6, leading to exclusion from per-protocol analyses, by randomized dose group

	Pasireotide 600 µg bid N=83	Pasireotide 900 µg bid N=82

	n (%)	n (%)
Any protocol deviation	5 (6.1)	4 (5.0)
Any inclusion criteria deviation	1 (1.2)	2 (2.5)
Cushing's disease not confirmed	1 (1.2)	2 (2.5)
Any exclusion criteria deviation	0	0
Other deviation	4 (4.9)	3 (3.8)
Pituitary irradiation <10 years prior to study	1 (1.2)	1 (1.3)
Subject was mis-dosed	2 (2.4)	1 (1.3)
Subject had <80% of study drug administration	1 (1.2)	1 (1.3)

There were 4 Protocol Deviations that led to discontinuation. These included:

- 1) A subject discontinued on Day 42 because he did not meet the IPSS criteria for diagnosis of Cushing's disease in a patient with microadenoma.
- 2) A subject discontinued on Day 336 because the patient had a surgical intervention to remove the pituitary tumor prior to the end of study visit.
- 3) A subject was discontinued on Day 4 because he was a screen failure.
- 4) A subject was discontinued on Day 13 because the baseline prothrombin time met the exclusion criteria.

6.1.4 Analysis of Primary Endpoint(s)

The Sponsor's analysis populations are summarized below. The full analysis set (FAS), the primary population for efficacy, consisted of 162 subjects who received at least one dose of pasireotide. The per-protocol analysis set consisted of all subjects from the FAS who did not have a major protocol deviation.

Table 12 Analysis set by randomized dose group

	Pasireotide 600 µg bid N=83 n (%)	Pasireotide 900 µg bid N=82 n (%)	Overall N=165 n (%)
Full analysis set	82 (98.8)	80 (97.6)	162 (98.2)
Safety analysis set	82 (98.8)	80 (97.6)	162 (98.2)
Per-protocol set	77 (92.8)	76 (92.7)	153 (92.7)
PK analysis set	80 (96.4)	79 (96.3)	159 (96.4)
PD analysis set	80 (96.4)	79 (96.3)	159 (96.4)

Clinical Study Report, Table 11-1

The primary efficacy endpoint was the proportion of responders at Month 6. A responder was defined as a subject with a $mUFC \leq ULN$ at Month 6 and whose dose was not increased prior to Month 6 (dose could be decreased due to tolerability issues). The analysis was performed separately for subjects randomized to pasireotide 600 µg bid and 900 µg bid.

Below are the results for the primary efficacy endpoint. The Applicant's results 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. This larger CI was used for the purpose of controlling type 1 error across the two doses.

Table 13 Primary responder's analysis at Month 6

Treatment	SOM230 600µg n=82	SOM230 900µg n=80	Total n=162
# patients with mUFC≤1 ULN/n (%)	12/82 (15%)	21 (26%)	33/162 (20%)
Sponsor's analysis [95% CI]*	[7%, 22%]	[17%, 36%]	[14%, 27%]
Hochberg step-down analysis [97.5% CI]*		[16%, 39%]	

Dr. Lee Ping Pian

Of the 12 responders in the 600 µg group, 2 had Month 6 mUFC values imputed. Of the 21 responders in the 900 µg group, 2 had Month 6 mUFC values imputed.

The Statistical Reviewer then compared the 2 doses using a logistic regression model to compare efficacy of the two doses. This model, used to compare efficacy of the 2 doses, was also important in potentially incorporating adjustment for the numerical imbalance in baseline mUFC values. The model was used to estimate the odds ratio (OR) with one analysis with adjustment for baseline (“adjusted”) and one without (“unadjusted”). Results are shown below. The unadjusted model shows a statistical trend for dose response (OR=2.1, p=0.07). In contrast, the adjusted model, which used log baseline mUFC as a covariate in the model, is not statistically significant but suggests a trend that even when the doses are adjusted for baseline mUFC, the two doses are not equivalent from an efficacy standpoint. Therefore, adjusting for baseline had a modest impact on the comparative efficacy of the two groups.

Table 14 Statistical Reviewer Responder's analysis at Month 6

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

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Issues with urine collections related to primary endpoint: As mentioned previously, adequate urine collection was necessary for reliable measurements and ultimately reliable primary efficacy data. In Study 2305, there were 53 subjects with at least one extremely low 24-hour urine creatinine value, defined by the Sponsor as a value that is 15% lower than the lower limit of normal, at anytime during the trial up to Month 6. 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. Furthermore, these subjects had repeated extremely low 24 hour urine

creatinine values. For example, one subject had extremely low values at Months 3, 4, 5, and 6. The other subject had extremely low values at Months 1, 2, 4 and 6.

The Sponsor did not exclude any UFC value due to an extremely low urine creatinine. Because of this, the Statistical Reviewer performed a responder analysis excluding the 2 subjects with inadequate urine collections. Results are shown below. With the exclusion of these subjects, results are comparable to the original efficacy analysis.

Table 15 Efficacy Analysis excluding subjects who were responders with insufficient urine collections at Month 6

Treatment	Pasireotide 600µg n=82	Pasireotide 900µg n=80
# (%) of responder	12/82 (14.6%)	19/80 (23.8%)
Normal approximation of the binomial distribution 95% CI	14.6% [7.0%, 22.3%]	23.8% [14.4%, 33.1%]
Exact 95% CI	[7.8%, 22.4%]	[15.0%, 34.6%]

Dr. Lee Ping Pian

It should be noted that a substantial number of subjects were not receiving the dose to which they were randomized, and results presented thus far account for randomized groups only. The Protocol allowed for down-titration for tolerability issues. Subjects with dose changes and their responses are discussed in more detail below.

Exploratory Analyses using alternate definition of responder

Given the stringent threshold required to meet the primary efficacy endpoint (i.e. 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, the Statistical Reviewer conducted a post-hoc categorical analysis, using an alternate and less restrictive definition of responder compared to the pre-specified primary efficacy endpoint, shown below. 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 bid and 41% in the 900 µg groups met this new criterion of efficacy at Month 6 (LOCF).

Table 16 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%]

Another way of analyzing whether dose increases led to further biochemical improvements is to examine the changes in mUFC for those subjects who had a dose increase at Month 3 (24 subjects in the 600 µg group and twelve in the 900 µg group).

Although the summary data (not shown) suggest that there is not much further reduction in mUFC, the Statistical Reviewer analyzed the individual graphs for subjects whose dose was increased at Month 3. These are provided in the Appendix. Additional analyses related to dose are found further below.

Analyses of Changes in mUFC by Randomization Group

Although assessing median UFC response was a listed Secondary Endpoint in this Application, all analyses related to UFC changes are presented in this section. The following table summarizes descriptive statistics for UFC at important time points. Standard deviations for all values are very large, but clearly mean UFC values decreased in both dose groups.

Table 17 Descriptive statistics for mUFC Values by Randomization Group through Month 6

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

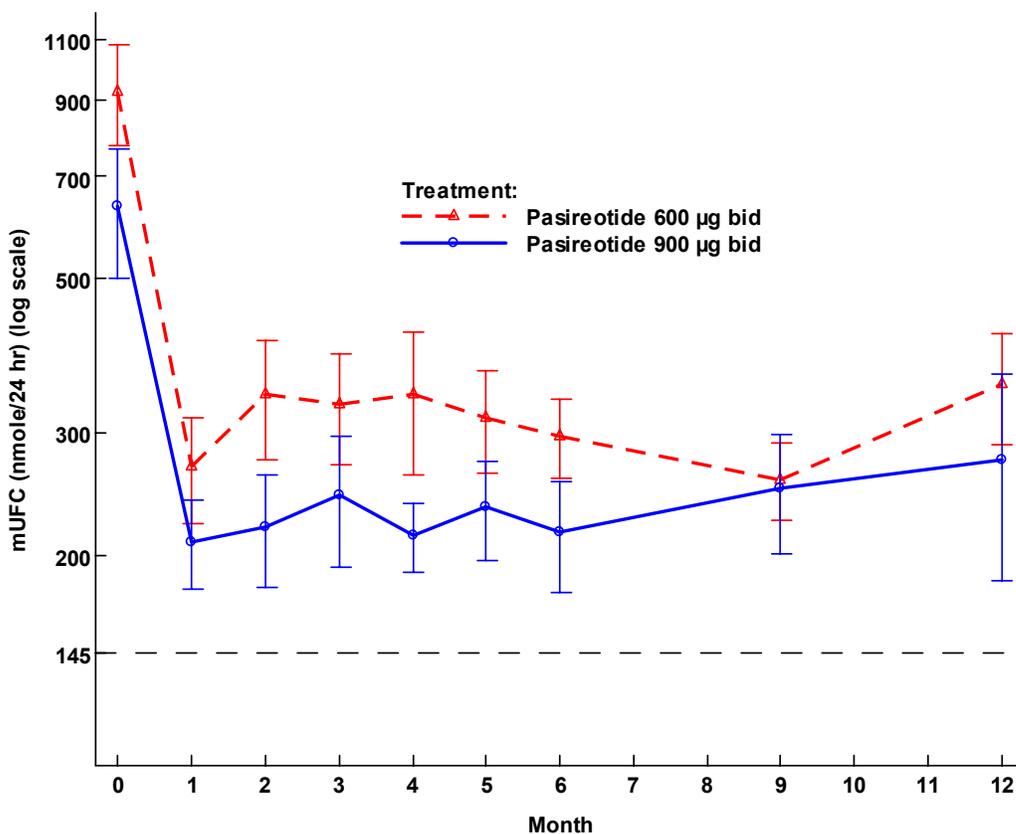
From Statistical Review

*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 (and appears to reach a nadir) by the Month 1 time point.

Figure 3 Mean (\pm SE) Urinary Free Cortisol (nmol/24h) at all Time Points up to Month 12 by Randomized Dose Group (Completers, n=39/group)



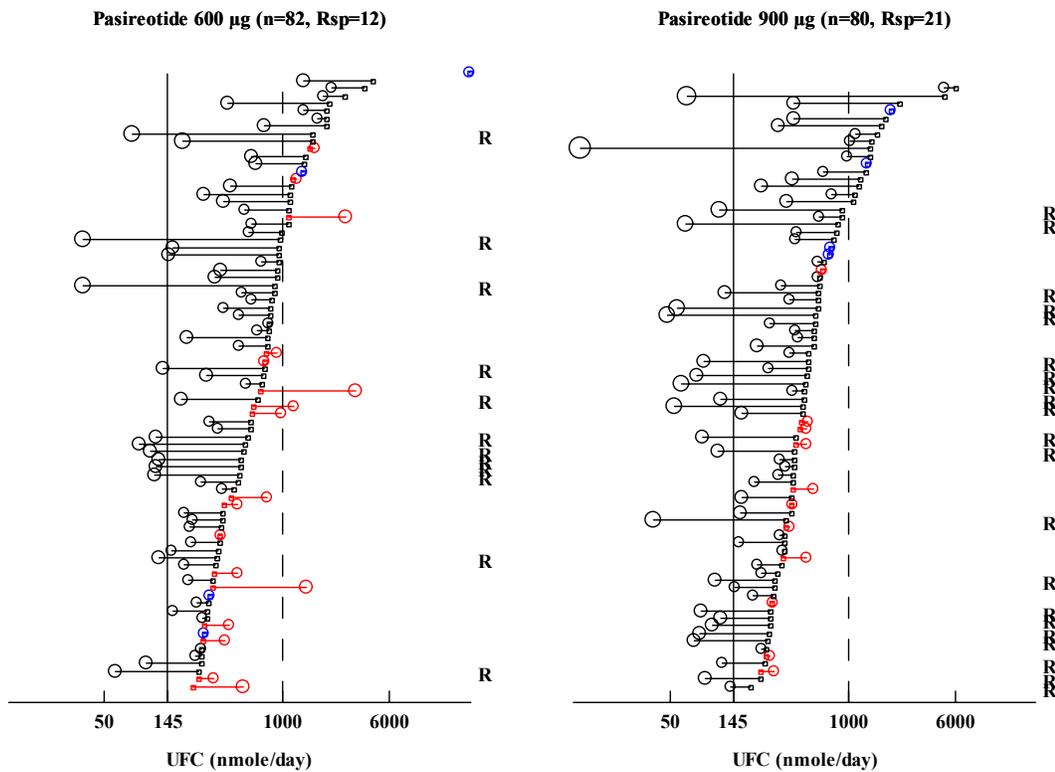
Analyses of Individual mUFC changes

Although mean changes in mUFC are important, examining individual changes is informative and provides insight into general patterns of subject response. 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.

Most of the larger mUFC increases were in the 600 µg group. Looking at subjects whose baseline mUFC was lower (closer to 145 nmol/day), it appears that those in the 900 µg group achieved normalization more than their “counterparts” in the 600 µg group.

Figure 4 Individual UFC Changes from baseline to Month 6 (LOCF, FAS) in Study 2305



Categorical Analyses Related to Baseline mUFC

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 (and that one in the 600 µg group) in the highest baseline UFC category.

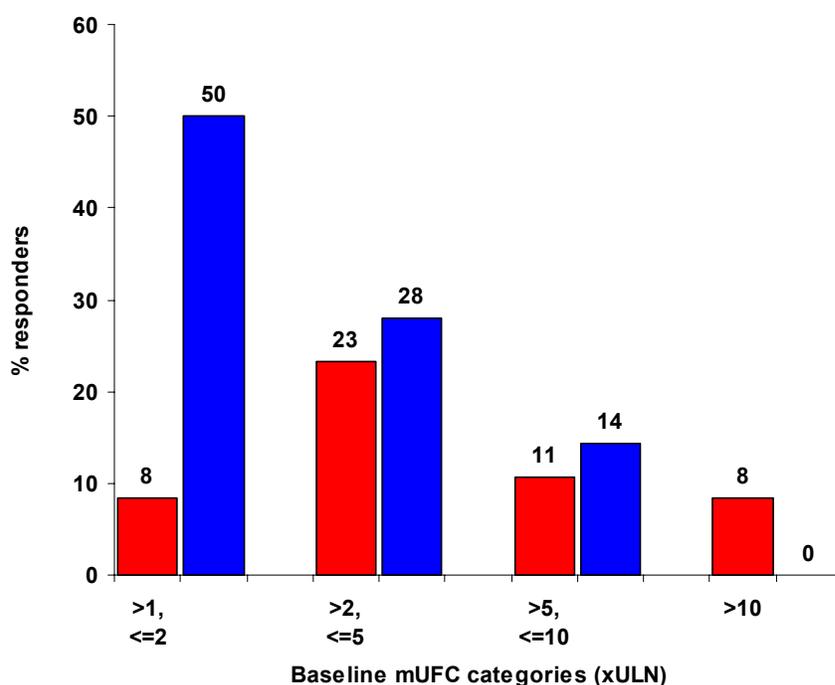
Table 18 Percentages of mUFC primary responders at Month 6 by baseline mUFC category (at least 2 samples) - FAS

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 (%) 95% CI	1/ 12 (8%) (0.2%, 38%)	7/ 14 (50%) (23%, 77%)	8/ 26 (31%) (14%, 52%)
> 2xULN to ≤5xULN	n/N (%) 95% CI	7/ 30 (23%) (9.9%, 42%)	12/ 43 (28%) (15%, 44%)	19/ 73 (26%) (16%, 38%)
> 5xULN to ≤10xULN	n/N (%) 95% CI	3/ 28 (11%) (2.3%, 28%)	2/ 14 (14%) (1.8%, 43%)	5/ 42 (12%) (4%, 26%)
> 10xULN	n/N (%) 95% CI	1/ 12 (8%) (0.2%, 38%)	0/ 9 (0.0%) -	1/ 21 (5%) (0.1%, 24%)

*95% CI from exact method
From Statistical Review

The figure below is a graphical display of the data shown in the table above. The numbers above the columns represent the percentage of responders in each category.

Figure 5 Percentages of mUFC Primary Responders by baseline mUFC category



An additional Statistical analysis looked at shifts on treatment (Month 6 LOCF) from baseline UFC categories. In general, there were shifts toward more favorable categories. All subjects in the 900 µg bid group stayed in the same baseline mUFC category or shifted to an improved category after treatment. No patients worsened from their baseline mUFC category. By comparison, 10 (12%) subjects in the 600 µg bid group worsened from their baseline mUFC category. These data can be found in the Appendix and Statistical Review.

Analyses of Dose

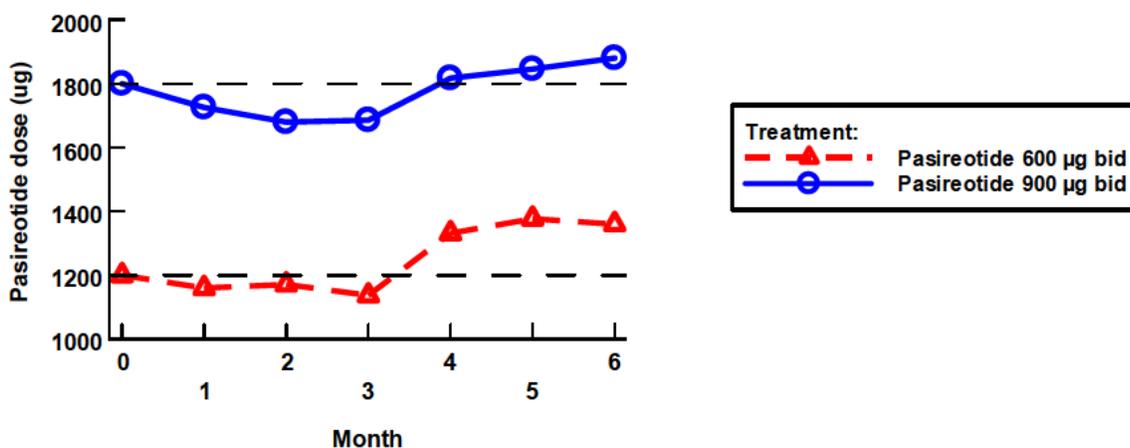
Although most of the analyses look at randomized doses, it is important to understand the actual doses that were taken. Doses could be decreased at anytime for tolerability

reasons and could be up-titrated at Month 3. Also, some subjects took incorrect doses. The table below presents data for total daily dose by month. The figure that follows displays the mean dose over time.

Table 19 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

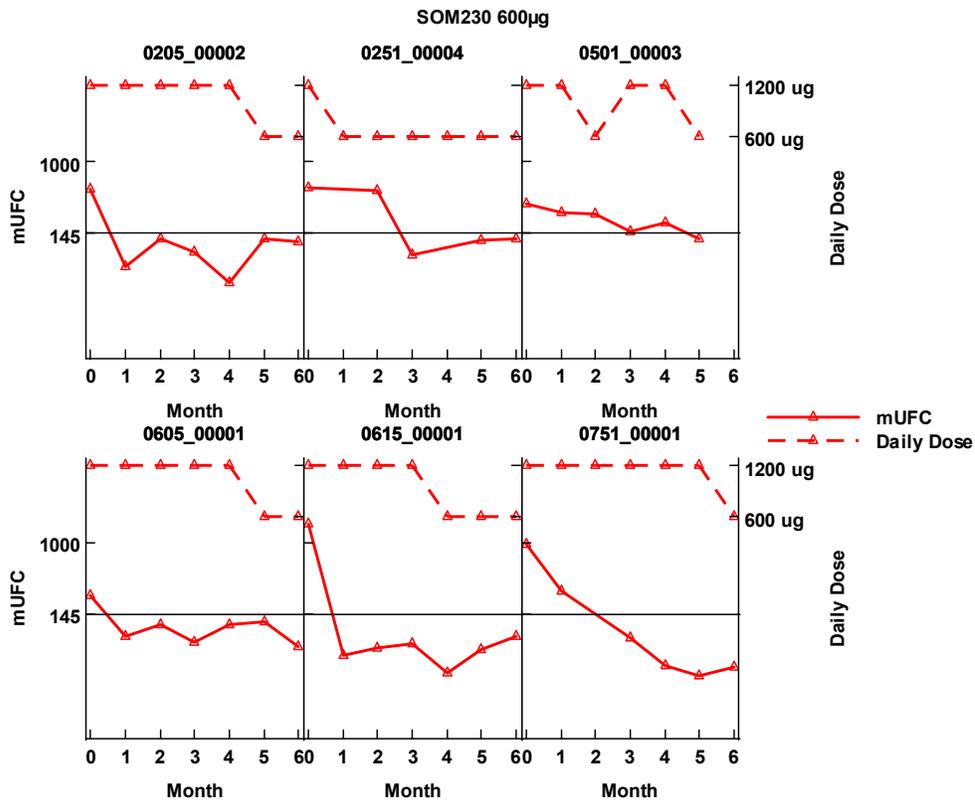


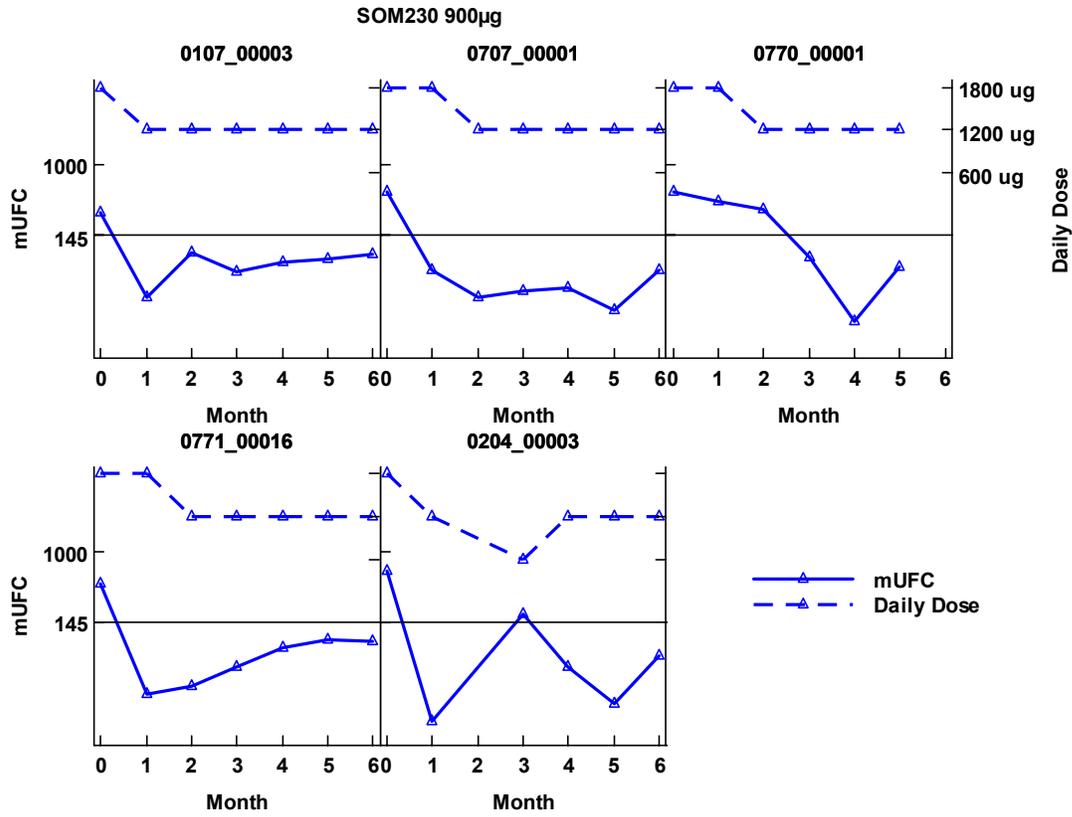
Dose Reduction in Responders: It should be noted that there were a total of 11 subjects who had normal mUFC levels at the Month 6 timepoint while on a dose lower than their randomized dose (decreased for tolerability reasons).

Specifically, at Month 6, of the 13 controlled subjects in the 600 µg bid group, there were 6 subjects taking a dose of 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 individual 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 in the 600 µg bid group who normalized their mUFC was down titrated in the first month (Subject 0251-00004). The other 5 subjects were on the randomized dose for 3 to 5 months.

Figure 7 mUFC (left y-axis) and daily dose (right axis) over monthly visits by responders with dose decrease





Overall, in the majority of these subjects, it appears that down-titration did not reverse the observed cortisol-lowering activity.

6.1.5 Analysis of Secondary Endpoints

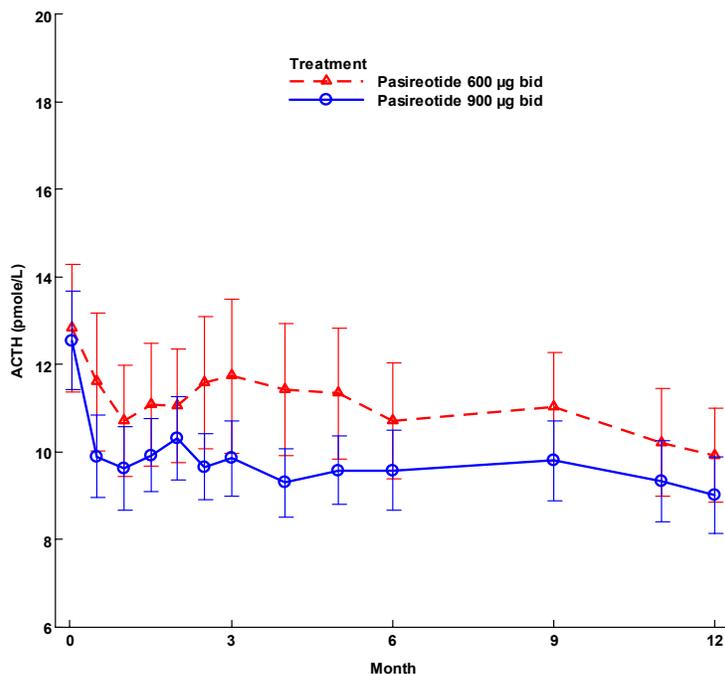
This document reviews the most important and clinically relevant secondary endpoints. There are limitations with interpretation of these secondary endpoints, including the fact that the primary endpoint for the 600 µg group did not reach statistical significance. Also, the Sponsor did not impute missing values for secondary endpoint analyses. On one hand, because of the limitations, these secondary endpoints should be viewed as supportive. On the other hand, the primary endpoint, complete normalization of mUFC, was a strict one. It is therefore useful to look at all changes in UFC, even those that did not meet the stricter criteria.

Additionally, since hypertension is a key feature of Cushing's disease, blood pressure is a particularly vital endpoint in this application. In this section, emphasis is placed on 1) UFC changes as support for efficacy and 2) blood pressure results and issues relating to the collection of BP data. Other secondary endpoints are also briefly discussed.

ACTH

Pasireotide acts at the level of the somatostatin receptor, and therefore one would expect declines in ACTH to accompany declines in cortisol. The figure below displays ACTH declines that were observed in both dose groups.

Figure 8 Mean ACTH plasma concentrations



Changes in Blood Pressure

Although blood pressure was measured as one of many clinical signs and symptoms, it is presented on its own in this section. The two key, objectively measured features of Cushing’s disease are insulin resistance and hypertension. In this Application, hyperglycemia/diabetes is presented in the Safety section. As an objective measurement, blood pressure changes would ideally serve to support the stringent primary efficacy endpoint.

Below are the mean changes in both systolic and diastolic blood pressure for the two doses. The largest decrease was for systolic blood pressure in the 900 µg group.

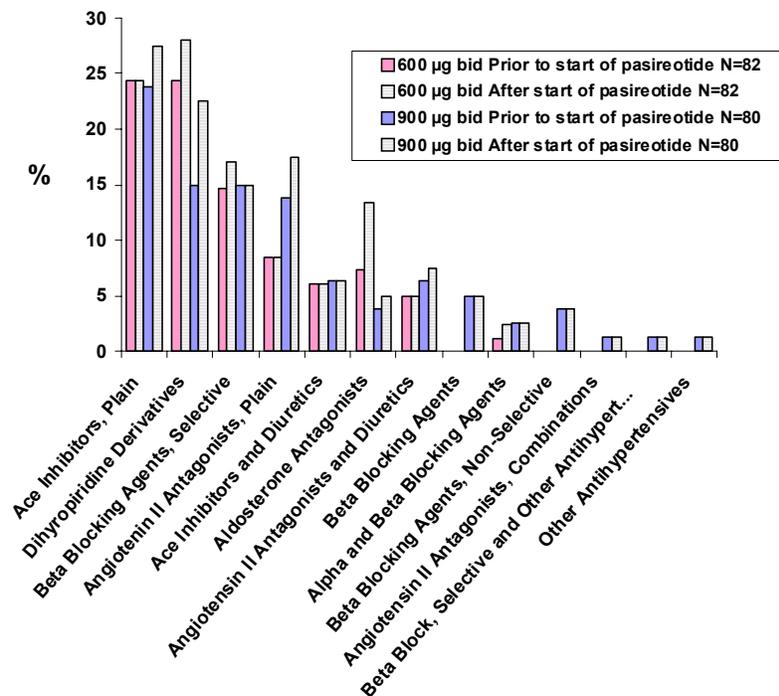
Table 20 Mean change from baseline in blood pressure by randomized dose group at Month 6

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)

Clinical Study Report

Patients enrolled in Study B2305 were allowed to use antihypertensive medications, and there were no restrictions to adding antihypertensive drugs during the trial. Unfortunately, data regarding the use of such drugs, particularly dose, was not recorded. The general use of anti-hypertensives was, however, recorded in the same way as any concomitant medication. A general comparison of anti-hypertensives used at baseline versus during the trial is presented in the graph below. The data in tabular form are presented in the Appendix. The graph indicates that there was an increase in use in some categories of anti-hypertensives. Conversely, given the decreases in blood pressure discussed above, one may have expected a decrease in the use of anti-hypertensives if the lowered cortisol was the etiology for lowered blood pressure. A general decrease in the use of anti-hypertensives was not observed. 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



Issues related to improper BP recordings were discussed in Section 3.2. These issues do not modify the overall conclusions regarding blood pressure changes.

Other clinical signs and symptoms of Cushing's disease

Aside from blood pressure, assessment of the change in improvement in various clinical signs and symptoms of Cushing's disease is a clinically important secondary endpoint. The table below summarizes these changes from baseline for both dose groups.

A mean benefit was observed in most of the measured categories; cholesterol and triglycerides had negligible changes from baseline. Although modest, there were some improvements in mean BMI, waist circumference, depression, and hirsutism scores. Standard deviations for some of these parameters were large. Again, lack of a comparator group limits the conclusions one can form from this data.

Table 21 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 change (SD)	n	Baseline mean (SD)	Mean change (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)

Applicant's Clinical Study Report

Quality of Life Data

A Cushing's syndrome health related quality of life (HRQL) questionnaire was used in this trial.¹¹ 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.

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

¹¹ 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.

- 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 HRQoI) to 100 (best HRQoI) 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 the standard deviations were large, mean and median values increased from baseline for both groups, indicating improvement.

Table 22: 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 (95% CI)	0.0, 86.4	-35.4, 52.1	-100.0, 400.0 (10.4, 52.3)	16.7, 91.7	-10.4, 52.1	-21.4, 1250.0 (25.2, 120.9)

Clinical Study Report, Table 11-11

A critical assessment was performed by the Study Endpoints and Labeling Development (SEALD) team and more detailed comments can be found in their Review. Although the questionnaire generally seems to capture important elements for Cushing's disease, the Review concludes that the evidence submitted by the Applicant does not demonstrate a clear measurable benefit in HRQL status. Because no dossier for the instrument was submitted in line with FDA Guidance, content validity for the instrument remains in doubt. Additional concerns include a lack of comparator and wide 95% confidence intervals reflecting statistically non-significant differences between dose groups.

Therefore, although these data may be supportive as a secondary endpoint, they would likely be inappropriate for labeling claims.

Tumor volume

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. Although it was reasonable to follow pituitary tumor growth in this patient population, there were a total of 49 subjects who had no measureable tumor at baseline. Therefore, these subjects were not included in the “percent change from baseline” analysis in the table below. This is because the denominator in the formula used to calculate the percent change was “baseline tumor volume” and a calculation could not be made with zero as the denominator. Therefore the sample sizes for the mean “percent change from baseline” values are small.

With these caveats, at Month 6, the 600 µg group showed a mean increase in tumor volume of 9% and the 900 µg group had a decrease of 19%.

Table 23 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
(95% CI)	(-0.032, 1.124)	(-0.011, 0.136)	(-8.88, 27.47)			

Source: Clinical Study Report, Table 14.2-2.8

Analysis of the primary efficacy endpoint by baseline characteristics

Categorical analyses related to baseline mUFC were discussed above.

The Sponsor also conducted some analyses and some are presented in the table below. Many data for subgroups are not listed here because too few subjects were included in each group to allow for meaningful conclusions.

The 600 µg group was comprised of 75% females and the proportion of responders between the genders was consistent in this group. However, in the 900 µg group, males comprised 20% of the group yet none were responders. Baseline mUFC levels were similar between genders. Attempting to explain the lack of male responders in the 900 µg group, the Sponsor performed some exploratory analyses. Clearly, small numbers of male subjects limit the utility of these analyses. Nevertheless, there are no obvious gender differences in both changes in mUFC at Month 6 (-41.4% and -37.2% respectively for males and females) as well as changes in clinical signs and symptoms.

The majority of enrolled subjects were Caucasian. Consistent with this, all responders in the 600µg group were Caucasian, and the majority of responders in the 900 µg group were Caucasian as well. The majority of enrolled subjects had persistent or recurrent Cushing's disease. This was consistent in the analysis below, as the majority of responders had recurrent or persistent disease.

Table 24 Proportion of UFC responders at Month 6 by randomized dose group and subgroup factors

	Pasireotide 600 µg bid N=82	Pasireotide 900 µg bid N=80	Overall N=162
Gender=female # subjects in analysis Response: n (%) 95% CI	62 9 (14.5) (7.4, 23.4)	64 21 (32.8) (21.3, 44.3)	126 30 (23.8) (16.4, 31.2)
Race=Caucasian # subjects in analysis Response: n (%) 95% CI	65 12 (18.5) (9.0, 27.9)	62 15 (24.2) (13.5, 34.9)	127 27 (21.3) (14.1, 28.4)
Cushing's Disease Status=Persistent/Recurrent # subjects in analysis Response: n (%) 95% CI	67 10 (14.9) (6.4, 23.5)	68 19 (27.9) (17.3, 38.6)	135 29 (21.5) (14.6, 28.4)

Clinical Study Report, Table 14.2-2.13

One additional analysis by baseline prior medical therapy (for Cushing's) done by the Agency is shown below. This was done to understand if subjects with prior medical therapy may respond differently to pasireotide. The analysis below shows that a higher percentage of responders among subjects who had previous medical therapy.

Table 25 Responders by prior medication (medical therapy for Cushing's) at baseline

Baseline Prior medication	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
No	5/46 (11%) [3.6%, 23.6%]	9/38 (24%) [11.4%, 40.2%]	14/84 (17%) [9.4%, 26.4%]
Yes	7/36 (19%) [8.2%, 36%]	12/42 (29%) [15.7%, 44.6%]	19/78 (24%) [15.4%, 35.4%]

Exact 95% Confidence Limits
 Dr. Lee Ping Pian

6.1.6 Other Endpoints

Midnight salivary cortisol

Salivary cortisol was considered an exploratory objective. This measurement was added after the 6 month interim database lock. Therefore, data from a small number of subjects contributed to this analysis. Because of this, meaningful interpretations of the data are limited. They are presented below as reference.

One midnight saliva sample was to be collected on the same day as one of the four 24 hour urine collections at baseline, Month 3, Month 6 and Month 12 and one of the two 24 hour urine collections at Month 9. Data and analyses up to Month 6 are presented below.

As reference, the normal laboratory range for midnight salivary cortisol is 0.83-8.30 nmol/L.

Figure 10 Change in midnight salivary cortisol (nmol/L) from baseline to time points up to Month12 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	48			45		
Mean	35.9			29.1		
SD	82.51			82.90		
Median	17.3			10.3		
Min, Max	1.7, 552.7			1.4, 549.5		
Month 3						
n	47	40	40	47	38	38
Mean	16.2	-4.5	-2.3	12.4	-19.3	36.5
SD	20.57	22.28	94.88	15.22	90389	223.32
Median	11.0	-4.4	-28.1	8.5	-1.9	-28.7
Min, Max	0.0, 132.2	-73.7, 84.9	-95.5, 323.0	0.8, 82.8	-532.4, 67.8	-96.9, 1035.9
Month 6						
n	41	34	34	33	28	28

Mean	13.1	-4.7	-2.8	11.0	-27.9	-4.8
SD	14.28	16.14	125.14	11.64	105.43	104.91
Median	7.8	-4.9	-26.5	6.9	-2.4	-41.8
Min, Max	0.0, 71.2	-31.5, 60.1	-88.7, 545.2	0.8, 42.3	-548.7, 29.3	-99.9, 378.9
95% CI		(-44.8, 39.3)				(-43.7, 34.0)

Clinical Study Report, Table 14.2-2.23

6.1.7 Subpopulations

Subgroup analyses are discussed in sections above.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

An initial discussion of dosing is in Section 1.2.

Prior to initiating the pivotal trial, the Applicant did not perform a wide dose-ranging study. The Phase 2 trial (2208) included only the 600 µg dose and the decision to use 600 and 900 µg in 2305 was based on the 2-week data of 2208. In the single-arm Study 2208 (reviewed in Appendix) in which 39 subjects were enrolled, there was a 17% responder rate.

In the initial submission, the Applicant proposed

(b) (4)

The clinical data, from both an efficacy and safety perspective—suggest subtle differences between the two doses. To be sure, only the 900 µg bid group met the primary efficacy endpoint. However, one can argue that the 600 µg bid dose, is efficacious. First, the 600 µg dose group (randomized) had a numerically higher baseline mUFC, and this may have contributed to the imbalance in responders between groups. On the other hand, when looking at the responders by baseline mUFC category, it is difficult to understand why only one subject in the 600 µg group in the lowest baseline mUFC category normalized their mUFC (compared to 50% of the 900 µg group in this category).

It is also important to understand that there were 11 subjects considered responders who were on a dose of pasireotide lower than their randomized dose. Nearly one-half of the responders in the 600 µg group were taking half the randomized dose at Month 6; approximately one-quarter of the responders in the 900 µg group were taking a lower-than-randomized dose.

Concurrently, and without obvious mechanistic explanation, dose increases do not appear to play major role in aggressively decreasing or normalizing UFC values.

From a safety perspective, the two doses appear to be similar in aggravating or causing hyperglycemia/diabetes. While both dose groups were similar in increasing FPG and HbA1c, the 900 µg dose group appeared to have a high number of diabetes-related SAEs. However, without a comparator group, one can not make firm conclusions about dose relationships.

The Pharmacometric analyses offer a different angle on the data. While the Statistical analyses look at randomized groups, pharmacometric data and analyses look at exposure-response relationships. These analyses are particularly important for several reasons. Some subjects were taking doses different than their randomized doses, and this must be taken into account. Also, the wide range of responses (particularly when looking at subgroups) adds to the complexity of conclusions one can make from the Statistical analyses alone.

The Pharmacometric data suggest important exposure-response relationship for safety and efficacy. The data also show substantial overlap in exposures between the two dose groups.

With all analyses in mind, a starting dose of 600 µg bid appears reasonable for most patients with the option for up-titration and down-titration. However, 900 µg bid may also be a reasonable starting dose for certain subjects. If normalization of UFC is achieved on this higher starting dose, down-titration is always an option for improving tolerability.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The evaluation of efficacy persistence is limited by the high numbers of dropouts as the trial progressed.

Of the twelve responders in the 600 µg group at Month 6, six (50%) had normal mUFC at Month 12. Of the other six, two had mUFC levels above normal and 4 dropped out at or prior to Month 12.

Similarly, of the twenty-one responders in the 900 µg group at Month 6, 12 (57%) still had normal mUFC levels at Month 12. Of the remaining 9 subjects who were responders at Month 6, 6 no longer had normal mUFC levels and 3 dropped out.

Below is a summary of the reasons for withdrawal of the 7 dropouts.

Table 26 General and Specific Reasons for Discontinuation in Subjects who were Responders at Month 6 but Dropped Out at or Prior to Month 12

General Reason for Discontinuation	Specific Reason for Discontinuation
600 dose group Adverse event Adverse event	Recurrence of elevated liver function tests Nausea

Adverse event Unsatisfactory Therapeutic Effect	Pregnancy Patient did not respond to maximum dose
900 dose group Subject withdrew consent Subject withdrew consent Adverse event	Patient did not want to comply with study requirements Patient withdrew consent to pursue elective surgery Adrenal insufficiency

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

In contrast to the efficacy data, the safety profile of pasireotide is derived from a number of different trials, including the pivotal study as well as mechanistic and safety studies. Reviewing data from all the sources was necessary to understand some of the specific and unexpected safety issues identified.

There were no deaths during the pivotal trial. Serious adverse events were reported in approximately 25% of overall subjects. Approximately 17% of subjects discontinued the trial because of adverse events, many related to hyperglycemia.

Nearly all subjects in the trial had at least one adverse event (AE), and rates of AEs were generally comparable between the 2 dose groups. Most AEs were in the following categories: gastrointestinal disorders, metabolism and nutrition disorders, and general disorders and administration site conditions. The most frequent individual AEs were diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus.

The Applicant pre-defined 20 so-called Adverse Events of special interest (each comprised of preferred terms) intended to broadly capture possible events based on the known somatostatin analogue class effects, Cushing's disease manifestations, and safety signals observed in pre-clinical studies. Because of a lack of specificity of the terms comprising the lists, the AEs of special interest were not always representative of actual events that occurred.

A number of safety issues known to be associated with somatostatin analogues were identified in the pivotal trial of pasireotide:

- Gastrointestinal events were commonly reported in the pivotal trial. Approximately 58% of subjects reported diarrhea and 52% had nausea.
- Cholelithiasis was reported for nearly one-third of subjects.

- QT prolongation was confirmed in two thorough QT trials. In the pivotal trial, QT prolongation was reported in approximately 6% of subjects.

Injection site reactions, not unexpected with a twice daily subcutaneous injection, were reported in 15% of subjects.

Certain laboratory abnormalities—both with uncertain clinical significance—were observed:

- PTT and PT/INR elevations: Approximately 52% of subjects had a post-baseline elevation of PTT or INR. The majority of elevations were minimal and there were no subjects with concomitant elevations of PTT or INR and total bilirubin.
- Hemoglobin decreases: mean values decreased but still stayed within the normal range.

Finally, two unexpected safety issues were identified: elevated liver tests and dramatic hyperglycemia.

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. Of particular concern were 4 subjects identified across the development program with concomitant elevations of ALT and total bilirubin: 3 healthy volunteers and one patient in a compassionate use study. Unfortunately an incomplete work-up was done to exclude other causes of hepatitis. Still, the pattern of elevations observed—with increased bilirubin concomitant or preceding the transaminase elevation—is not consistent with drug-induced liver injury. Furthermore, there were no clinical sequelae to the elevated laboratory values. Still, the mechanism of these findings is unclear and is worthy of further study.

Finally, 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 one would expect an improvement in insulin resistance with a cortisol-lowering drug, pasireotide appear to be responsible for a reduction in insulin production with subsequent development and/or worsening in hyperglycemia and diabetes. Sharp increases in FPG were seen as early as 2 weeks, and HbA1c increases (approximately 1.4% mean absolute change on treatment relative to baseline) were seen in both dose groups by Month 2. Extensive use of anti-hyperglycemic medications was seen in the trial. A Phase 1 study preliminarily explored the use of various anti-hyperglycemic medications for the treatment of pasireotide-induced hyperglycemia. However, aggressive monitoring and management of hyperglycemia was not done in the pivotal trial. What the optimal regimen is and whether subjects will tolerate the addition of anti-diabetic drugs (including injections) remains an unanswered question.

Comparing the two doses in terms of safety has limitations, but overall there were no major differences in the safety profile of the two doses.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The trials used to support safety are summarized in Table 2 above. The focus of this safety Review is on the Phase 3 trial B2305. Supportive data are derived from the Phase 2 trial B2208.

Specific safety concerns are also analyzed using data from Phase 2 trials of pasireotide in other indications, namely acromegaly and carcinoid syndrome. Finally, to address specific safety concerns, including hyperglycemia, elevated liver tests, and QT prolongation, data from multiple clinical studies of healthy volunteers and one study with subjects with hepatic impairment were used. These trials are summarized in the Appendix.

7.1.2 Categorization of Adverse Events

Adverse event coding for the submitted data utilized version 13.0 of the Medical Dictionary for regulatory activities (MedDRA). There were no major concerns specifically with the categorization of adverse events from the submitted data.

The Sponsor compiled a list of Adverse Events of Special Interest that were intended to capture events related to specific safety concerns. These specific concerns are discussed further below. Because many of the preferred terms (PTs) were not specific to the actual safety concern of interest, the percentages of subjects with AEs in these categories is not reflective of the AE of concern.

For example, one of the AEs of Special Interest is Pancreatitis-related AEs. This category was comprised of events coded to the following PTs: abdominal distension, blood amylase increase, lipase increased. Because a total of 21 subjects had one of these PTs reported as an AE, the data state that 13% of subjects overall had a Pancreatitis-related AE. However, there was no confirmed case of pancreatitis in the trial. Therefore, the adverse of events of special interest should not be viewed as a wide net to capture potential AEs. Further information was needed to confirm that certain PTs actually correlated with specific AEs.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Neither efficacy nor safety data were pooled. The pivotal trial was starkly different in design and duration from the other trials used in the review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the Phase 3 program safety information was obtained using two dosing regimens: 600 µg bid (1200 µg daily) and 900 µg bid (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 bid group, and 514 to 2273 for the 900 µg bid group; the mean dose of 1334.9 ± 325.3 µg/day was slightly above the randomized dose for the 600 µg bid group, and the mean daily dose of 1758.4 ± 286.4 µg/day was only slightly below the randomized dose for the 900 µg bid group.

Duration of exposure is summarized below. Overall exposure between the 2 groups was comparable, particularly in the 6 months category. Exposure dropped at the 12 month category and beyond.

Table 27 Duration of exposure to study drug by randomized dose group, up to data cut-off for Study 2305

	Pasireotide 600 µg bid N=82 N (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Exposure category (months)			
≥1	76 (92.7)	74 (92.5)	150 (92.6)
≥2	72 (87.8)	69 (86.3)	141 (87.0)
≥3	68 (82.9)	64 (80.0)	132 (81.5)
≥4	65 (79.3)	60 (75.0)	125 (77.2)
≥5	59 (72.0)	57 (71.3)	116 (71.6)
≥6	55 (67.1)	55 (68.8)	110 (67.9)
≥9	45 (54.9)	45 (56.3)	90 (55.6)
≥12	28 (34.1)	35 (43.8)	63 (38.9)
≥15	20 (24.4)	16 (20.0)	36 (22.2)
≥18	15 (18.3)	11 (13.8)	26 (16.0)
≥21	7 (8.5)	9 (11.3)	16 (9.9)
≥24	6 (7.3)	7 (8.8)	13 (8.0)
Exposure (months)			
Mean	10.66	10.89	10.77
SD	7.645	8.232	7.916
Median	10.58	10.22	10.37
Min, Max	0.03, 31.1	0.03, 37.8	0.03, 37.8

Full Clinical Study Report, Table 12-1

7.2.2 Explorations for Dose Response

A proper dose finding study evaluating a range of doses was not conducted. In the Phase II study 2208, patients with Cushing's disease were treated with pasireotide 600 µg bid were treated for 15 days. Five out of 29 patients showed normalization of UFC following 15 days of treatment. Nineteen of these 29 participated in an extension phase with the option of receiving higher doses: 900 µg bid or 600 µg three times daily (tid). After 6 months of follow-up, 18 subjects were included in the efficacy analysis. At the 6 month time point, 4 out of 18 subjects showed normalization of UFC. Based on these results, 600 µg bid and 900 µg bid were chosen as the randomized doses for the Phase III study in Cushing's disease patients.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

The safety assessments specified in the Protocol were generally adequate given the known safety profile of somatostatin analogues. However, the subjects with elevated liver tests--consistent with biochemical Hy's law—did not have adequate assessment following the elevations to determine the cause of the elevated bilirubin and transaminases. These subjects should have had evaluations to rule out Gilbert syndrome and other causes of hepatitis. Failing to perform a full work-up of the liver test abnormalities contributes to the difficulty in assessing the underlying cause of this safety issue.

7.2.5 Metabolic, Clearance, and Interaction Workup

This is discussed in Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Sponsor's study, as mentioned above in Section 7.1.2, the Sponsor compiled a pre-specified list of "adverse events of special interest". Some of these were based on known adverse events associated with somatostatin analogues: gastrointestinal reactions, QT prolongation, bradycardia, hyperglycemia, gallbladder and biliary disorders, hematological abnormalities, liver safety related, injection site reactions, pancreatitis, hypopituitarism. Each of these categories, in turn, contained a list of PTs

intended to capture possible events. While this method cast a wide net, the PTs were not always specific for the actual adverse event of interest.

Collection of these preferred terms related to the safety profile of SSAs as well as routine assessments of EKGs and gallbladder ultrasound underscored the Sponsor's intention to capture these events.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during the clinical program. One subject died during screening (no treatment received), reportedly from dementia, pituitary tumor, and hypotension. Another subject died 2 months after the last dose of pasireotide due to post-surgical complications after bilateral adrenalectomy. This subject did not complete the study and underwent surgery approximately one month after discontinuation. Causes of death were acute renal failure and disseminated intravascular coagulation.

7.3.2 Nonfatal Serious Adverse Events

The number of subjects who experienced a SAE is summarized below. Overall, nearly 25% of study subjects experienced an SAE, and approximately 5 % of study subjects discontinued because of an SAE.

Table 28 Serious Adverse Events (SAEs) by randomized dose group, up to data cut-off (Safety analysis set)

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
SAEs	19 (23.2)	21 (26.3)	40 (24.7)
Discontinued due to SAEs	3 (3.7)	5 (6.3)	8 (4.9)

From Clinical Study Report, Table 12-6

SAEs were most frequently observed in the MedDRA Metabolism and Nutrition Disorders System Organ Class (SOC). Frequencies for all SOCs are summarized below, up to data cut-off.

Table 29 SAEs, by SOC 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 (%)
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Subjects with any SAEs	19 (23.2)	21 (26.3)	40 (24.7)
Primary SOC			
Metabolism and nutrition disorders	4 (4.9)	7 (8.8)	11 (6.8)
Diabetes mellitus	1 (1.2)	3 (3.8)	4 (2.5)
Food intolerance	0 (0.0)	1 (1.3)	1 (0.6)
Hyperglycemia	1 (1.2)	3 (3.8)	4 (2.5)
Hypoglycemia	1 (1.2)	0 (0.0)	1 (0.6)
Type 2 diabetes mellitus	1 (1.2)	0 (0.0)	1 (0.6)
Endocrine disorders	3 (3.7)	5 (6.3)	8 (4.9)
Adrenal insufficiency	0 (0.0)	2 (2.5)	2 (1.2)
Pituitary-dependent Cushing's syndrome	3 (3.7)	3 (3.8)	6 (3.7)
Hepatobiliary disorders	4 (4.9)	2 (2.5)	6 (3.7)
Cholecystitis	0 (0.0)	1 (1.3)	1 (0.6)
Cholecystitis acute	1 (1.2)	0 (0.0)	1 (0.6)
Cholelithiasis	3 (3.7)	1 (1.3)	4 (2.5)
Infections and infestations	4 (4.9)	2 (2.5)	6 (3.7)
Abscess intestinal	1 (1.2)	0 (0.0)	1 (0.6)
Cellulitis	0 (0.0)	1 (1.3)	1 (0.6)
Cervicitis	0 (0.0)	1 (1.3)	1 (0.6)
Diverticulitis	1 (1.2)	0 (0.0)	1 (0.6)
Escherichia urinary tract infection	1 (1.2)	0 (0.0)	1 (0.6)
Nail infection	1 (1.2)	0 (0.0)	1 (0.6)
Pneumonia	1 (1.2)	0 (0.0)	1 (0.6)
General disorders and administration site conditions	2 (2.4)	2 (2.5)	4 (2.5)
Disease progression	1 (1.2)	1 (1.3)	2 (1.2)
Drug ineffective	1 (1.2)	1 (1.3)	2 (1.2)
Neoplasms benign, malignant and unspecified	1 (1.2)	3 (3.8)	4 (2.5)
Pituitary tumor benign	1 (1.2)	2 (2.5)	3 (1.9)
Secretory adenoma of pituitary	0 (0.0)	1 (1.3)	1 (0.6)
Nervous system disorders	0 (0.0)	3 (3.8)	3 (1.9)
Cerebrovascular accident	0 (0.0)	1 (1.3)	1 (0.6)
Cranial nerve paralysis	0 (0.0)	1 (1.3)	1 (0.6)
Dizziness	0 (0.0)	1 (1.3)	1 (0.6)
Dysarthria	0 (0.0)	1 (1.3)	1 (0.6)
Intracranial aneurysm	0 (0.0)	1 (1.3)	1 (0.6)
Somnolence	0 (0.0)	1 (1.3)	1 (0.6)
Tongue paralysis	0 (0.0)	1 (1.3)	1 (0.6)
Gastrointestinal disorders	1 (1.2)	2 (2.5)	3 (1.9)
Abdominal Pain	0 (0.0)	1 (1.3)	1 (0.6)
Constipation	0 (0.0)	1 (1.3)	1 (0.6)
Diverticular perforation	1 (1.2)	0 (0.0)	1 (0.6)
Inguinal hernia	0 (0.0)	1 (1.3)	1 (0.6)
Umbilical hernia	0 (0.0)	1 (1.3)	1 (0.6)
Investigations	1 (1.2)	1 (1.3)	2 (1.2)
Electrocardiogram QT prolonged	0 (0.0)	1 (1.3)	1 (0.6)
Lipase increased	1 (1.2)	0 (0.0)	1 (0.6)
Reproductive system and breast disorders	1 (1.2)	1 (1.3)	2 (1.2)
Adenomyosis	0 (0.0)	1 (1.3)	1 (0.6)
Uterine polyp	1 (1.2)	1 (1.3)	2 (1.2)

Respiratory, thoracic and mediastinal disorders	2 (2.4)	0 (0.0)	2 (1.2)
Epistaxis	1 (1.2)	0 (0.0)	1 (0.6)
Oropharyngeal pain	1 (1.2)	0 (0.0)	1 (0.6)
Vascular disorders	1 (1.2)	1 (1.3)	2 (1.2)
Hypotension	1 (1.2)	1 (1.3)	2 (1.2)
Cardiac disorders	0 (0.0)	1 (1.3)	1 (0.6)
Atrioventricular block 2°	0 (0.0)	1 (1.3)	1 (0.6)
Ear and labyrinth disorders	0 (0.0)	1 (1.3)	1 (0.6)
Vertigo positional	0 (0.0)	1 (1.3)	1 (0.6)
Injury, poisoning and procedural complications	1 (1.2)	0 (0.0)	1 (0.6)
Therapeutic agent toxicity	1 (1.2)	0 (0.0)	1 (0.6)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.3)	1 (0.6)
Musculoskeletal chest pain	0 (0.0)	1 (1.3)	1 (0.6)
Pregnancy, puerperium and perinatal conditions	1 (1.2)	0 (0.0)	1 (0.6)
Pregnancy	1 (1.2)	0 (0.0)	1 (0.6)

From Clinical Study Report, Table 14.3.1-1.32

The following table summarizes frequent SAEs, defined as more than 2% in any group.

Table 30 Frequent serious adverse events (> 2% in any group) by preferred term and randomized dose group, up to data cut-off (Safety analysis set)

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Pituitary-dependent Cushing's syndrome	3 (3.7)	3 (3.8)	6 (3.7)
Diabetes mellitus	1 (1.2)	3 (3.8)	4 (2.5)
Hyperglycemia	1 (1.2)	3 (3.8)	4 (2.5)
Cholelithiasis	3 (3.7)	1 (1.3)	4 (2.5)
Pituitary tumor benign	1 (1.2)	2 (2.5)	3 (1.9)
Adrenal insufficiency	0 (0.0)	2 (2.5)	2 (1.2)

Clinical Study Report, Table 12-7

Below are narratives for SAEs in Study 2305. Narratives for all SAEs in Study 2305 are not included here. In general, this includes events that were considered particularly notable. In addition, all narratives for the same SAE (e.g. diabetes) are not included since the narrative(s) included are fairly representative of other similar events that occurred. Narratives for events that are expected for this drug class (e.g. cholelithiasis) are not included, unless they were accompanied by other unusual findings.

SAE Narratives for subjects randomized to 600 µg pasireotide bid

Subject B2305-0101/00007 is a 55 year old woman with a long-standing diagnosis of Cushing's disease and type 2 diabetes mellitus. At screening, her HbA1c was 7.6% and she treated with metformin and 30/70 insulin. On Day 15 of study drug was interrupted because of worsening of DM. Further anti-diabetic therapy was added,

including insulin glargine and fast-acting insulin. On Day 120 her HbA1c was 9.0%. On Day 210, study drug was discontinued because of “lack of efficacy”. On Day 211, she was diagnosed with **hypoglycemia** and was admitted to the hospital for glucose monitoring. She was discharged the same day. It appears that her insulin requirements quickly decreased with the discontinuation of pasireotide.

Subject B2305-0205/00002 is a 58 year old woman with no prior treatment for Cushing’s disease. She did not have a diagnosis of DM at baseline and HbA1c was 6.3%. On Day 15, she was diagnosed with **pneumonia** and was hospitalized. She was concurrently diagnosed with **type 2 DM** (FPG was 254 mg/dL). Study drug was continued while she was treated with antibiotics, insulin, and repaglinide. She was discharged on Day 25. Her DM improved and she remained on gliclazide. On Day 255, she was hospitalized for worsening DM. Study drug was continued and she received repaglinide, gliclazide, and metformin. She was discharged 2 days later with improving glycemia. On Day 369, she was hospitalized for **hypotension**. This was felt to be secondary the flu and there was no mention of possible adrenal insufficiency. This resolved on Day 370. Cortisol levels were not measured at the time of the event.

Subject B2305-0251/00013 is a 67 year old man with a long-standing history of Cushing’s disease which included surgery and off-label medical therapies. He had no baseline diagnosis of DM and his baseline fasting plasma glucose was 81 mg/dL. On Day 15 he was diagnosed with **DM** with a FPG of 227 mg/dL. Study drug was permanently discontinued. He was started on insulin and reportedly recovered from the event. FPG on Day 22 was 97 mg/dL.

Subject B2305-0601/00002 is a 37 year old woman who had no prior medical treatment for Cushing’s. On Day 4, she was diagnosed with **adrenal insufficiency**, on clinical grounds alone. The dose of pasireotide was reduced and she was treated with hydrocortisone. Although this subject’s mUFC decreased from baseline, she was considered a non-responder at Month 6.

Subject B2305-0659/00002 (SAE and Discontinuation due to SAE) is a 67 year old woman with long-standing Cushing’s disease and diabetes mellitus. At screening, her HbA1c was 7.2%. On Day 76, her **diabetes mellitus** was considered “unstable” and she study drug was discontinued. Her FPG at that time was 198 mg/dL. Insulin was added to her oral antidiabetic therapy. Of note, on Day 96, she was diagnosed with a **diverticular perforation** with a **pericolonic abscess**. She was treated and recovered. Her last dose of study drug was on Day 106.

Subject B2305-0701/00002 is a 32 year old woman who was diagnosed with **pregnancy** on Day 87. The last dose of study drug was Day 148. She underwent a planned abortion on Day 186.

Subject B2305-0770/00003 is a 20 year old man who had minimally elevated ALT and GGT at baseline with a normal gallbladder ultrasound. On Day 30, he was diagnosed with increased ALT, increased GGT, **increased lipase**, and increased amylase. Bilirubin was mildly elevated. On Day 89, an ultrasound confirmed cholelithiasis. According to the narrative, no treatment was given. The dose of pasireotide was initially reduced but then discontinued on Day 88. The events were ongoing at the time of last reporting.

Subject B2305-0771/00013 is a 32 year old woman who presented with severe bleeding of the left ear and right nostril following tympanic membrane perforation on Day 328. She had mildly elevated PT and PTT at the time of the event, although her PTT was mildly elevated at baseline and during the trial. She was treated and the **epistaxis** resolved on Day 332. Coagulation parameters at key time points are summarized here:

Study Day	INR (NR 0.8-1.2 secs)	aPTT (NT 22-35 secs)
Screening	1.1	40
Day 29	1.0	40
Day 179	1.2	47
Day 330	1.3	51
Day 362	1.6	76
Day 454	1.3	45

Subject B2305-0906/00001 is a 27 year old woman with diabetes mellitus at baseline. HbA1c was 9% at baseline. She was started on insulin approximately one week before study drug was initiated. On Day 133, she was hospitalized for **hyperglycemia**. With treatment she improved and was discharged. Study drug was discontinued on Day 155 due to “unsatisfactory therapeutic effect”. HbA1c on Day 121 was 9.8%.

SAE Narratives for subjects randomized to 900 µg pasireotide bid

Subject B23-5-0101/00004 (SAE and Discontinuation due to SAEs) is a 41 year old man with hyperglycemia at baseline. His HbA1c at baseline was 7.1%. On Day 15, he was noted to have worsening hyperglycemia. On Day 21, he was diagnosed with type 2 diabetes mellitus and started on insulin. On Day 30, he was diagnosed with **progression of Cushing’s disease**. Study drug was discontinued on Day 42 due to diabetes and **lack of efficacy**.

Subject B2305-0107/00003 is a 46 year old woman who was diagnosed with adrenal **insufficiency (AI)** on Day 17. Study drug was temporarily interrupted, but she was given no specific treatment for the AI. Her 24 hour UFC on Day 29 was below the lower limit of normal. The event reportedly resolved on Day 22 and study drug was restarted at a lower dose. She also had SAEs of **cholecystitis** and **biliary colic** on Day 338. She was a responder at Month 6, consistent with the low mUFC values following the AI event.

Subject B2305-0251/00003 is a 41 year old woman who had diabetes mellitus at baseline. Metformin was her only antidiabetic drug and **baseline HbA1c was 6.9%**. **On Day 28, she was hospitalized with uncontrolled** diabetes and insulin was started. The event resolved by Day 36. Her peak HbA1c was 10.1% on Day 172.

Subject B2305-0506/00003 is a 47 year old woman who presented with impaired tongue movement and **dysarthria** on Day 26. She was diagnosed with **tongue paralysis** due to **invasive adenoma** located at the base of the skull leading to **cranial nerve paralysis**. Study drug was discontinued. She underwent a tracheostomy and gastrostomy with feeding tube. She was treated with dexamethasone and pituitary irradiation. By Day 57 the event resolved and she was transferred to a rehabilitation center. This subject only had a mUFC collected at baseline and no radiologic data was provided.

Subject B2305-0602/00001 (SAE and Discontinuation due to SAE) is a 54 year old woman with no baseline diagnosis of DM but with a screening HbA1c of 7%. On Day 4, she noted have **hyperglycemia** and on Day 13 her FPG was 301 mg/dL (FPG on Day 1 was 106 mg/dL). She withdrew consent on Day 12. She was hospitalized and treated with metformin and a sulfonylurea. The event was ongoing at the time of reporting.

Subject B2305-0770/00001 is a 41 year old woman who diagnosed with **adrenal insufficiency** on Day 85 as per laboratory abnormalities. Her UFC at this time was below the limit of normal and further decreased on Day 120. Her baseline UFC was 4x ULN. It is unclear from the report whether the subject was symptomatic, but she was discontinued from the trial and hospitalized for treatment with hydrocortisone. She was considered a responder at the primary efficacy time point.

Subject B2305-0771/00003 (SAE and Discontinuation due to SAE) is a 28 year old man who had a **prolonged QT** on Day 30. The QT was prolonged according to Bazett's correction formula (QTcV) but was normal according to the Fredericia correction formula (QTcF). Study drug was discontinued due to the event. This was reportedly resolved 57 days after the least dose of study drug.

Subject B2305-0842/00007 is a 46 year old woman with diabetes mellitus with an HbA1c of 6.3% at baseline. She was on metformin at baseline. Starting on Day 5, she was noted to be hyperglycemic which continued and worsened throughout the trial. Insulin was added in addition to metformin. On Day 393, HbA1c was 10.3%. Despite the **worsening of diabetes**, she completed the trial and was considered a responder at Month 6.

Subject B2305-0842/00009 is a 52 year old woman with type 2 diabetes on insulin with a baseline HbA1c of 9.1%. Starting on Day 6, **hyperglycemia** was worsening. Insulin was increased and metformin was added. Although the report states that the even

resolved on Day 78, her Day 305 HbA1c was 12.6%. Her UFC response was uncontrolled at month 6.

Subject B2305-0906/00003 is a 39 year old woman with no previous diagnosis of diabetes and a baseline HbA1c of 6.0%. On Day 11, the subject had fatigue, weight loss, blurred vision, polydypsia and polyuria--glucose was 504 mg/dL. Study drug was discontinued and treatment for the hyperglycemia was not noted. She was reportedly improved on Day 19, although the hyperglycemia was ongoing. HbA1c measured on Day 47 was 8.1%.

7.3.3 Dropouts and/or Discontinuations

Overall numbers of dropouts have already been discussed.

Below is the summary of AEs leading to drug discontinuation. Overall, 28 subjects had at least one AE leading to discontinuation: 13 patients (15.9%) in the 600 µg dose group and 15 patients (18.8%) in the 900 µg dose group. The most common AEs leading to discontinuation overall were GGT increased, hyperglycemia, and diabetes mellitus.

Table 31 AEs causing study drug discontinuation by SOC and PT up to data cut-off (Safety Analysis Set)

SOC PT	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Total	13 (15.9)	15 (18.8)	28 (17.3)
Endocrine Disorders	0 (0.0)	2 (2.5)	2 (1.2)
Adrenal Insufficiency	0 (0.0)	1 (1.3)	1 (0.6)
Pituitary-dependent Cushing's syndrome	0 (0.0)	1 (1.3)	1 (0.6)
Gastrointestinal Disorders	2 (2.4)	3 (3.8)	5 (3.1)
Diarrhea	1 (1.2)	2 (2.5)	3 (1.9)
Fecal incontinence	0 (0.0)	1 (1.3)	1 (0.6)
Nausea	1 (1.2)	1 (1.3)	2 (1.2)
General Disorders and Administration Site Conditions	1 (1.2)	2 (2.5)	3 (1.9)
Asthenia	0 (0.0)	1 (1.3)	1 (0.6)
Fatigue	1 (1.2)	1 (1.3)	2 (1.2)
Hepatobiliary Disorders	1 (1.2)	0 (0.0)	1 (0.6)
Cholelithiasis	1 (1.2)	0 (0.0)	1 (0.6)
Investigations	5 (6.1)	4 (5.0)	9 (5.6)
ALT increased	0 (0.0)	2 (2.5)	2 (1.2)
AST increased	0 (0.0)	1 (1.3)	1 (0.6)
Immunoglobulin E increased	0 (0.0)	1 (1.3)	1 (0.6)
QT prolonged	0 (0.0)	1 (1.3)	1 (0.6)
GGT increased	3 (3.7)	2 (2.5)	5 (3.1)
Hepatic enzyme increased	1 (1.2)	0 (0.0)	1 (0.6)
Lipase increased	1 (1.2)	0 (0.0)	1 (0.6)

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

Metabolism and Nutrition Disorders	4 (4.9)	6 (7.5)	10 (6.2)
Diabetes mellitus	2 (2.4)	2 (2.5)	4 (2.5)
Hyperglycemia	2 (2.4)	3 (3.8)	5 (3.1)
Type 2 DM	0 (0.0)	1 (1.3)	1 (0.6)
Neoplasms	0 (0.0)	1 (1.3)	1 (0.6)
Pituitary Tumor Benign	0 (0.0)	1 (1.3)	1 (0.6)
Nervous System Disorders	1 (1.2)	1 (1.3)	2 (1.2)
Cranial nerve paralysis	0 (0.0)	1 (1.3)	1 (0.6)
Tongue paralysis	0 (0.0)	1 (1.3)	1 (0.6)
Tremor	1 (1.2)	0 (0.0)	1 (0.6)
Pregnancy-related Conditions	1 (1.2)	0 (0.0)	1 (0.6)
Pregnancy	1 (1.2)	0 (0.0)	1 (0.6)
Psychiatric Disorders	0 (0.0)	1 (1.3)	1 (0.6)
Confusional State	0 (0.0)	1 (1.3)	1 (0.6)
Renal and Urinary Disorders	0 (0.0)	1 (1.3)	1 (0.6)
Urinary incontinence	0 (0.0)	1 (1.3)	1 (0.6)
Skin Disorders	0 (0.0)	1 (1.3)	1 (0.6)
Urticaria	0 (0.0)	1 (1.3)	1 (0.6)
Vascular Disorders	0 (0.0)	2 (2.5)	2 (1.2)
Hot flush	0 (0.0)	1 (1.3)	1 (0.6)
Hypotension	0 (0.0)	1 (1.3)	1 (0.6)

Clinical Study Report, Table 14.3.1-1.33

Below are narratives for discontinuations due to adverse events. Many of these events were hyperglycemia/diabetes, and GGT and liver test elevations. The narratives for cases associated with liver test elevations were already included under Hepatic Safety and are mostly not repeated in this section. To avoid redundancy, not all narratives of cases of hyperglycemia/diabetes and GGT elevations are mentioned here. The ones included are fairly representative of other events.

Narratives for discontinuations due to adverse events in the 600 µg bid group

Subject B2305-0361/00004 is a 48 year old woman with type 2 diabetes at baseline (treated with glimepiride) with a screening HbA1c of 7.3%. On Day 7, she was diagnosed with **hyperglycemia** and the dose of glimepiride was increased and rosiglitazone was added. Study drug was discontinued because of this event. Her Day 35 HbA1c was 8.4%.

Subject B2305-0382/00003 is a 47 year old woman with normal liver tests at baseline. On Day 85, she was diagnosed with increased GGT (other liver tests normal). By Day 171, this abnormality worsened. Study drug was discontinued because of this event. The GGT normalized by Day 211. GGT values during the trial are summarized below.
Reviewer comment: Elevated GGT (often alone without other elevations in liver tests) was commonly seen. Its clinical significance is not known.

Study Day	GGT (NR 2-65 U/L)
Day 1	28
Day 29	76
Day 58	62

Day 85	174
Day 113	149
Day 143	100
Day 171	228
Day 211	46

Of note, there were multiple discontinuations due to increased GGT. Upon review of these, some subjects had increased GGT at baseline.

Narratives for discontinuations due to adverse events in the 900 µg bid group

Subject B2305-0659/00001 is a 38 year old woman who developed **urticaria** on Day 1 after having received one dose of study drug. This was accompanied by hypotension and blood immunoglobulin E increased. Study drug was discontinued. No treatment was given for the event and it resolved on the same day.

7.3.4 Significant Adverse Events

A total of 55 subjects had at least one AE requiring dose adjustment or study drug Interruption: 31 subjects (37.8%) in the 600 µg bid group and 24 subjects (30.0%) in the 900 µg bid group. The SOCs with the highest frequencies of such AEs (in the 600 and 900 µg groups) were Gastrointestinal disorders (14.6% and 8.8% of subjects) and Metabolism and Nutrition disorders (9.8% and 11.3% of subjects).

Overall, the most common AEs leading to dose adjustment or interruption of study drug were: nausea (6.8% of subjects), diarrhea (4.9% of subjects), hyperglycemia (4.9% of subjects), and adrenal insufficiency (4.9%).

7.3.5 Submission Specific Primary Safety Concerns

A number of concerning and important safety issues were analyzed during the review. This section contains a discussion of each of these, but focuses on the two most overwhelming concerns: hyperglycemia/diabetes and elevated liver tests.

Hyperglycemia/Diabetes

Insulin resistance is a central feature in patients with Cushing's disease, and hyperglycemia and diabetes are common manifestations in patients. The hypercortisolemia effects metabolism via redistribution of free fatty acids to central fat, increased gluconeogenesis, inhibition of glucose uptake by peripheral tissues, and impairment of insulin function.^{12,13}

¹² Pasquali et al. The Hypothalamic-Pituitary-Adrenal Axis Activity in Obesity and the Metabolic Syndrome. Annals of New York Academy of Sciences 2006.

Aggravating this baseline insulin resistance, somatostatin analogues are associated with hyperglycemia which is primarily related to impairment of insulin secretion. Given that hyperglycemia is a central feature of the disease at hand and is a known effect of the drug class, analyses of glycemia in this development program are of particular importance in assessing the safety profile of pasireotide.

Fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) were the 2 key measures of glycemia measured and analyzed in Study 2305. The safety analyses presented below were performed according to the dose to which subjects were randomized; therefore dose changes are not taken into account. Also, because the number of subjects decreased over the trial period (including discontinuations for hyperglycemia) the analyses may not accurately portray the effect of the drug on glycemic control. This becomes particularly problematic at later timepoints.

In order to make the analyses more clinically relevant, the Sponsor applied the 2013 American Diabetic Association classification and prior history of diabetes mellitus or anti-diabetic medication use at baseline to define subjects as 'diabetic', 'pre-diabetic', or 'normal'.

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

These categories are used in some of the analyses below.

The FPG and HbA1c data from Study 2305 are reviewed first. As per the Division's request, the Sponsor also submitted a document entitled "Glucose Metabolism Report" that was intended to characterize the effects of pasireotide on glucose metabolism in Phase 1-3 clinical trials of this development program. These additional analyses are covered after the primary data.

FPG

Mean FPG by randomization group and time points are presented below. In Study 2305, at baseline, the mean FPG was 98.6 and 97.0 mg/dL, respectively for the 600 and 900 μ g bid groups. A distinct elevation of FPG was seen starting at Week 2. Mean FPG levels peaked at Month 1, gradually decreased, but never returned to normal. Of note, between Month 3 and Month 12 there were a substantial number of subjects who discontinued the trial for a variety of reasons, including hyperglycemia and diabetes.

¹³ Wajchenberg et al. Subcutaneous and Visceral Adipose Tissue: Their Relation to the Metabolic Syndrome. Endocrine Reviews 2000.

Therefore, one cannot support the conclusion that there was a decline in mean FPG through Month 12.

Table 32 Summary of mean fasting plasma glucose by randomized group and visit—Study 2305 (Safety analysis set)

Visit	Pasireotide 600 µg bid		Pasireotide 900 µg bid	
	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)

Full Clinical Study Report, Table 12-14

Shifts in fasting blood glucose from baseline to Month 6 are summarized in the table below, which reproduces one of the applicant's analyses. The overwhelming trend was shifting to worsening glycemic categories. 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 33: 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

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 (%)
	Total	162 (100)	58 (36)	43 (27)	48 (30)	10 (6)	3 (2)

HbA1c

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 did not return to baseline values.

Table 34: Summary of mean HbA1c (%) by randomized group and visit (Safety analysis set)

Visit	Pasireotide 600 µg bid		Pasireotide 900 µg bid	
	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 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 35: Shift in HbA1c from baseline to last value up to Month 6 by randomized dose group (safety analysis set, LOCF)

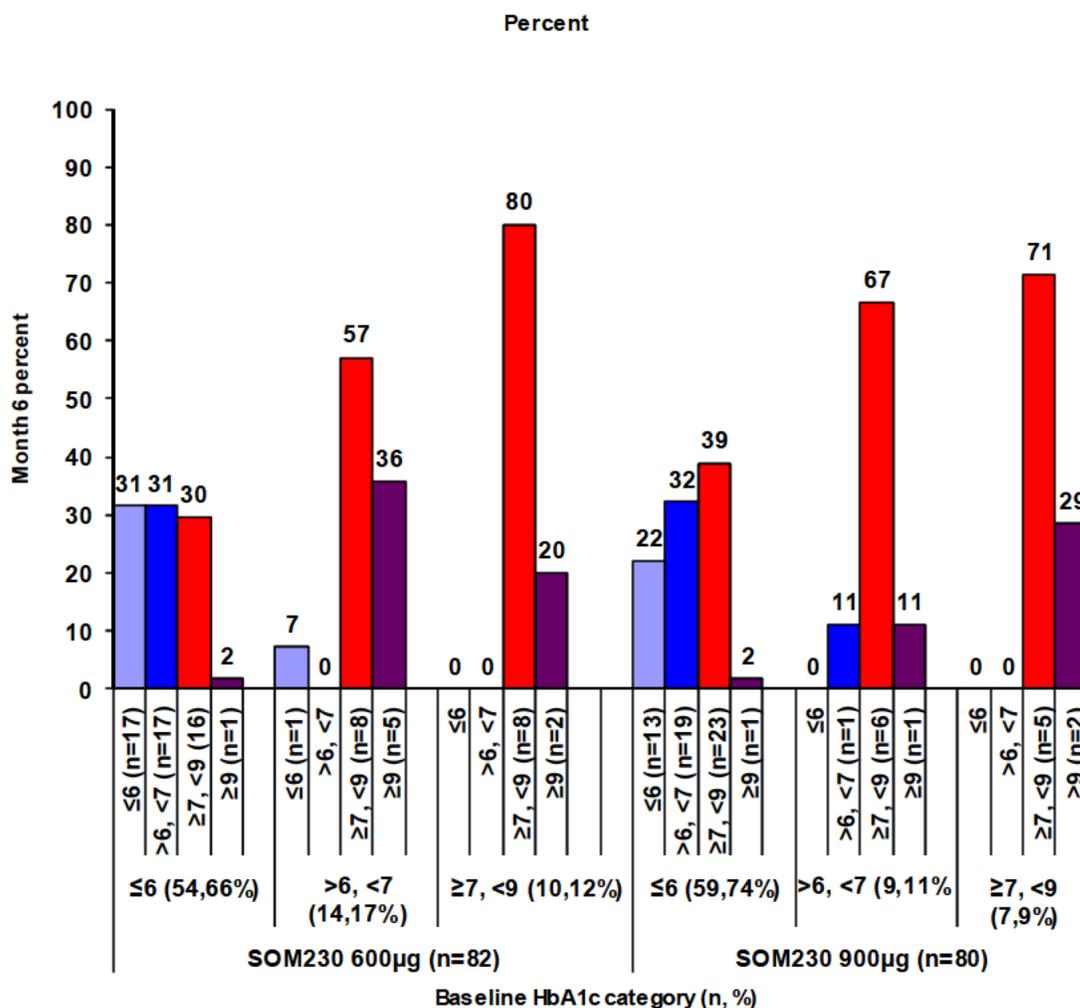
Dose group	Baseline		Month 6 (LOCF)				
		n (%)	HbA1c≤6 n (%)	6<HbA1c<7% n (%)	7%≤HbA1c<9% n (%)	HbA1c≥9% n (%)	Missing n (%)
600 µg bid	HbA1c≤6	54 (66)	17 (32)	17 (32)	16 (30)	1 (2)	3 (6)
	6<HbA1c<7%	14 (17)	1 (7)	0	8 (57)	5 (36)	0
	7%≤HbA1c<9%	10 (12)	0	0	8 (80)	2 (20)	0
	%	0	0	0	0	0	0
	HbA1c≥9%	4 (5)	1 (25)	2 (50)	0	0	1 (25)
	Missing	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)

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

	7%≤HbA1c<9%	7 (9) 1 (1)	0 0	0 0	5 (71) 0	2 (29) 1 (100)	0 0
	HbA1c≥9%	4 (5)	0	1 (25)	3 (75)	0	0
	Missing	80 (100)	13 (16)	21 (26)	37 (46)	5 (6)	4 (5)
	Total						
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
	%	1 (1)	0	0	0	1 (100)	0
	HbA1c≥9%	8 (5)	1 (13)	3 (38)	3 (38)	0	1 (13)
	Missing	162 (100)	32 (20)	40 (25)	69 (43)	13 (8)	8 (5)
	Total						

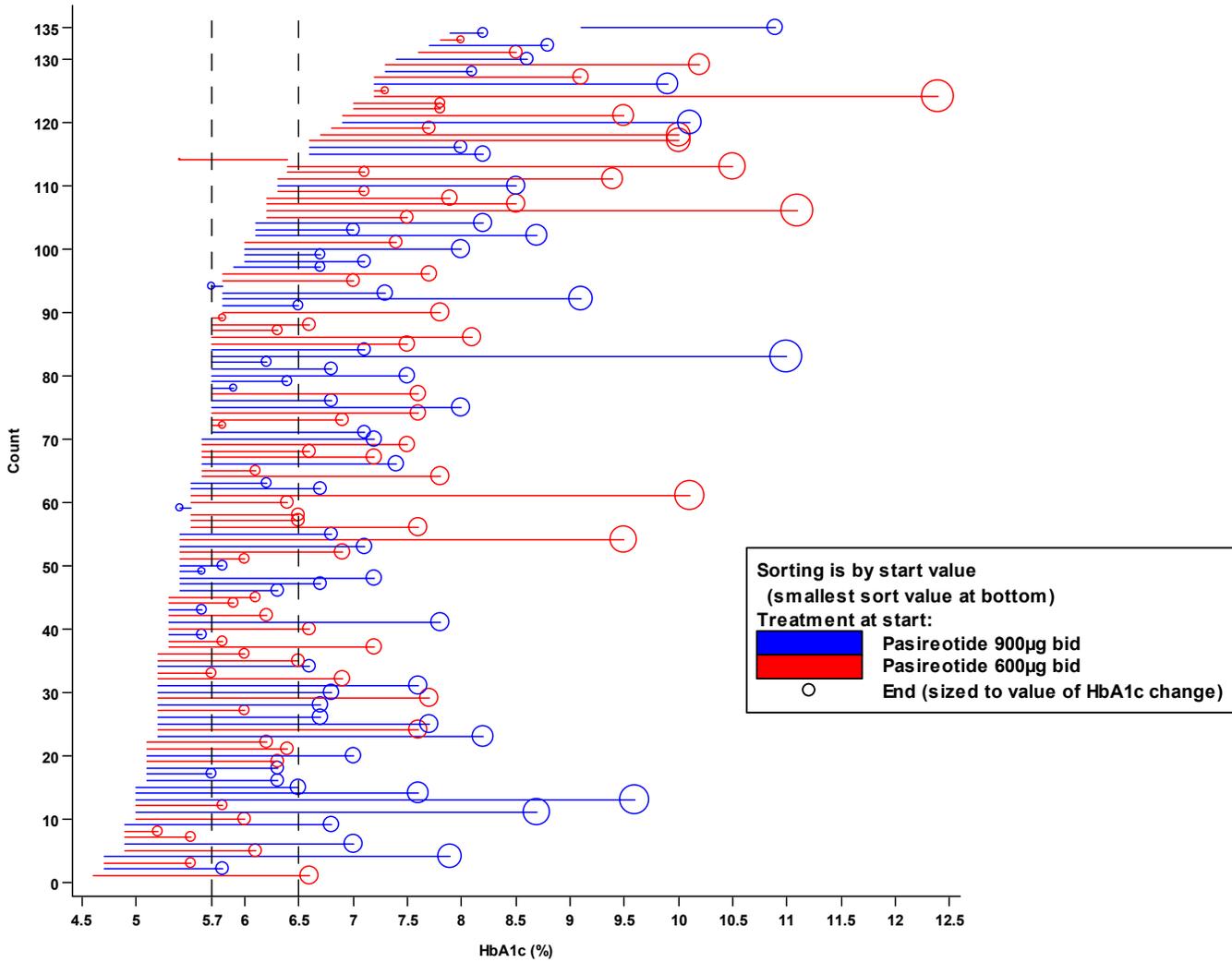
The data provided in the table above is displayed in the graph below. The “missing” categories are excluded from the figure.

Figure 11: Shift in HbA1c from baseline to last value up to Month 6 by randomized dose group



Finally, 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 and with more detail are displayed are provided in the Appendix.

Figure 12: Individual changes in HbA1c from baseline to Month 6



Shift 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. These terms have been defined above. According to these definitions, approximately 41% of patients enrolled in trial 2305 had normal glucose status at baseline, 24% had pre-diabetes, and 34% were diabetic. The table below summarizes baseline diabetic status by dose group. Glycemic status was reasonably balanced between the two groups.

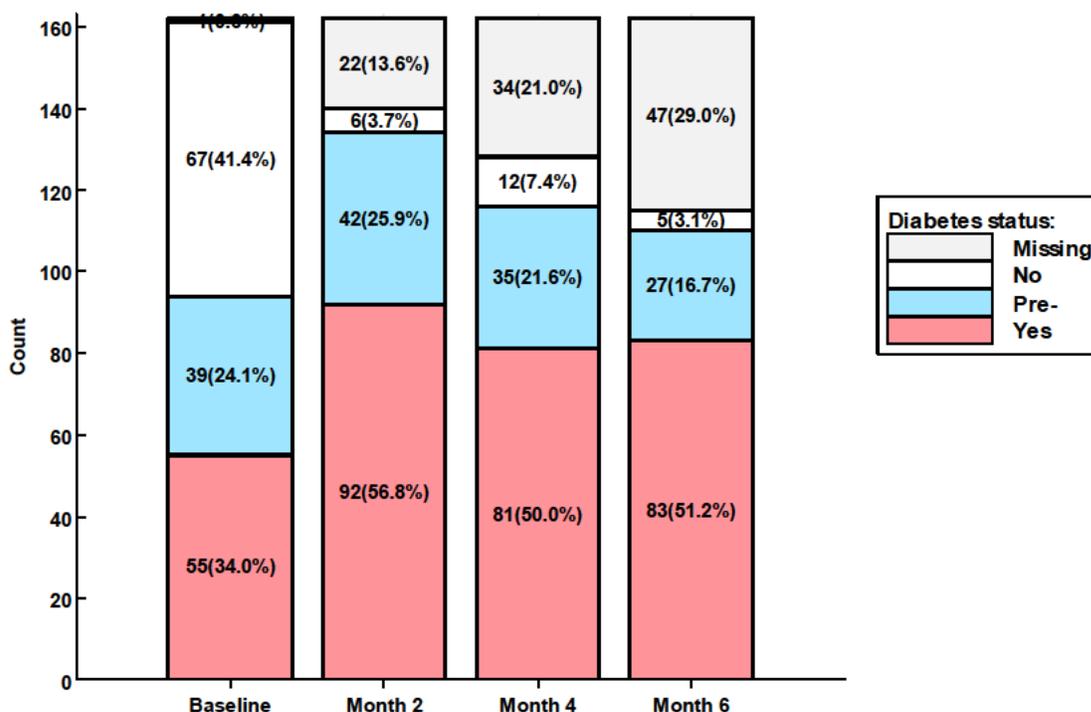
Table 36 Summary of baseline diabetic status by randomized dose group (Study 2305)

Diabetic status at baseline	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Normal glucose tolerance	35 (42.7)	32 (40.0)	67 (41.4)
Pre-diabetic	18 (22.0)	21 (26.3)	39 (24.1)
Diabetic	28 (34.1)	27 (33.8)	55 (34.0)
Missing	1 (1.2)	0	1 (0.6)

Sponsor's Glucose Metabolism Report, Table 5-34

The bar graph below illustrates the changes (dose groups combined) in diabetic status over the trial. 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 13: Changes in pre-diabetes and diabetes status



Having already seen the baseline diabetic status for both groups and keeping the results for the primary efficacy endpoint in mind, the table below summarizes the responders by baseline diabetic status. Overall, the majority of responders had normal glycemia at baseline. This may be consistent with the observation that, in general, subjects with baseline mUFC categories closer to normal were more likely to achieve normalization of mUFC.

Table 37 Summary of responders by baseline diabetic status (Full analysis set-Study 2305)

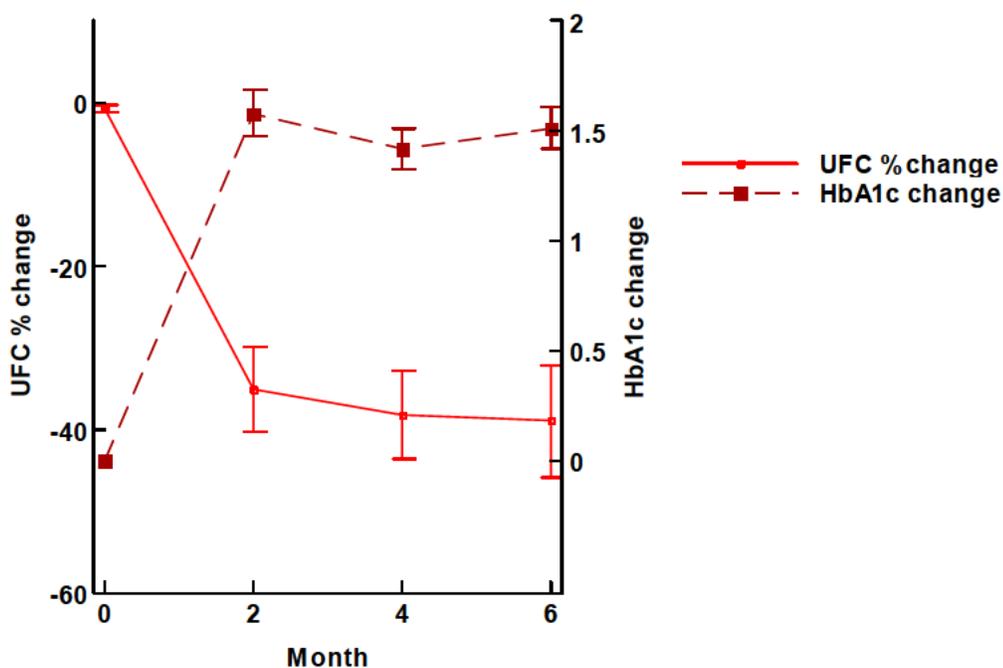
Baseline Diabetic Status	Pasireotide 600 µg bid N=82 N	Pasireotide 900 µg bid N=80 n	Overall N=162 n
Normal	6	9	15
Pre-diabetic	4	3	7
Diabetic	1	9	10
Missing	1	0	1

Sponsor's Glucose Metabolism Report, Table 5-41

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

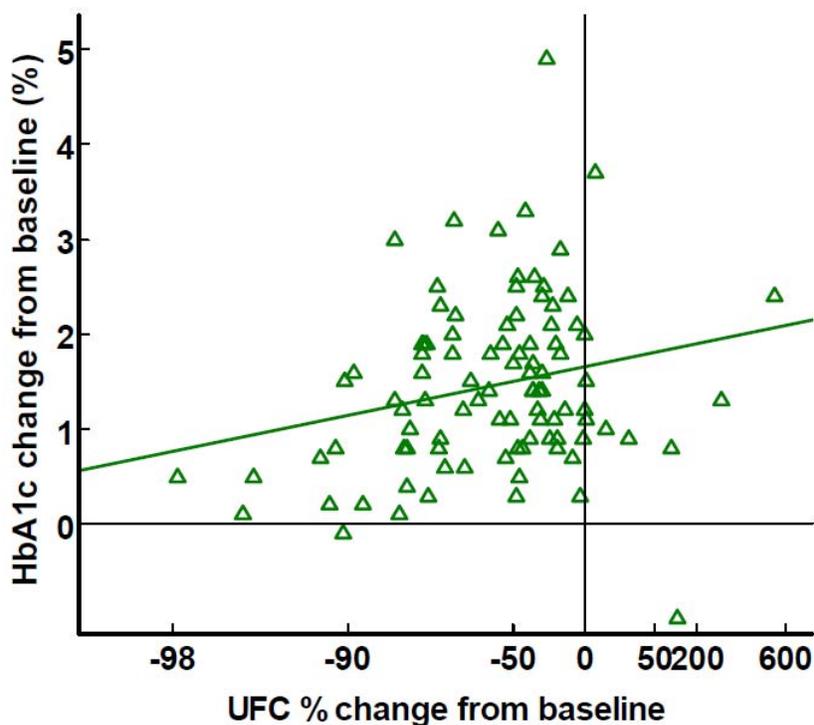
The graph below displays the concomitant changes for mUFC and HbA1c to Month 6 for all subjects with available data. The percent change in mUFC and the absolute HbA1c values followed a similar temporal pattern of change but quantitatively moved in opposite directions: HbA1c increased as mUFC decreased.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

Figure 14: mUFC and HbA1c changes from Baseline (Completers)



Finally, shown below is a correlation analysis for completers at Month 6. This shows paired data for individual subjects and yields a weak positive correlation ($r=0.23$, $r^2=0.05$, $p=0.02$) suggesting that for any one subject a larger decrease in mUFC correlates with a larger decrease in mUFC.

Figure 15 Change in HbA1c as UFC changes from baseline (Completers at Month 6)



Use of anti-diabetic medications

Use of antihyperglycemic medication at baseline and during the trial is discussed in this section. It is important to note that information regarding dose was not collected.

The following table summarizes the percentages of subjects on anti-diabetic treatment at baseline and those who were initiated on such treatment during the trial. The majority of subjects were not on anti-diabetic treatment at baseline (76.9% subjects, $n=129$). These data should be interpreted with caution, since 22 diabetic subjects (categorized by Sponsor, see below) were not treated with anti-diabetic medications even at baseline. Approximately one-third of subjects (53 subjects) who did not have anti-diabetic treatment at baseline were started on anti-diabetic treatment during the trial. Given the high number of diabetics who were not on anti-diabetics at baseline, it is unclear how much the initiation of anti-diabetic drugs is related to pasireotide-induced

hyperglycemia and how much is related to participation and heightened medical supervision in a clinical trial. The table below does not reflect increases in dosage for anti-diabetic drugs taken at baseline nor does it reflect the number of anti-diabetic therapies initiated.

Table 38 Summary of anti-diabetic medication at baseline and post-baseline

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Patients with anti-diabetic treatment at baseline	20 (24.4)	13 (16.3)	33 (20.4)
Patients who did not have anti-diabetic treatment at baseline and started anti-diabetic treatment during the study	24 (29.3)	29 (36.3)	53 (32.7)
Patients who did not have anti-diabetic treatment during the trial	38 (46.3)	38 (47.5)	76 (46.9)

Sponsor's Glucose Metabolism Report

Regarding use of specific anti-hyperglycemic drugs, the table below shows that their dramatically increased during the trial. For instance, use of insulin increased from 6.2% to 22.8%, use of glinides increased from 0.6% to 9.3%, use of sulphonamides increased from 1.9% to 21.6%, and use of metformin increased from 15.4% to 43%. Given the decreases in cortisol observed, one would not have expected these sharp increases in the use of anti-diabetic therapy.

Table 39: Concomitant antidiabetic medication use prior to and following pasireotide dosing

ATC class Preferred Term	Prior to pasireotide dosing			Following pasireotide dosing		
	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)
Rapaglinide	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)
Thiazolidinediones	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 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) 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 anti-hyperglycemic effect. This study is further discussed below. The hyperglycemia observed in this trial should also be viewed in the context of the widespread use of metformin. Clearly, more data regarding the treatment of pasireotide-induced hyperglycemia is needed.

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 40: 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)

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

Analyses of HbA1c and FPG by responder status

The Statistical Reviewer also performed an analysis to look at how the changes in mUFC related to a shift in diabetic status during the trial. In other words: did a subject whose diabetic status worsened during treatment with pasireotide (from normal to pre-diabetic or diabetic) have less of a decrease in mUFC? The table seems to suggest that indeed this was the case. This is clearly an exploratory analysis that is limited by the fact that no subjects who were pre-diabetic or diabetic at baseline shifted to normal glycemic status at Month 6.

Table 41 Percent change in mUFC from baseline to End of Treatment (EOT) by subjects' diabetic status at baseline and EOT

Baseline diabetic status	Diabetes status – EOT to Month 6			
	Normal N Mean (median) [min, max]	Pre-diabetic N Mean (median) [min, max]	Diabetic N Mean (median) [min, max]	Total N Mean (median) [min, max]
Normal	N=5	N=20	N=31	N=56

	-76% (-78%) [-92%, -48%]	-47% (-58%) [-98%, +134%]	+2% (-41%) [-89%, +542%]	-23% (-51%) [-98%, +542%]
Pre-diabetic	N=0	N=7 -47% (-54%) [-96%, +55%]	N=26 -33% (-31%) [-83%, +45%]	N=33 -36% (-34%) [-96%, +55%]
Diabetic	N=0	N=5 -22% (-56%) [-91%, +148%]	N=41 -40% (-44%) [-92%, +96%]	N=46 -38% (-44%) [-92%, +148%]

Hyperglycemia-related Adverse Events

Hyperglycemia was an AE of special interest with pre-specified terms. Overall, “hyperglycemia” was the third most frequently reported adverse event, reported in 40% of all subjects. It was slightly more frequent in the 900 µg group.

In terms of hyperglycemia-related AEs (pre-specified terms), 72.8% of total subjects had such an event. The table below summarizes these events.

Table 42 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)

From Sponsor’s Glucose Metabolism Report

There were a total of 10 subjects with hyperglycemia-related SAEs:

Table 43 Hyperglycemia-related SAEs by PT and randomized dose group in Study 2305

	Pasireotide 600 µg b.i.d. N = 82 n (%)	Pasireotide 900 µg b.i.d. N = 80 n (%)	Overall N = 162 n (%)
Patients with any SAE(s)	4 (4.9)	6 (7.5)	10 (6.2)
Preferred term			
Diabetes mellitus	1 (1.2)	3 (3.8)	4 (2.5)
Hyperglycemia	1 (1.2)	3 (3.8)	4 (2.5)
Hypoglycemia	1 (1.2)	0 (0.0)	1 (0.6)
Type 2 diabetes mellitus	1 (1.2)	0 (0.0)	1 (0.6)

Glucose Metabolism Report, Table 5-51

A total of 10 subjects with a hyperglycemia-related AE discontinued the trial. Although they were balanced between the 2 dose groups, 9 of 10 subjects were in the uncontrolled responder category at Month 6.

Additional Analyses of Pasireotide-induced Hyperglycemia

The effect of pasireotide on glucose control was studied in Phase 1, 2, and 3 of the program.

Healthy volunteers

In Phase 1, healthy subjects were administered pasireotide as a single dose and up to twice daily over 7-8 days. In a Sponsor's analysis from 5 pooled studies, rapid and transient increases in blood glucose were observed. The hyperglycemia occurred with initial pasireotide exposure, but attenuated with multiple doses (1-2 days).

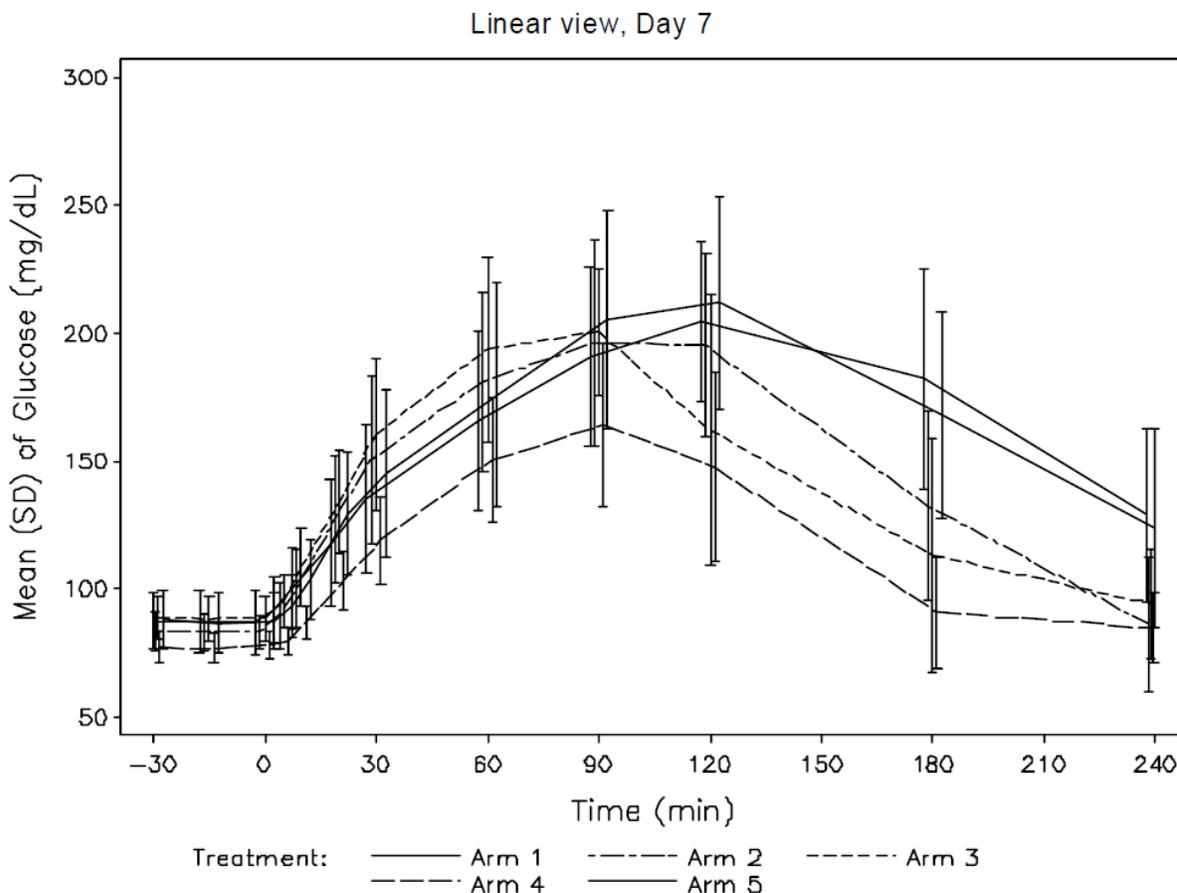
Another Phase 1 study (2124) entitled "A randomized, open-label, single center, phase I study to evaluate the effects of the co-administration of anti-hyperglycemic drugs and pasireotide s.c. compared to pasireotide s.c. alone on glucose metabolism in healthy male volunteers" was initiated to understand 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_{0-4hr} 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.¹ The greatest effect was seen with 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 16 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

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_{0-4h} 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 was 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 a safety perspective, the co-administration of pasireotide with liraglutide appeared to be 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.

This study has important implications for the PI and management of pasireotide-induced hyperglycemia. Incretin enhancers may be important in this management and metformin, an obvious choice, may not be helpful.

In an Investigator-initiated Phase 2 study (2216) designed to elucidate the mechanisms of pasireotide-associated hyperglycemia, measurements of insulin sensitivity, hepatic glucose output, and pancreatic beta-cell function were calculated from 45 healthy men. Subjects were randomized to 600 and 900 µg groups (1200 µg group was terminated early because adverse events of nausea and vomiting). OGTT and clamp tests were performed at baseline and on study days 8-10. In both dose groups, pasireotide was associated with hyperglycemia and reduced insulin secretion as well as reduced secretion of C-peptide, glucagon, GLP-1, and GIP. There was no evidence of a dose-dependent effect. The hyperglycemia did not appear to be associated with a decrease in insulin sensitivity in the liver or muscles.

Patient studies

This review focuses on studies of patients with Cushing's disease. The Sponsor also performed several analyses on acromegaly and carcinoid subjects, but these were not pooled with the Cushing's disease population. The analyses examine the glycemic effects of pasireotide with regard to HbA1c and FPG, as well as the changes in pancreatic hormone levels. The Phase 2 trials of Cushing's disease the Sponsor used for the analysis were:

Study No.	Indication	N	Study Design	Treatment (Dose, Route)	Study duration
SOM230B2208	Cushing's disease	39	Open-label, single arm	600 µg bid s.c.	15 days
SOM230B2208E1	Cushing's disease	19	Open-label, single arm	600-900 µg bid (or tid) s.c.	Up to 58 months

The mean total daily dose over time for the Cushing's Phase 2 program is summarized below.

Table 44 Mean total daily dose (µg) over time in Cushing’s Phase 2 trials

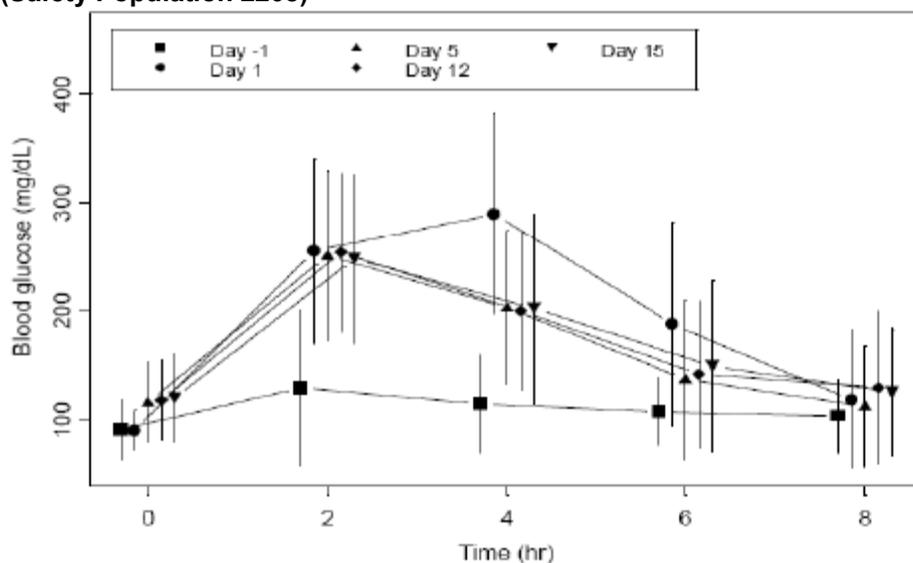
Day	N=39	
	N	mean (µg)
Day 15	36	1183.3
Day 30	7	1285.7
Day 60	11	1254.6
Day 90	13	1361.5
Day 180	11	1336.4
Day 270	9	1433.3
Day 360	6	1450.0

Sponsor’s Glucose Metabolism Report, Table 5-22

8-hour profiles

In Study 2208, the effect of pasireotide s.c. on 8-hour glucose, insulin and glucagon profiles was evaluated in patients with Cushing’s disease treated with pasireotide 600 µg bid for 15 days. The figure below depicts mean glucose values versus time by study day. Glucose values rose with the injection and returned closer to pre-dose values within 8 hours.

Figure 17 Mean (SD) blood glucose versus time profiles after pasireotide s.c. dosing by study day (Safety Population 2208)



Glucose Metabolism Report, Figure 5-13

There appeared to be a reduction in 2-hour post-prandial blood insulin levels in pasireotide-treated subjects compared to baseline values, but values were similar 4 to 8 hours after drug administration. Changes in glucagon were less defined.

Profiles over time

In Study 2208, as expected, mean glucose values increased from baseline starting at Day 15 and continuing until Day 360. Overall, subject numbers were low and

decreased with time. Therefore, all results are not displayed here in tabular form. The highest mean FLG value (for all doses) was 181.3 mg/fL observed on Day 270. In general, higher dose levels were associated with higher FPG levels, however this was not consistent.

Hepatic Events

The association between somatostatin analogues and cholelithiasis is well-recognized and is discussed in the Package Inserts (PI) of the approved somatostatin analogues (SSAs). However, the effect of SSAs on hepatic tests unrelated to cholelithiasis is not as well-defined.

The Sandostatin PI lists “hepatitis” and “increase in liver enzymes” under Warning and Precautions (under Other Adverse Events <1%). The Sandostatin LAR PI lists “increased liver enzymes” and “hepatitis” under Postmarketing Experience.

The Somatuline Depot PI lists the following laboratory abnormalities as “common” under Investigations: ALT increased, AST abnormal, ALT abnormal blood bilirubin increased.

The literature contains reports of hepatic abnormalities associated with the use of somatostatin analogues:

- Two recent review articles discuss the use of somatostatin analogues in patients with acromegaly. One states that liver-function disturbances are an infrequently reported adverse effect.¹⁴ Another review states that in a comparative clinical trial of patients with acromegaly, elevations of transaminases >3xULN were reported in up to 7% of patients given octreotide LAR.¹⁵
- There are isolated reports of patients treated with somatostatin analogues for various indications who have had liver tests elevations. The literature suggests that the reported elevations were transient and/or reversible.

Investigator Notification

The issue of hepatic safety related to pasireotide arose in 2010, when the Sponsor reported an increase in liver enzymes in association with bilirubin elevations in a patient given pasireotide for compassionate use. The Sponsor convened an Advisory Board with hepatologists and this led to a comprehensive review of other such cases. The review identified 3 healthy volunteers (2 from Study CSOM230B2124 and 1 from study CSOM230B2125) with concomitant elevations of ALT>3xULN and total bilirubin>2xULN. The cases were asymptomatic and there was no clinical intervention. The Sponsor then conducted a program-wide dataset for LFT categorical outliers. Following this, an Investigator Notification (IN) was submitted to health authorities worldwide where studies with pasireotide were being conducted.

¹⁴ Feelders et al. Medical Therapy of Acromegaly. Medical Therapy of Acromegaly Efficacy and Safety of Somatostatin Analogues. *Drugs* 2009; 69 (16): 2207-2226.

¹⁵ Yang et al. Octreotide Long-Acting Release (LAR) A Review of Its Use in the Management of Acromegaly. *Drugs* 70 (13); 1745-1769.

In this NDA, the Sponsor has 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 the following populations and clinical studies:

- Healthy volunteer studies: B2101, B2102, B2106, B2107, B108, B2112, B2110, B2124, B2125, and C2101
- Hepatic impairment study: B2114
- Investigator-initiated trial (IIT): B2216
- Cushing’s disease patient studies: B2208, B2208E, and B2305
- Acromegaly patient studies: B2103, B2201, and B2201E
- Carcinoid syndrome patient study: B2202

Details of these studies are in the Appendix.

First, the Sponsor assessed the frequency of subjects and patients with outlying elevations by summarizing categorical elevations in ALT or AST, elevations in total bilirubin, and a combination of both elevations. The results for the healthy volunteers and patients are summarized below.

Healthy volunteer studies

Overall, elevations in total bilirubin (>ULN to <2xULN) were the most commonly observed parameter. From this table, there were 3 subjects who had concomitant elevations of ALT>3xULN and TB≥2xULN, and 2 of these, from a strictly biochemical perspective, met Hy’s law criteria. 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 patients).

Table 45 Liver enzyme and total bilirubin outlier summary—healthy volunteers (single & multiple day dosing) and hepatic impairment study

Study	N	AxT ¹ >3xULN N n (%)	AxT >5xULN N n (%)	AxT >10xU LN 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								

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

≥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
B2113 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

¹AxT=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 \geq 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 μ g/d had elevated liver tests (mostly Grade 1 ALT increases). Therefore a second 1800 μ g/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 studies

There were no cases meeting Hy’s Law criteria in the patient trials. Out of 138 subjects, 15 (4.7%) had ALT or AST $>$ 3xULN, including 5 patients with $>$ 5xULN.

Table 46 Liver enzyme and total bilirubin outlier summary—Cushing’s disease, acromegaly and carcinoid syndrome studies

Study	N	AxT ¹ >3xULN n (%)	AxT >5xULN n (%)	AxT >10xU LN n (%)	AxT >20xULN n (%)	Tbili >ULN to <2xULN n (%)	Tbili \geq 2xULN n (%)	ULNs $>$ 3x AxT, \geq 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
B2305² 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

²Percentages 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.

Narratives for subjects with concomitant elevations of ALT/AST >3xULN and total bilirubin ≥2xULN (Hy's law)

The Sponsor identified 4 cases of concomitant elevations of ALT/AST >3xULN and total bilirubin ≥2xULN: 3 healthy volunteer cases (mentioned above) and one additional case of a patient receiving pasireotide on a compassionate use basis, identified from an ARGUS (see below) search. The 3 volunteer cases were the subjects of an IN released on October 31, 2011 and the 4th case was the subject of a September 22, 2010 IN.

- Subject B2124-0001/10116 is a 47 year old man with no baseline laboratory abnormalities who received pasireotide 600 µg for 7 days. On Day 7, he presented with elevated liver tests (shown below). He completed the study and was 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 47 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)

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

Day 30	ND	ND	ND	ND	61.0 (x1.02)
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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

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 48 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 to evaluate 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 elevated liver tests.

Table 49 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 (b) (6) O2010AU13717 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.

Table 50 Liver laboratory values—Subject (b) (6) O2010AU13717

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 (1.060)	25 (0.42)
Day 46 off pasireotide	14 (0.58)	44 (0.80)	24 (0.53)	89 (0.81)	25 (0.42)

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

Three of these cases meet criteria for Hy's law. The third case is suggestive of Hy's law, but because the ALP value is missing, can not definitively be considered as such.

Subjects and patients with ALT or AST>5xULN (not meeting Hy's law criteria)

There are a total of 9 cases with ALT or AST>5xULN (4 healthy volunteers and 5 patients) (2 tables above). The cases in healthy volunteers were similar in that elevations were noted within 5-7 days, decreases were observed within 3 days after discontinuation of study drug and complete normalization occurred within 16 days after discontinuation of study drug:

- Subject B2124-0001.10134 is a 23 year old healthy volunteer who received the first dose of pasireotide 600 µg bid on Day 1 and first dose of nateglinide on Day 2. He completed the 7 days study and liver test elevations were noted on Day 7. Although the total bilirubin (x1.98 ULN, bolded below) did not technically meet the numerical criteria of Hy's law (x2 ULN), it nearly did and should, for the purpose of evaluating the hepatic safety of pasireotide, be considered another case reflective of Hy's law. Value peaked at Day 8 and returned to normal at Day 23.

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	6.7	31.4	24.0	54.0	17.0
Day 7	33.8 (x1.98)	186.9 (x3.74)	105.7 (x2.11)	71.0	104.0 (x1.74)
Day 8	21.7 (x1.27)	267.7 (x5.35)	162.9 (x3.26)	ND	126.0 (x2.10)
Day 12	ND	144.4 (x2.89)	44.2	ND	88.0 (x1.47)
Day 23	8.4	33.8	28.5	64.0	44.0

From Sponsor's Hepatic Report, Table 4-7
 ND=not done

- Subject B2124-0001/10158 is a 48 year old man who received the first dose of pasireotide 600 µg bid on Day 1 and first dose of metformin on Day 2. He completed the study and elevations were noted on Day 7. He was asymptomatic. Elevations were decreasing 2 days later and were normal 16 days after the last dose of study drug.

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	12.4	23.5	22.4	43.0	14.0
Day 7	18.6 (x1.09)	305.5 (x6.11)	162.8 (x3.26)	76.0	62.0 (x1.04)
Day 8	ND	344.8 (x6.90)	158.7 (x3.17)	ND	72.0 (1.20)
Day 10	ND	166.5 (x3.33)	42.8	ND	50.0
Day 23	10.6	25.4	21.0	49.0	24.0

From Sponsor's Hepatic Report, Table 4-8
 ND=not done

- Subject B2125-0001/10080 is a 46 year old who received the following:
 - 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

The subject completed the study on Day 50. Elevations were noted on Day 51. These elevations normalized by Day 66.

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	4.7	13.1	17.8	57.0	11.0
Day 46	4.2	13.5	17.4	53.0	19.0
Day 51	26.2 (x1.53)	175.2 (x5.01)	98.0 (x2.8)	64.0	43.0 (1.08)
Day 57	6.1	80.6 (x2.30)	26.2	ND	57.0 (x1.43)
Day 66	ND	22.4	ND	ND	35.0

From Sponsor's Hepatic Report, Table 4-8
 ND=not done

A 4th case was a subject was in the moxifloxacin treatment sequence of Study B2113 and is not discussed here.

There were five subjects with disease who met the ALT or AST>5xULN criteria. This included 2 with Cushing's disease, 1 with acromegaly, and 2 with metastatic carcinoid syndrome. (In 3 of the cases the events normalized or improved while still on pasireotide).

- Subject B2208-0011/00004 is a 35 year old man with Cushing's with elevated liver tests at baseline. Although reported as an adverse event, the ALT decreased over the study period in which he received pasireotide 600 µg bid.
- Subject B2305-0501/00003 is a 40 year old man with Cushing's. Baseline ALT was 1.5xULN but increased to 6.0xULN on Day 30. Pasireotide 600 µg bid was interrupted on Day 32. The elevations decreased and study drug was restarted, at a lower does, on Day 46. However, drug was discontinued on Day 123 due to an elevated GGT 7.6xULN. It appears the elevations improved.
- Subject B2201E-0505/00004 is a 36 year old man with acromegaly who received pasireotide 600 µg bid. ALT elevations of 4.0 and 5.5xULN were noted on Days 596 and 624, respectively, but AST was normal on Day 662 while still on pasireotide.
- Subject B2202-0001/00004 is a 70 year old woman with metastatic carcinoid syndrome. ALT was 1.1xULN and 1.6xULN on Days 1 and 29, respectively. Five days after the last dose of pasireotide 300 µg bid (Day 33) AST was 10.9xULN, ALP was 2.5xULN, and total bilirubin was 1.6xULN.
- Subject B2202-0001/00006 is a 65 year old woman with metastatic carcinoid syndrome. On Day 339 AST was 58.2xULN. Pasireotide 300 µg bid was continued and ON Day 374, ASE was normal.

Mean changes

Healthy volunteers

Below are the mean changes of liver tests over time for healthy volunteer studies 2124 and 2125. These studies were chosen by the Sponsor as meaningful because of their sufficiently large sample size per arm and multiple days of exposure to pasireotide.

In Study 2124, after the first day of pasireotide treatment subjects were randomized to the groups below. Liver tests were done at baseline, Day 7, and the follow-up visit (14 days after the last dose of study medication). For ALT (and AST to a lesser extent), there were increases on Day 7 that were still considered within the upper limits of normal. The steepest increases were observed in the metformin and vildagliptin groups, although the pasireotide 600 µg only group nearly doubled the ALT at Day 7. The greatest increases for total bilirubin at Day 7 were seen in the vildagliptin and liraglutide groups.

Table 51 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
Day 7 change from baseline		n=17	n=18	n=18	n=17	n=17
	Mean (SD) Median	47.6 (82.0) 17.5	17.56 (41.7) 2.1	35.2 (46.3) 16.8	11.6 (27.7) 1.1	19.8 (46.1) -0.2
FU change from baseline		n=18	n=18	n=18	n=17	n=18
	Mean (SD) Median	3.14 (7.7) 3.7	0.7 (4.7) 1.9	4.8 (7.7) 3.7	2.5 (10.6) 1.1	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
Day 7 change from baseline		n=17	n=18	n=18	n=17	n=17
	Mean (SD) Median	21.0 (39.7) 8.2	7.2 (21.1) -0.6	16.4 (25.9) 6.0	6.7 (14.8) 1.1	5.2 (18.9) -0.1
FU change from baseline		n=18	n=18	n=18	n=17	n=18
	Mean (SD) Median	1.8 (9.3) 0.5	1.6 (3.3) 2.2	2.0 (4.8) 1.25	2.8 (4.3) 1.9	0.8 (3.5) 1.3
Total bilirubin (umol/L)		n=17	n=18	n=18	n=17	n=17
	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
Day 7 change from baseline		n=17	n=18	n=18	n=17	n=17
	Mean (SD) Median	4.45 (4.7) 5.2	2.8 (7.9) 1.5	7.5 (11.7) 4.1	9.54 (18.4) 4.2	6.7 (12.2) 2.5
FU change from baseline		n=18	n=18	n=18	n=17	n=18
	Mean (SD) Median	-3.3 (4.3) 2.2	-3.9 (4.3) -2.7	-2.5 (4.0) -2.1	-0.2 (10.4) -3.2	-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)

Detailed results for Study 2113 are not shown. In this study, subjects were treated with pasireotide 1950 µg bid for 5 days, moxifloxacin for 1 day and placebo for 5 days with a washout period of 10 days between each medication. For the pasireotide group, mean ALT approximately doubled in value (still below the ULN). Bilirubin was essentially

unchanged. The results for Study 2125 (second thorough QT study) were similar to the results seen for the pasireotide 1950 µg group in 2113. Results were different for the pasireotide 600 µg group (which showed no change in ALT and AST) and for total bilirubin, which tended to slightly increase in all groups.

Patient Studies

Study 2208: During the core period of Study 2208, subjects received 600 µg bid for 15 days. Results are not shown in table form. On Days 5 and 8, there were very slight increases in ALT. However, values for Day 12 and 15 were essentially unchanged. Total bilirubin values did not increase. The mean values for the extension period (2208E) showed no increases in any of the three parameters.

Study 2305: Below are the mean changes over time for AST, ALT, and bilirubin for the pivotal 6 month trial. There appeared to be some increase in ALT (and AST to a lesser extent) in the initial months of treatment but attenuated over time.

Table 52 Mean changes in liver enzymes and total bilirubin over time—Study 2305

Visit		Pasireotide 600 µg bid N=82	Pasireotide 900 µg bid N=80	Pasireotide Any dose N=162
ALT (U/L) baseline	Mean (SD)	n=82 30.8 (15.98)	n=80 29.4 (14.82)	n=162 30.1 (15.39)
	Median	27.0	25.5	26.5
Month 1 change from baseline	Mean (SD)	n=77 9.3 (29.17)	n=73 9.7 (22.85)	n=150 9.5 (26.20)
	Median	4.0	4.0	4.0
Month 2 change from baseline	Mean (SD)	n=73 6.2 (20.54)	n=67 5.5 (19.31)	n=140 5.8 (19.89)
	Median	3.0	2.0	3.0
Month 4 change form baseline	Mean (SD)	n=68 6.1 (23.29)	n=61 1.0 (10.76)	n=129 3.7 (18.57)
	Median	2.5	-1.0	0.0
Month 6 change from baseline	Mean (SD)	n=57 2.2 (16.79)	n=55 1.1 (11.04)	n=112 1.6 (14.21)
	Median	1.0	0.0	1.0
AST (U/L) baseline	Mean (SD)	n=82 19.8 (7.48)	n=80 19.8 (5.30)	n=162 19.8 (6.48)
	Median	19.0	19.0	19.0
Month 1 change from baseline	Mean (SD)	n=77 5.1 (15.65)	n=73 8.0 (17.61)	n=150 6.5 (16.64)
	Median	3.0	3.0	3.0
Month 2 change from baseline	Mean (SD)	n=73 4.0 (11.90)	n=67 3.8 (7.97)	n=140 3.9 (10.17)
	Median	3.0	3.0	3.0
Month 4 change form baseline	Mean (SD)	n=68 5.2 (20.07)	n=61 2.0 (6.87)	n=129 3.7 (15.34)
	Median	1.5	1.0	1.0
Month 6 change	Mean (SD)	n=57 3.1 (7.67)	n=55 2.3 (7.32)	n=112 2.7 (7.48)

from baseline	Median	2.0	1.0	1.0
Total bilirubin (umol/L) baseline		n=82	n=80	n=162
	Mean (SD)	7.6 (4.61)	7.3 (5.07)	7.5 (4.83)
Month 1 change from baseline	Median	7.0	7.4 6.0	7.6 7.0
	Mean (SD)	n=78	n=73	n=151
Month 2 change from baseline	Median	0.8 (3.49)	0.5 (2.72)	0.6 (3.13)
	Mean (SD)	0.5	0.0	0.0
Month 4 change from baseline	Median	n=73	n=67	n=140
	Mean (SD)	1.1 (2.95)	0.4 (3.230)	0.8 (3.08)
Month 6 change from baseline	Median	1.2 1.0	0.0	0.0
	Mean (SD)	n=68	n=61	n=129
Month 1 change from baseline	Median	0.9 (3.11)	-0.2 (4.04)	0.4 (3.61)
	Mean (SD)	1.0	0.0	0.0
Month 2 change from baseline	Median	n=59	n=55	n=114
	Mean (SD)	1.1 (2.69)	-0.7 (4.29)	0.2 (3.65)
Month 4 change from baseline	Median	1.0	0.0	0.0
	Mean (SD)			

Adapted from Sponsor's Hepatic Safety Report, Table 4-15

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

	N	Serious Adverse Events		Discontinuations due to AEs	
		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 drug was discontinued. All three events resolved 47 days after receiving the last dose 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 U/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 0711/00002 (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 GGT=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 liver-related SAEs. Both had hepatic artery embolism and both were likely unrelated to study drug.

The Sponsor also conducted a cumulative search of the Novartis safety database (ARGUS) using MedDRA 14.1 Standardized MedDRA Query (SMQ) "Drug related hepatic disorders—comprehensive search." A total of 64 cases were identified. The majority of these cases were isolated increases in ALT/AST or bilirubin which appeared related to underlying disease or were biliary-related.

There were three cases with notable AST/ALT elevations. Two of these were in patients with advanced neuroendocrine malignancy with hepatic involvement. The third, in a patient with Cushing's disease, had elevations of ALT/AST >3xULN and TB \geq 2xULN, and was the subject of an Investigator Notification (IN) in 2010.

Pre-defined Adverse of Events of Special Interest

The Sponsor pre-defined 20 groups of AEs of special interest, which were based on the safety profile of somatostatin analogues in general as well as the development of pasireotide. Three areas of risk were identified: risks which are known somatostatin analogue class effects, risks which are specific for patients with Cushing's disease, and risks which were observed mainly in pre-clinical studies. Hyperglycemia and liver safety have already been discussed.

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

	Pasireotide 600 μ g bid N=82 n (%)	Pasireotide 900 μ g 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 Clinical Study Report, Table 12-8

This Section reviews the categories with notable observations. For the AEs that are considered somatostatin analogue class effects, this Review makes comparisons to other somatostatin analogues. Clearly there are limitations (e.g. different patient populations) to such comparisons. Other somatostatin analogues have not been extensively studied in the Cushing's disease population. Still, it will be noted where major differences exist.

Gallbladder and biliary related AEs

In Study 2305, cholelithiasis 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 55 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 Clinical Study Report, Table 14.3.1-1.37
 ALP=alkaline phosphatase

By comparison, cholelithiasis was reported in 13.4% of Sandostatin LAR Phase 3 subjects and 20% of patients in pooled clinical trials of Somatuline Depot.

Gallbladder Ultrasound Results

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

Dose group	Baseline value		Extreme value			
			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)

Clinical Study Report, Table 12-18

baseline n=number of subjects who had the particular baseline level and at least one post-baseline value
 post-baseline n=number of subjects who had the specified level of baseline value and the specified level
 of last post-baseline value

Liver safety related AEs

Liver safety has been discussed above. Below is the breakdown of PTs as part of this special category:

Table 57 Liver safety 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	17 (20.7)	9 (11.3)	26 (16.0)
ALT increased	11 (13.4)	6 (7.5)	17 (10.5)
AST increased	6 (7.3)	3 (3.8)	9 (5.6)
GGT increased	10 (12.2)	7 (8.8)	17 (10.5)
Hepatic enzyme increased	1 (1.2)	0 (0.0)	1 (0.6)
Hepatic function abnormal	0 (0.0)	1 (1.3)	1 (0.6)
Liver function test abnormal	1 (1.2)	0 (0.0)	1 (0.6)

From Clinical Study Report, Table 14.3.1-1.37

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase

Gastrointestinal AEs

Diarrhea was reported for 58% of subjects overall. The occurrence of diarrhea is substantially higher in comparison to trials of other somatostatin analogues in acromegalic patients. For example, in the Sandostatin LAR Phase 3 studies of patients with acromegaly, diarrhea was reported in 35.6% of subjects.¹⁶ In the Somatuline Depot program, diarrhea was reported in 37% of subjects from pooled clinical trials.¹⁷

For the category of nausea, 52% of subjects receiving pasireotide were reported. By general comparison, nausea was reported in 11% of subjects in the Somatuline Depot pooled trials and 15.8% of subjects in a Phase 4 Sandostatin LAR trial in acromegalic patients.

Finally, constipation was reported in 6.8% of pasireotide-treated subjects, compared to 17.6% in the Sandostatin LAR Phase 3 program and 8% in the overall pooled clinical trial data for Somatuline Depot.

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.

Bradycardia and QT prolongation

Considered a class effect, AEs related to bradycardia were observed in 14.2% of subjects. The PTs comprising this category are summarized here. QT prolongation and sinus bradycardia made up the majority of events. Comparing to Sandostatin, 25%

¹⁶ Sandostatin LAR Full Prescribing Information, Novartis, Initial US Approval 1988.

¹⁷ Somatuline Depot Injection, Full Prescribing Information, Initial US Approval 2007.

of acromegalic subjects developed bradycardia and 10% had conduction abnormalities during Sandostatin Injection therapy. The PI for Sandostatin states that QT prolongation has been observed during octreotide therapy. For Somatuline Depot, sinus bradycardia occurred in 3% in the overall pooled studies; QT prolongation is not mentioned in the PI.

Table 58 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 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 the cases of QT prolongation, most were sporadic. None were associated with any AEs and none required dose interruption or medical intervention

For this Application, the Sponsor conducted two thorough QT studies. Testing was conducted with one of the therapeutic doses (600 µg) and with a supra-therapeutic 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 QTc 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.

Pancreatitis

Pancreatitis was observed in 13% of subjects. The terms and incidence of such event are summarized below.

Table 59 Pancreatitis 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	11 (13.4)	10 (12.5)	21 (13.0)
Abdominal distension	4 (4.9)	5 (6.3)	9 (5.6)
Blood amylase increased	4 (4.9)	0 (0.0)	4 (2.5)
Lipase increased	7 (8.5)	5 (6.3)	12 (7.4)

From Clinical Study Report, Table 14.3.1-1.37

The terms captured are not specific and no PT of “pancreatitis” was reported. Pancreatitis has rarely been reported in other somatostatin analogues.

Low blood cell related AEs

Anemia (in 6 subjects overall) comprised the majority of cases in this category. This has been reported at higher frequencies for other SSAs.

Injection site reactions

Injection site reactions were recorded for approximately 15% of subjects overall. There were no injection-related SAEs. The PTs for both dose groups were spread over a number of terms, including injection site hematoma, hemorrhage, pain, rash, and reaction.

Coagulation related AEs and PTT, PT-INR elevations

The Sponsor observed increased PT and PTT in rodents in the nonclinical program; these findings were not observed in monkeys.

In order to monitor for potential problems related to bleeding and coagulation abnormalities, the Sponsor performed several analyses:

- Changes in PTT and PT-INR by evaluating shifts from baseline to highest value by maximum CTC grade.
- Subjects with clinically relevant coagulation abnormalities, including bleeding. This included 2 searches with PTs intended to capture events with coagulation-related low blood cell-related abnormalities.
- The Sponsor would complete a narrative if a subject had a grade 3 or 4 coagulation related AE of special interest, an SAE or discontinuation due to an AE in this category.
- The Sponsor provided a listing of subjects with concomitant newly occurring elevations in PTT or PT/INR and newly occurring elevations in AST/ALT and/or bilirubin.

Changes in coagulation tests: The most frequently reported hematological abnormalities were increased PTT and INR. Overall 84 subjects (51.9%) had a post-baseline

elevation of PT-INR or PTT during the trial: 47 (58.8%) in the 600 µg group and 37 (47.4%) in the 900 µg group. Of these 84, 74 had CTC grade 1 elevations.

The table below summarizes the shifts in PTT from baseline to extreme value up to data cut-off. Approximately 75% of subjects had a normal PTT at baseline, while 45% continued to have normal values during the trial. When looking at the last values, however, the majority of subjects had normal values or Grade 1 elevations. There were 3 subjects with Grade 3 elevations for PTT as their last value. All 3 were in the 600 µg group: all 3 discontinued the study before 12 months for various reasons unrelated to the PTT elevation. Concomitant medications could not account for the elevations. The clinical importance of these laboratory abnormalities is unclear.

Table 60 PTT Shift table by dose group—baseline versus extreme lab value up to data cut-off based on CTC grades

	Baseline	n (%)	Highest grade during trial					Missing
			Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	
600 µg bid	Grade 0	66 (80.5)	34 (41.5)	26 (31.7)	0	4 (4.9)	0	2 (2.4)
	Grade 1	15 (18.3)	5 (6.1)	8 (9.8)	1 (1.2)	1 (1.2)	0	0
	Missing	1 (1.2)	0	1 (1.2)	0	0	0	0
900 µg bid	Grade 0	55 (68.8)	39 (48.8)	13 (6.3)	1 (1.3)	0	0	2 (2.5)
	Grade 1	20 (25.0)	1 (1.3)	18 (22.5)	1 (1.3)	0	0	0
	Missing	5 (6.3)	5 (6.3)	0	0	0	0	0
All	Grade 0	121 (74.7)	73 (45.1)	39 (24.1)	1 (0.6)	4 (2.5)	0	4 (2.5)
	Grade 1	35 (21.6)	6 (3.7)	26 (16.0)	2 (1.2)	1 (0.6)	0	0
	Missing	6 (3.7)	5 (3.1)	1 (0.6)	0	0	0	0

From Sponsor's Response to FDA Questions, August 8, 2012, Table 14.3-2.20

The table below summarizes the shifts in PT (INR) from baseline to extreme value up to data cut-off. While 95% of subjects had a normal PT (INR) at baseline, 70% continued to have normal values throughout the trial. Similarly to PTT, when looking at final PT-INR values most subjects had normal values or Grade 1 elevations. The same 3 subjects with Grade 3 elevations of PTT mentioned above also had Grade 3 elevations for PT-INR.

Table 61 PT Shift table by dose group—baseline versus extreme lab value up to data cut-off based on CTC grades

	Baseline	n	Highest grade during trial					Missing
			Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
600 µg bid	Grade 0	79 (96.3)	57 (69.5)	17 (20.7)	0	3 (3.7)	0	2 (2.4)
	Grade 1	1 (1.2)	0	1 (1.2)	0	0	0	0
	Grade 3	1 (1.2)	0	1 (1.2)	0	0	0	0
	Missing	1 (1.2)	1 (1.2)	0	0	0	0	0
900 µg bid	Grade 0	75 (93.8)	57 (71.3)	13 (16.3)	2 (2.5)	1 (1.3)	0	2 (2.5)
	Grade 1	1 (1.3)	0	1 (1.3)	0	0	0	0
	Missing	4 (5.0)	4 (5.0)	0	0	0	0	0
All	Grade 0	154 (95.1)	114 (70.4)	30 (18.5)	2 (1.2)	4 (2.5)	0	4 (2.5)
	Grade 1	2 (1.2)	0	2 (1.2)	0	0	0	0

	Grade 3	1 (0.6)	0	1 (0.6)	0	0	0	0
	Missing	5 (3.1)	5 (3.1)	0	0	0	0	0

From Sponsor's Response to FDA Questions, August 8, 2012, Table 14.3-2.20

The Sponsor performed a search for coagulation-related AEs within the SMQ of 'Liver related coagulation and bleeding disturbances'. Few events, all coded as 'prothrombin time prolonged', were found.

The literature suggests that Cushing's patients have increased PT values but shortened PTT values.¹⁸ These study results are not entirely consistent with that picture and the clinical significance is unclear.

There were no subjects with a Grade 3 or Grade 4 coagulation related AE of special interest.

The Division asked the Sponsor to analyze whether any subjects with coagulation abnormalities had concomitant liver test elevations. Of the 84 subjects with a post-baseline elevation in PTT or PT-INR, 19 subjects (15 from the 600 µg group and 4 subjects from the 900 µg group) had concomitant elevations of ALT, AST, or TB. All of the 19 had Grade 1 elevations:

- 16 subjects had ALT/AST >ULN and <3xULN
- 2 subjects had ALT/AST ≥3xULN and <5xULN
- One subject had ALT/AST ≥5xULN and was discontinued because of the elevated ALT levels.
- None of the subjects had concomitant elevations of PT or PTT and total bilirubin.

Given that elevated bilirubin did not accompany the coagulation abnormalities, the abnormal PT-INR and PTT levels are not a result of liver damage resulting in decreased hepatic function.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All but 3 subjects were reported to have at least one AE during the trial. The most frequently reported AEs are summarized below. AEs that were reported in more than 15% of subjects overall were: diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus. Clearly, a number of these would be expected in patients with Cushing's disease; a lack of comparator for this

¹⁸ Erem C et al. Blood coagulation and fibrinolysis in patients with Cushing's syndrome: Increased plasminogen activator inhibitor-1, decreased tissue factor pathway inhibitor, and unchanged thrombin-activatable fibrinolysis inhibitor levels. *Journal of Endocrinological Investigation* 32: 169-174, 2009.

analysis limits overall conclusions about AEs and also limits an analysis of AEs as related to dose.

Table 62 Most frequently reported AEs (>10% in any group) by preferred term (PT), up to data cut-off (Safety Analysis Set)

PT	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Diarrhea	48 (58.5)	46 (57.5)	94 (58.0)
Nausea	38 (46.3)	46 (57.5)	84 (51.9)
Hyperglycemia	31 (37.8)	34 (42.5)	65 (40.1)
Cholelithiasis	25 (30.5)	24 (30.0)	49 (30.2)
Headache	23 (28.0)	23 (28.8)	46 (28.4)
Abdominal pain	19 (23.2)	20 (25.0)	39 (24.1)
Fatigue	12 (14.6)	19 (23.8)	31 (19.1)
Diabetes mellitus	13 (15.9)	16 (20.0)	29 (17.9)
Nasopharyngitis	10 (12.2)	11 (13.8)	21 (13.0)
Alopecia	10 (12.2)	10 (12.5)	20 (12.3)
Asthenia	13 (15.9)	5 (6.3)	18 (11.1)
Increased HbA1c	10 (12.2)	8 (10.0)	18 (11.1)
ALT increased	11 (13.4)	6 (7.5)	17 (10.5)
GGT increased	10 (12.2)	7 (8.8)	17 (10.5)
Peripheral edema	9 (11.0)	8 (10.0)	17 (10.5)
Upper Abdominal pain	10 (12.2)	6 (7.5)	16 (9.9)
Decreased appetite	7 (8.5)	9 (11.3)	16 (9.9)
Hypercholesterolemia	7 (8.5)	9 (11.3)	16 (9.9)
Hypoglycemia	12 (14.6)	3 (3.8)	15 (9.3)
Type 2 DM	10 (12.2)	5 (6.3)	15 (9.3)
Anxiety	5 (6.1)	9 (11.3)	14 (8.6)
Influenza	9 (11.0)	5 (6.3)	14 (8.6)
Insomnia	3 (3.7)	11 (13.8)	14 (8.6)
Myalgia	10 (12.2)	4 (5.0)	14 (8.6)

HbA1c=glycosylated hemoglobin; ALT=alanine aminotransferase; GGT=gamma-glutamyltransferase; DM=diabetes mellitus

From Clinical Study Report, Table 12-4

By SOC, Gastrointestinal Disorders was the most frequently reported AE overall (80.9%), followed by Metabolism and Nutrition Disorders (74.7%), General Disorders and Administration Site Conditions (54.3%), Investigations (45.7%), Infections and Infestations (45.1%).

7.4.2 Laboratory Findings

Hematology

The abnormalities related to PTT and PT-INR are discussed above under Adverse Events of Special Interest. For other hematology parameters, below is a table of newly occurring or worsening abnormalities. The most frequent abnormalities were those for

hemoglobin in the 900 µg group: there were 12 subjects with Grade 1 abnormalities. There were very few abnormalities in WBC counts.

Table 63 Newly occurring or worsening CTC hematology abnormalities up to data cut-off by randomized dose group (safety analysis set)

Test	Worsening from baseline to:	Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80			Overall N=162		
		Total	n	%	Total	n	%	Total	n	%
Absolute Lymphocytes	Grade 1	75	0	0	68	0	0	143	0	0
	Grade 2	75	3	4.0	68	3	4.4	143	6	4.2
	Grade 3	76	0	0	74	1	1.4	150	1	0.7
	Grade 4	76	1	1.3	74	0	0	150	1	0.7
Absolute Neutrophils	Grade 1	76	4	5.3	74	1	1.4	150	5	3.3
	Grade 2	76	2	2.6	74	1	1.4	150	3	2.0
	Grade 3	76	0	0	74	0	0	150	0	0
	Grade 4	76	1	1.3	74	1	1.4	150	2	1.3
Hemoglobin	Grade 1	75	5	6.7	73	12	16.4	148	17	11.5
	Grade 2	76	1	1.3	74	3	4.1	150	4	2.7
	Grade 3	77	0	0	74	1	1.4	151	1	0.7
	Grade 4	77	0	0	74	0	0	151	0	0
Platelet count	Grade 1	77	3	3.9	72	0	0	149	3	2.0
	Grade 2	77	0	0	74	0	0	151	0	0
	Grade 3	77	0	0	74	0	0	151	0	0
	Grade 4	77	0	0	74	0	0	151	0	0
WBC	Grade 1	76	1	1.3	74	1	1.4	150	2	1.3
	Grade 2	76	1	1.3	74	0	0	150	1	0.7
	Grade 3	76	0	0	74	0	0	150	0	0
	Grade 4	76	0	0	74	0	0	150	0	0

Clinical Study Report, Table 12-9

Below are mean values for hemoglobin. While there was some decrease over time, mean values remained within the normal ranges.

Table 64 Mean hemoglobin (g/dL) over time

Month	600 µg bid N=82		900 µg bid N=80		Overall N=162	
	n	Mean (SD)	N	Mean (SD)	n	Mean (SD)
Baseline	80	14.4 (1.6)	79	14.2 (1.3)	159	14.3 (1.5)
1	69	14.3 (1.4)	68	14.1 (1.3)	137	14.2 (1.4)
6	57	14.1 (1.4)	53	13.3 (1.5)	110	13.7 (1.5)
12	37	13.8 (1.5)	38	13.1 (1.3)	75	13.5 (1.4)

Sponsor's Response to FDA, October 16, 2012

Finally, I reviewed the 12 subjects in the 900 µg group with Grade 1 abnormalities; many had confounding co-morbidities and the abnormalities were not clinically meaningful.

Chemistry

Below is a table of newly occurring or worsening abnormalities for chemistry parameters. Although liver test abnormalities have been discussed above, they are only included here for completeness.

Hypokalemia was observed in 17% of subjects overall. Cushing's disease is associated with hypokalemia (cortisol behaving like a mineralocorticoid) and it is difficult to relate pasireotide itself to this finding. There were high percentages of subjects with abnormalities of cholesterol and triglycerides, mostly Grade 1.

Table 65 Newly occurring or worsening CTC biochemistry abnormalities up to data cut-off by randomized dose group (safety analysis set)

Test	Worsening from baseline to:	Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80			Overall N=162		
		Total	n	%	Total	n	%	Total	n	%
Total cholesterol	Grade 1	27	18	66.7	25	9	36.0	52	27	51.9
	Grade 2	73	9	12.3	74	10	13.5	147	19	12.9
	Grade 3	79	1	1.3	76	0	0	155	1	0.6
	Grade 4	79	0	0	77	0	0	156	0	0
Creatinine	Grade 1	71	17	23.9	74	18	24.3	154	35	24.1
	Grade 2	79	1	1.3	77	1	1.3	156	2	1.3
	Grade 3	79	0	0	77	0	0	156	0	0
	Grade 4	79	0	0	77	0	0	156	0	0
Fasting hyperglycemia	Grade 1	71	20	28.2	75	18	24.0	146	38	26.0
	Grade 2	74	18	24.3	76	18	23.7	150	36	24.0
	Grade 3	77	16	20.8	78	20	25.6	155	36	23.2
	Grade 4	77	0	0	78	0	0	155	0	0
Fasting hypoglycemia	Grade 1	77	11	14.3	78	7	9.0	155	18	11.6
	Grade 2	77	3	3.9	78	3	3.8	155	6	3.9
	Grade 3	77	0	0	78	0	0	155	0	0
	Grade 4	77	0	0	78	0	0	155	0	0
Hyperkalemia	Grade 1	76	1	1.3	76	1	1.3	152	2	1.3
	Grade 2	78	5	6.4	76	2	2.6	154	7	4.5
	Grade 3	79	1	1.3	77	2	2.6	156	3	1.9
	Grade 4	79	0	0	77	0	0	156	0	0
Hypokalemia	Grade 1	77	10	13.0	76	16	21.1	153	26	17.0
	Grade 2	79	0	0	77	0	0	156	0	0
	Grade 3	79	2	2.5	77	0	0	156	2	1.3
	Grade 4	79	0	0	77	0	0	156	0	0
Hypernatremia	Grade 1	79	1	1.3	77	0	0	156	1	0.6
	Grade 2	79	1	1.3	77	0	0	156	1	0.6
	Grade 3	79	0	0	77	1	1.3	156	1	0.6
	Grade 4	79	0	0	77	0	0	156	0	0
Hyponatremia	Grade 1	78	5	6.4	77	3	3.9	155	8	5.2
	Grade 2	79	0	0	77	0	0	156	0	0
	Grade 3	79	0	0	77	0	0	156	0	0
	Grade 4	79	0	0	77	0	0	156	0	0
Triglycerides	Grade 1	43	20	46.5	44	20	45.5	87	40	46.0
	Grade 2	78	8	10.3	74	10	13.5	152	18	11.7
	Grade 3	79	2	2.5	76	2	2.6	155	4	2.6
	Grade 4	79	0	0	77	0	0	156	0	0

Clinical Study Report, Table 12-10

Table 66 Newly occurring or worsening CTC hepatobiliary and pancreatic biochemistry abnormalities up to data cut-off by randomized dose group (safety analysis set)

Test	Worsening from baseline to:	Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80			Overall N=162		
		Total	n	%	Total	n	%	Total	n	%
Total bilirubin	Grade 1	77	3	3.9	76	1	1.3	153	4	2.6
	Grade 2	79	2	2.5	76	0	0	155	2	1.3
	Grade 3	79	0	0	77	0	0	156	0	0
	Grade 4	79	0	0	77	0	0	156	0	0
Serum alkaline phosphatase	Grade 1	78	14	17.9	76	15	19.7	154	29	18.8
	Grade 2	79	1	1.3	77	1	1.3	156	2	1.3
	Grade 3	79	0	0	77	0	0	156	0	0
	Grade 4	79	0	0	77	0	0	156	0	0
Amylase	Grade 1	72	6	8.3	75	4	5.3	147	10	6.8
	Grade 2	78	1	1.3	77	1	1.3	155	2	1.3
	Grade 3	79	1	1.3	77	0	0	156	1	0.6
	Grade 4	79	0	0	77	0	0	156	0	0
GGT	Grade 1	67	18	26.9	66	13	19.7	133	31	23.3
	Grade 2	76	6	7.9	74	13	17.6	150	19	12.7
	Grade 3	78	5	6.4	77	2	2.6	155	7	4.5
	Grade 4	79	0	0	77	0	0	156	0	0
Lipase	Grade 1	70	11	15.7	73	11	15.1	143	22	15.4
	Grade 2	75	2	2.7	77	5	6.5	152	7	4.6
	Grade 3	78	4	5.1	77	3	3.9	155	7	4.5
	Grade 4	79	0	0	77	0	0	156	0	0
AST	Grade 1	78	17	21.8	77	18	23.4	155	35	22.6
	Grade 2	79	2	2.5	77	1	1.3	156	3	1.9
	Grade 3	79	0	0	77	0	0	156	0	0
	Grade 4	79	0	0	77	0	0	156	0	0
ALT	Grade 1	66	24	36.4	66	18	27.3	132	42	31.8
	Grade 2	79	8	10.1	77	7	9.1	156	15	9.6
	Grade 3	79	1	1.3	77	0	0	156	1	0.6
	Grade 4	79	0	0	77	0	0	156	0	0

Clinical Study Report, Table 12-9

7.4.3 Vital Signs

Discussion of blood pressure as a secondary endpoint has been discussed. Although limited by the methodology of the trial, a trend of decreased systolic and diastolic blood pressures was observed.

Overall, vital sign abnormalities (as per the Sponsor's defined thresholds) were not frequent. Increased diastolic blood pressure was seen most frequently (11.4%) in the 900 µg group. It was also seen in 5 subjects (6.3%) in the 600 µg group.

In the 600 µg group, 8 subjects (10.1%) had a low pulse, defined as ≤50bpm with decrease from baseline of ≥15 bpm. Five subjects (6.3%) in the 900 µg group met this threshold.

Body weight was measured at every visit. The Sponsor considered a reduction of 5% to be a clinically relevant threshold. While there were a few subjects who met this threshold, the mean changes observed were -3.22 kg in the 600 µg group and -5.33 kg in the 900 µg group.

Below is a summary of subjects with vital sign abnormalities using the Sponsor's threshold values.

Table 67 Number (%) of subjects with past-baseline abnormality in vital signs up to data cut-off by randomized dose group (Safety analysis set)

Vital sign (thresholds exceeded)	Pasireotide 600 µg b.i.d. N=82			Pasireotide 900 µg b.i.d. N=80			Overall N=162		
	Total	n	%	Total	n	%	Total	n	%
Seated SBP ≥ 180 mmHg with increase from baseline of ≥ 20 mmHg	80	0	0	79	3	3.8	159	3	1.9
Seated SBP ≤ 90 mmHg with decrease from baseline of ≥ 20 mmHg	80	2	2.5	79	4	5.1	159	6	3.8
Seated DBP ≥ 105 mmHg with increase from baseline of ≥ 15 mmHg	80	5	6.3	79	9	11.4	159	14	8.8
Seated DBP ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg	80	0	0	79	1	1.3	159	1	0.6
Seated Pulse ≥ 120 bpm with increase from baseline of ≥ 15 bpm	79	0	0	79	1	1.3	158	1	0.6
Seated Pulse ≤ 50 bpm with decrease from baseline of ≥ 15 bpm	79	8	10.1	79	5	6.3	158	13	8.2
BMI < 18.5 kg/m ²	79	1	1.3	79	1	1.3	158	2	1.3
Weight gain ≥ 10% from baseline	79	2	2.5	79	1	1.3	158	3	1.9

Total is the number of patients with a baseline measurement as well as a post-baseline measurement. Clinical Study Report, Table 12-12

7.4.4 Electrocardiograms (ECGs)

This has been discussed in the discussion of QT prolongation above.

7.4.5 Special Safety Studies/Clinical Trials

Special safety studies have already been discussed in the context of specific safety issues.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This trial was not designed to compare the two doses. Nevertheless, in the discussion of specific AEs above, notable differences in the adverse event profile of the 2 doses are mentioned.

7.5.2 Time Dependency for Adverse Events

Important issues related to timing of adverse events, such as hyperglycemia, are discussed.

7.5.3 Drug-Demographic Interactions

Subgroup analyses have been presented.

7.5.4 Drug-Disease Interactions

Pasireotide is also being studied in patients with acromegaly and neuroendocrine tumors. Data are not available to compare safety profiles.

7.5.5 Drug-Drug Interactions

There is no drug interaction potential to or from pasireotide.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was no evidence of carcinogenicity in the non-clinical program. The pivotal trial was not of sufficient duration to assess for long-term carcinogenicity. No unusual neoplasms were reported in the clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy rarely occurs during the course of Cushing's syndrome.¹⁹ When it does occur, the disease increases the rate of spontaneous abortion, perinatal death, premature birth, and intrauterine growth retardation.

There are no studies of pasireotide in pregnant women. Animal studies have not shown reproductive toxicity.

Two pregnancies were reported during 2 different pasireotide clinical studies:

- The first subject (Study 2305) was reported pregnant on Day 87 of the trial. She was discontinued from the study because of the pregnancy and underwent an elective abortion, which was reported as an SAE.
- The second subject (acromegaly patient in Study 2001) had an SAE of pregnancy on Day 49 of the trial. Her last day of study drug was Day 65, after which she was discontinued from the trial. She experienced a miscarriage on Day 73.

It is not known whether pasireotide is excreted in human milk. Animal data confirm excretion of pasireotide in milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

Cushing's disease is seen in the adult population. It has not been studied in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no specific reports regarding overdose of pasireotide. Doses up to 2100 µg bid have been used in healthy volunteers (Study 2113). Diarrhea was a common adverse event at this dose.

There is no known or expected abuse potential for pasireotide. No signs of dependency have been observed in clinical trials.

¹⁹ Lindsay JR et al. Cushing's Syndrome during Pregnancy: Personal Experience and Review of the Literature. The Journal of Clinical Endocrinology and Metabolism 2005; (-)(5): 3077-3083.

In the pivotal clinical trial, cortisol levels were not assessed upon discontinuation of pasireotide. It is possible that elevations of ACTH and cortisol can occur with discontinuation, although no withdrawal or rebound effects were noted.

7.7 Additional Submissions / Safety Issues

The Sponsor submitted a 4 month Safety Update, based on data from Study 2305 up to 33 months of treatment (12 months in core and 21 months in the optional extension). It also includes data from the Phase 2 extension study B2208E1 and the Phase 2 extension study in acromegalic patients 2291E1.

At the time of the 33 month cut-off, the median duration of treatment was 10.58 months and 10.22 months in the 600 µg and 900 µg groups, respectively. The mean duration of treatment was 14.44 and 15.73 months in the two groups. Overall, 40.7% of subjects had at least 12 months exposure and 24.7% had at least 24 months exposure.

Subject disposition at the time of the Month 33 data cut-off is summarized in the table below. Of the 162 randomized subjects, 78 subjects (48.1%) completed the core phase (Month 12). Of these 78, 58 subjects entered the extension, and 20 chose not to continue. A higher proportion of subjects in the 900 µg group (40%) compared entered the extension phase compared to the 600 µg group (31.7%).

A total of 121 subjects (74.75) discontinued the study (core or extension) at any time. The most frequent reason for discontinuation was unsatisfactory therapeutic effect (30.9%).

Of the 58 subjects who entered the extension, 37 subjects discontinued and 21 subjects were ongoing at the time of the Month 33 cut-off.

Disposition Reason	Pasireotide 600 µg bid N=83	Pasireotide 900 µg bid N=82	Overall N=165
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)
Ongoing	10 (12.2)	11 (13.8)	21 (13.0)
Discontinued at any time*	59 (72.0)	62 (77.5)	121 (74.7)
Reason for discontinuation			
Adverse event	17 (20.7)	18 (22.5)	35 (21.6)
Abnormal test procedure result	0	1 (1.3)	1 (0.6)
Unsatisfactory therapeutic effect	23 (28.0)	27 (33.8)	50 (30.9)
Subject withdrew consent	15 (18.3)	15 (18.8)	30 (18.5)
Lost to follow-up	0	1 (1.3)	1 (0.6)
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 (38.8)	78 (48.1)
Completed Month 12 and did not enter extension phase	13 (15.9)	7 (8.8)	20 (12.3)
Completed Month 12 and entered extension phase	26 (31.7)	32 (40.0)	58 (35.8)
Ongoing in extension phase	10 (12.2)	11 (13.8)	21 (13.0)
Discontinued study in extension phase	16 (19.5)	21 (26.3)	37 (22.8)
Discontinued extension at or prior to Month 18	4 (4.9)	7 *8.8)	11 (6.8)
Discontinued at or prior to Month 24 but after month 18	5 (6.1)	3 (3.8)	8 (4.9)
Discontinued at or prior to Month 30 but after month 24	4 (4.9)	4 (5.0)	8 (4.9)
Discontinued at or prior to Month 33 but after month 30	3 (3.7)	4 (5.0)	7 (4.3)

Applicant's Clinical Safety Update, Table 1-3

*Subjects who completed Month 12 and did not enter extension phase are not counted as discontinuations

Adverse events during the extension phase of Study 2305: There were no deaths during the extension study. The percentage of subjects with an SAE or an AE was similar to the data presented in the initial application. Compared to the initial analysis of specific adverse events, some of the AEs with an increase in incidence of $\geq 1\%$ (in the overall group) in the extension data were:

- Diabetes mellitus: five additional subjects—4 in the 600 μg group and 1 in the 900 μg group
- Cholelithiasis: three additional subjects—all in the 600 μg group
- Hypoglycemia: two additional subjects—all in the 900 μg group

One additional subject in the 600 μg group had an increased GGT, and one additional subject in the 600 μg group had an increased ALT.

Subjects in the extension phase had some notable SAEs in the following SOCs:

- Hepatobiliary disorders: two subjects in the 600 μg group (acute cholecystitis and cholangitis) and two subjects in the 900 μg group (bile duct stone and cholelithiasis)
- Gastrointestinal disorders: four subjects in the 600 μg group (two events of diarrhea, pancreatitis, and anal fistula) and one subject in the 900 μg group (abdominal pain)
- Vascular disorder: one subject in the 900 μg group with a hypertensive emergency. This subject had baseline hypertension and also had a previous AE of QT prolongation. On Day 871 of study drug, he experienced chest pain,

diaphoresis, and dyspnea and was hospitalized for a hypertensive emergency (no BP measurements provided). The event resolved several days later and he was discharged. The Investigator did not suspect a relationship to study drug.

- Psychiatric disorder: one subject in the 900 µg group with agitation

Compared to the initial analysis, the following were additional AEs leading to study discontinuation in the extension phase:

- In the 600 subject in the 600 µg group: diarrhea and inadequate DM control in one subjects; hyperglycemia in one subject; diarrhea, hematochezia, and decreased weight in one subject
- In the 900 subject in the 600 µg group: hypoglycemia, cholelithiasis and dyspepsia in one subject; constipation, diarrhea, and abdominal pain in one subject; agitation in one subject; tumor hemorrhage in one subject

Regarding adverse events of special interest not already mentioned, the following are categories with increased incidence of AEs in the extension phase:

- Bradycardia-related AEs: one subject in the 900 subject in the 600 µg group was reported to have a QT prolongation
- Coagulation-related AEs: one subject in the 600 µg group and 2 subjects in the 900 µg group reported PTT prolonged
- Hyperglycemia-related AEs: one subject in the 600 µg group had inadequately controlled diabetes mellitus and three had diabetes mellitus; in the 900 µg group, two subjects had reported hyperglycemia and 2 had reported hypoglycemia.
- Hypocortisolism-related AEs: one subject in the 600 µg group had reported adrenocortical insufficiency. This subject withdrew consent on Day 784. Two days later, the subject had pituitary surgery for Cushing’s disease and the patient was noted with secondary adrenal insufficiency. This event was not a clinically important event related to pasireotide.
- Pancreatitis-related AEs: one subjects in the 600 µg group had reported pancreatitis
- QT prolongation-related AEs: one subject in the 900 µg group was reported to have QT prolongation.
- Hypotension-related AEs: Compared to no events in the initial analysis, there were a total of 11 events in the extension phase.

The extension phase allowed the opportunity to follow hyperglycemia. Despite limitations, including low numbers of subjects by Month 33 (some of whom discontinued because of uncontrolled hyperglycemia) and the confounding intervention of antidiabetic medications, the tables below summarize mean FPG and HbA1c up to Month 33. In the subjects that continued to this time point, glycemia improved but did not normalize.

Table 68 Mean fasting plasma glucose by randomized group for Study 2305

Visit	Pasireotide 600 µg bid		Pasireotide 900 µg bid	
	n	Mean (SD) mg/dL	n	Mean (SD) mg/dL

Baseline	79	98.6 (23.61)	79	97.0 (18.69)
Month 1	76	138.8 (68.64)	72	153.4 (71.54)
Month 2	70	133.7 (51.39)	67	138.4 (60.31)
Month 4	68	122.1 (41.80)	61	124.9 (43.14)
Month 6	57	125.1 (34.61)	55	128.0 (54.63)
Month 9	46	126.9 (35.94)	48	119.4 (33.14)
Month 12	39	120.9 (40.52)	38	114.4 (36.34)
Month 18	26	130.5 (42.18)	25	108.2 (21.25)
Month 24	18	125.0 (31.97)	22	115.0 (40.29)
Month 30	14	124.7 (39.63)	18	113.4 (25.29)
Month 33	12	114.4 (27.34)	13	109.4 (21.91)

Adapted from Clinical Safety Update, Table 3-3

Table 69 Mean HbA1c (%) by randomized group for Study 2305

Visit	Pasireotide 600 µg bid		Pasireotide 900 µg bid	
	n	Mean (SD) mg/dL	n	Mean (SD) mg/dL
Baseline	78	5.83 (0.79)	76	5.76 (0.80)
Month 2	73	7.24 (1.66)	66	7.41 (1.51)
Month 4	68	7.23 (1.49)	61	7.15 (1.17)
Month 6	59	7.24 (1.42)	56	7.34 (1.19)
Month 12	40	7.25 (1.32)	38	7.21 (1.60)
Month 18	26	7.08 (1.13)	25	6.60 (0.69)
Month 24	18	7.03 (1.22)	22	6.56 (0.58)
Month 30	14	7.10 (1.30)	19	6.88 (0.86)
Month 33	12	6.64 (0.81)	11	6.59 (0.71)

Adapted from Clinical Safety Update, Table 3-5

Overall, the safety data from the Clinical Safety Update are consistent with those provided in the original Application.

8 Postmarket Experience

This drug is not marketed in the US. With recent approval in the EU, postmarketing experience is limited.

9 Appendices

9.1 Literature Review/References

Referenced literature is cited in the body of the Review.

9.2 Labeling Recommendations

The label will be reviewed separately.

9.3 Advisory Committee Meeting

There is an upcoming advisory committee (AC) meeting scheduled for November 7, 2012. While the main points for discussion will be efficacy and safety related to hyperglycemia/diabetes and elevated liver tests, the points for discussion and voting questions are not finalized as of the submission of this Review. An Addendum will be written following the AC meeting.

Appendix 1: Review of Study 2208

Study 2208

This was a proof-of-concept, open-label, single-arm, multi-center trial. All subjects were Cushing's disease patients who received pasireotide 600 µg s.c. every 12 hours for 15 days. Subjects were candidates for surgical intervention as well as patients who had persistent or recurrent Cushing's disease post-pituitary resection, who had not received any pituitary irradiation. Dose could be reduced by 150 µg per injection at any time of there was likely drug-related toxicity.

The dose of 600 µg bid was selected based on the PK profile of the drug. At this dose and schedule, the peak drug plasma level at steady state was predicted to be approximately 15 ng/mL, with a trough concentration of 2 ng/mL. According to the Sponsor, 1 ng/mL is considered to the level at which most neuropeptides exert pharmacological activity.

The primary goal of treatment was normalization of UFC, after 15 days of treatment, based on a mean of 2 consecutive 24-hour urine collections. There were 2 stages to enrollment: a cohort of 10 was enrolled in the first stage and another cohort of 16 subjects was to have been accrued in the second stage if there were at least 2 responders in the first cohort. A responder was defined as a subject with normalization of UFC after 15 days of treatment.

There was an extension period for subjects who were believed to be deriving benefit from pasireotide. They were followed every 2 weeks until treatment was discontinued.

The primary objective of this trial was to assess the efficacy of pasireotide in patients with Cushing's disease as measured by normalization of UFC. There were multiple secondary objectives.

The primary efficacy endpoint was the normalization of UFC at the end of 15 days, determined from a mean of 2 consecutive 24-hour UFC assessment conducted at baseline and at the end of the trial.

Inclusion criteria included:

- Age ≥ 18 years
- Patients with ACTH-dependent, clinically- and biochemically-confirmed Cushing's disease, verified within 2 months prior to study, as evidenced by:
 - Two consecutive 24-hour UFC measurements of at least 2xULN
 - Morning plasma ACTH normal or above normal range
 - Either MRI confirmation of pituitary macroadenoma, or for microadenomas an inferior petrosal sinus gradient >3 after stimulation
- Patients who were candidates for pituitary surgery of who had recurrent Cushing's disease post-pituitary resection who had not received any prior pituitary irradiation.

Exclusion criteria included:

- Pregnant or lactating
- Cushing's syndrome due to ectopic ACTH secretion
- Not euthyroid
- Uncontrolled infection
- Patients who received Sandostatin LAR or any other long-acting somatostatin analogue within the last 8 weeks prior to starting the study
- Major surgery within 1 month
- Poorly controlled DM indicated by ketoacidosis of HbA1c $>10\%$
- Congestive heart failure, unstable angina, sustained ventricular tachycardia, ventricular fibrillation,
- Liver disease
- Abnormal coagulation parameters
- HIV
- Active gallbladder disease
- Active malignant disease

A total of 39 subjects were enrolled and 38 completed the trial. One was discontinued because of an AE of hyperglycemia. This subject had diabetes at baseline. There were no deaths during the trial.

The following summarizes major protocol deviations:

Table 70 Major protocol deviations (safety population)

Disposition/Reason	SOM230 600 µg bid
	N=39 n (%)
Liver disease and/or abnormal laboratory tests	1 (2.6)
Defined abnormality in hematology tests	7 (17.9)
Baseline UFC in laboratory normal range	4 (10.3)
<2 UFC samples at baseline or end-core phase	6* (15.4)
Discontinued study drug before Day 14	1 (2.6)

*One of these 6 was found after database lock to have been erroneously excluded from the primary efficacy population. This subject did not collect any post-baseline UFC values since they were discontinued because of an adverse event. According to the definition of the primary efficacy population the subject should have remained in the primary efficacy population.

Two of the major protocol deviations led to exclusion of subjects from the primary efficacy population: 1) baseline UFC within normal range, and 2) <2 UFC samples at baseline or end-of-study. Overall, this resulted in the exclusion of 10 subjects from the primary efficacy population.

The ITT population consisted of 39 subjects and the Primary Efficacy Population 29 subjects. The safety population was approximately 75% female, approximately 95% Caucasian, and the median age was 42 years. Information on previous treatment of Cushing's disease was not explicitly collected for this trial. The most common medical histories and current medical conditions at baseline (≥10%) were hypertension (71.8%), depression (20.5%), and osteoporosis (20.5%). Interestingly, diabetes or hyperglycemia was not captured as a common baseline medical condition.

Primary efficacy analysis: Five of the 29 subjects (17.2%) in the primary efficacy population had normalization of UFC and were considered to be responders. Had the subject who was erroneously excluded from the primary efficacy population (described above) been included in the analysis (and counted as a non-responder) the rate would have been 5/30 (16.7%). The following table summarizes the UFC levels of the 5 responders:

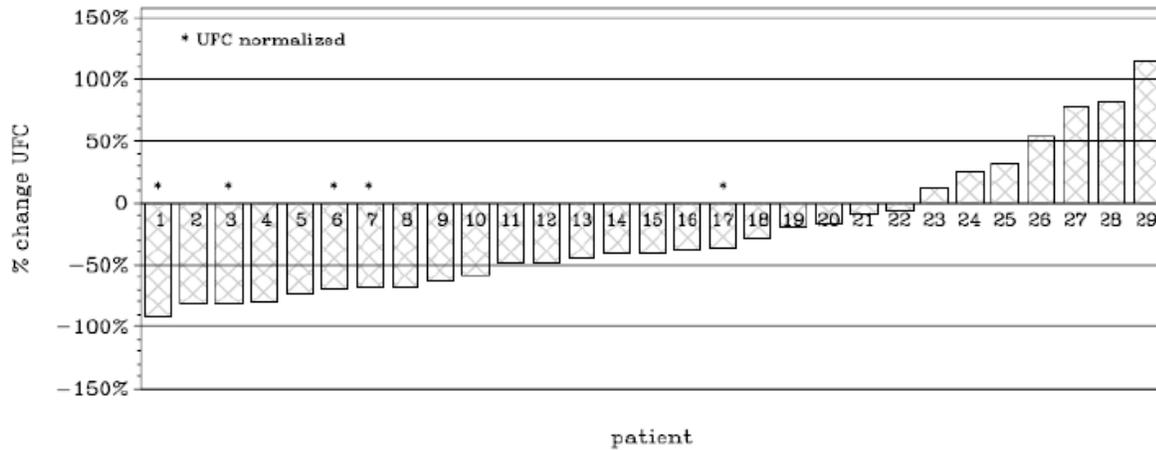
Table 71 Summary of responders based on mean UFC levels (Efficacy population)

Patients who were responders	UFC levels			
	Baseline	Day 15	Change from baseline	% change from baseline
B2208-0001/00001	2546.5	207.0	-2339.5	-91.9
B2208-0001/00009	825.0	263.5	-561.5	-68.1
B2208-0011/00005	520.5	157.5	-363.0	-69.7
B2208-0031/00003	1469.5	269.0	-1200.5	-81.7
B2208-0505/00002	299.4	190.9	-108.5	-36.2

Clinical Study Report, Table 11-5

The following figure summarizes the individual patient percent changes in mean UFC. There were 7 subjects whose UFC increased by the trial's end.

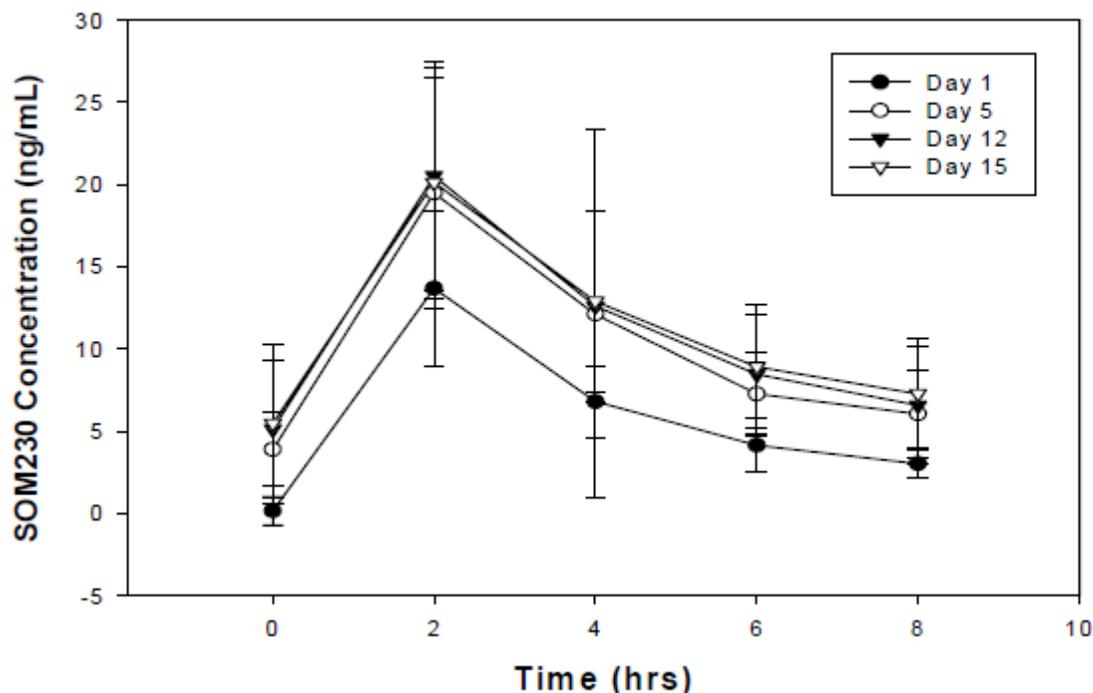
Table 72 Individual patient % change in mean UFC at End of Study (Day 15) (Primary Efficacy population)



Clinical Study Report, Figure 11-1

All 38 subjects were included in the PK analyses. Of note, there were 2 subjects whose doses were reduced to 450 µg s.c. bid on Day 5 and Day 11 due to adverse events. The figure below suggests that steady state was achieved by Day 5 in this trial.

Figure 18 Mean (SD) pasireotide plasma concentration versus time profiles



Clinical Study Report, Figure 11-3

Secondary and other clinical endpoints are not covered here as a 2 week trial is not considered sufficient to observe clinically important changes in signs and symptoms of Cushing’s disease.

Safety

Thirty six subjects (92.3%) experienced at least one AE. The 3 most common AEs were diarrhea, hyperglycemia, and nausea. The entire list is shown below. There were many separate PTs related to injection site reactions.

Table 73 Most common (≥5%) adverse events regardless of study drug relationship by preferred term (Safety population)

Preferred Term	Pasireotide 600 µg s.c. bid N=39 n (%)
Diarrhea	20 (51.3)
Hyperglycemia	14 (35.9)
Nausea	12 (30.8)
Headache	9 (23.1)
Fatigue	8 (20.5)
Abdominal pain	7 (17.9)
Asthenia	6 (15.4)
Hypotension	5 (12.8)

Clinical Review
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Pasireotide (Signifor®, SOM230)

Dizziness	4 (10.3)
Injection site erythema	4 (10.3)
Chills	3 (7.7)
Dyspepsia	3 (7.7)
Hyperhidrosis	3 (7.7)
Injection site pain	3 (7.7)
Vomiting	3 (7.7)
Constipation	2 (5.1)
Erythema	2 (5.1)
Hypertension	2 (5.1)
Injection site irritation	2 (5.1)
Injection site edema	2 (5.1)
Injection site pruritus	2 (5.1)
Injection site reaction	2 (5.1)
Paresthesia	2 (5.1)

Clinical Study Report, Table 12-5

There were 14 subjects with hyperglycemic adverse events. The following table summarizes the characteristics of these subjects. There were 2 hyperglycemia-related SAEs. The majority of subjects with the events below did not have a baseline diagnosis of DM or IFG/IGT.

Subject	Baseline history: DM or IFG/IGT	Baseline FPG (mg/dL)	Highest FPG (mg/dL)	Last FPG (mg/dL)	Grade ¹	Specific Treatment	Action taken ²
0001/00003	Yes: DM	92.98	198.04	198.04	G3	Hospitalization; change of medicine	1,2,3,5, (SAE)
0001/00006	Yes: DM	69.02	101.09	85.96	G1	Repaglinide	3
0001/00007	No	78.03	109.02	101.09	G1	Diet	4
0001/00008	Yes: IGT	121.09	127.94	127.94	G1	Diet	4
0001/00009	No	85.96	158.04	158.04	G1	Repaglinide + diet	3,4
0001/00011	No	61.09	189.03	189.03	G1	Repaglinide + diet	3,4
0002/00002	No	83.07	136.05	134.07	G2	Hospitalization	5 (SAE)
0021/00003	Yes: IFG	123.08	201.1	201.1	G1	n/a	No action
0011/00002	No	78.93	123.98	123.08	G1	n/a	No action
0011/00003	No	98.93	125.06	125.06	G1	n/a	No action
0011/00004	No	107.01	174.04	120.01	G1	n/a	No action
0011/00005	Yes: DM	101.09	129.02	129.02	G1	n/a	No action
0502/00001	No	154.00	267.00	267.00	G1	Metformin	3
0502/00002	No	79.00	111.00	111.00	G1	n/a	No action

Clinical Study Report, Table 12-9

FPG=fasting plasma glucose; IFG=impaired fasting glucose; IGT=impaired glucose tolerance

¹Action taken: 1=study drug adjusted/temporarily interrupted 2=study drug permanently discontinued due to AE 3=concomitant medication taken 4=non-drug therapy given 5=hospitalization

²Grade provided by investigator (not in all cases consistent with CTCAE criteria): G1: >ULN-160 mg/dL; G2: >160 mg/dL-250 mg/dL; G3: >250 mg/dL-500 mg/dL; G4: >500 mg/dL

There were no deaths during the trial. The following table summarizes other important AEs.

Table 74 Serious or Significant Events in Trial 2208

	Pasireotide 600 µg s.c. bid N=39 n (%)
Serious or significant events	18 (46.2)
SAEs	3 (7.7)
Discontinued due to AEs	1 (2.6)
AEs requiring dose adjustment or study-drug interruption	3 (7.7)
AEs requiring additional therapy	17 (43.6)

Clinical Study Report, Table 12-10

There were 3 subjects with SAEs. Two subjects experiences hyperglycemia requiring hospitalization. A third subject had an acute myocardial infarction that was considered unrelated to study drug. This was a subjects with a history of hypertension who had mild chest pain on Day 5. This event resolved, but the subject then experienced hypotension on Day 9, which also resolved. On Day 15, the subjects was found to have new or worsened ischemic t wave inversions and ST segment elevations and was diagnosed with acute myocardial infarction. The subjects underwent cardiac catheterization which revealed ventricular dysfunction and greater than 90% stenosis of the left ascending coronary artery. The Investigator considered this event to be unrelated to study drug.

Laboratory Evaluations

There were no patients who met the biochemical criteria for Hy's law. There were some mild shifts in AST, ALT, total bilirubin, and GGT and these are shown below. The clinical importance of these changes is unclear. Other analyses (including outlier summaries) related to hepatic safety are found in the discussion of Hepatic Safety.

Table 75 Liver tests: shift tables of baseline versus highest CTC grade post baseline—Liver function tests

		Highest CTC grade post-pasireotide s.c. baseline			
		Grade 0	Grade 1	Grade 2	Grade 3
Test	Baseline CTC Grade	n (%)	n (%)	n (%)	n (%)
AST	Grade 0	31 (81.6)	6 (15.8)	1 (2.6)	0
	Grade 1	1 (100.0)	0	0	0
ALT	Grade 0	20 (57.1)	14 (40.0)	1 (2.9)	0
	Grade 1	0	2 (66.7)	1 (33.3)	0
	Grade 3	0	0	1 (100.0)	0
Total bilirubin	Grade 0	36 (94.7)	2 (5.3)	0	0
	Grade 1	1 (100.0)	0	0	0
GGT	Grade 0	21 (75.0)	7 (25.0)	0	0
	Grade 1	2 (22.2)	5 (55.6)	2 (22.2)	0

	Grade 2	0	0	1 (100.0)	0
	Grade 3	0	0	0	1 (100.0)

Adapted from Clinical Study Report, Table 12-12

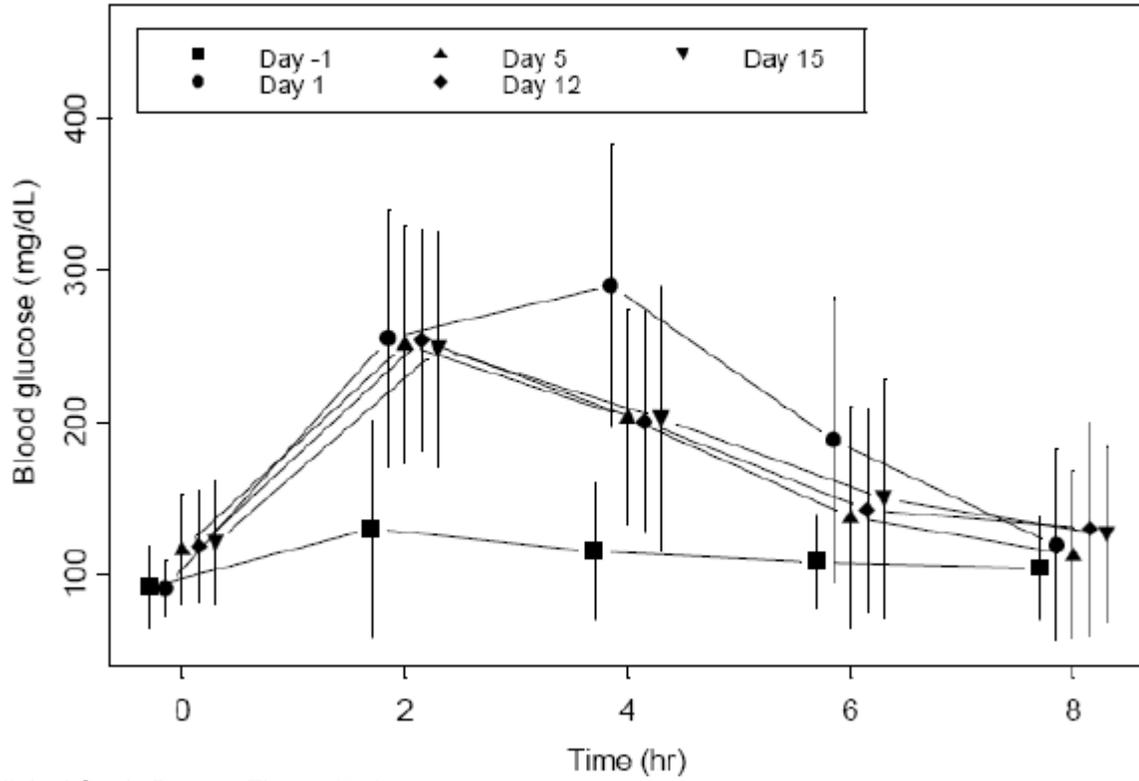
Changes in fasting blood glucose were analyzed. There were 31 subjects with normal baseline glucose values (<100 mg/dL):

- Of these 31 subjects, five had levels that remained normal. Seventeen had at least one FPG between 100-125 mg/dL and 9 had at least one value ≥ 126 mg/dL.
- At baseline, 5 subjects had FLG levels between 100-125 mg/dL. One subject stayed at this level and 4 had at least one value ≥ 126 mg/dL.
- Two subjects had baseline FPG levels ≥ 126 mg/dL and had at least one post baseline value ≥ 126 mg/dL.

Eight hour glucose, insulin, and glucagon profiles: On study days -1, 1, 5, 12, and 15 subjects had collections for blood glucose, insulin, and glucagon over an 8 hour period. Samples were collected pre-dose (time 0) and 2, 4, 6, and 8 hours post morning injection. Subjects were fasting at time 0 but then ate a light breakfast and lunch at 4 hours post-injection. The mean blood glucose concentration versus time profiles by days are shown below.

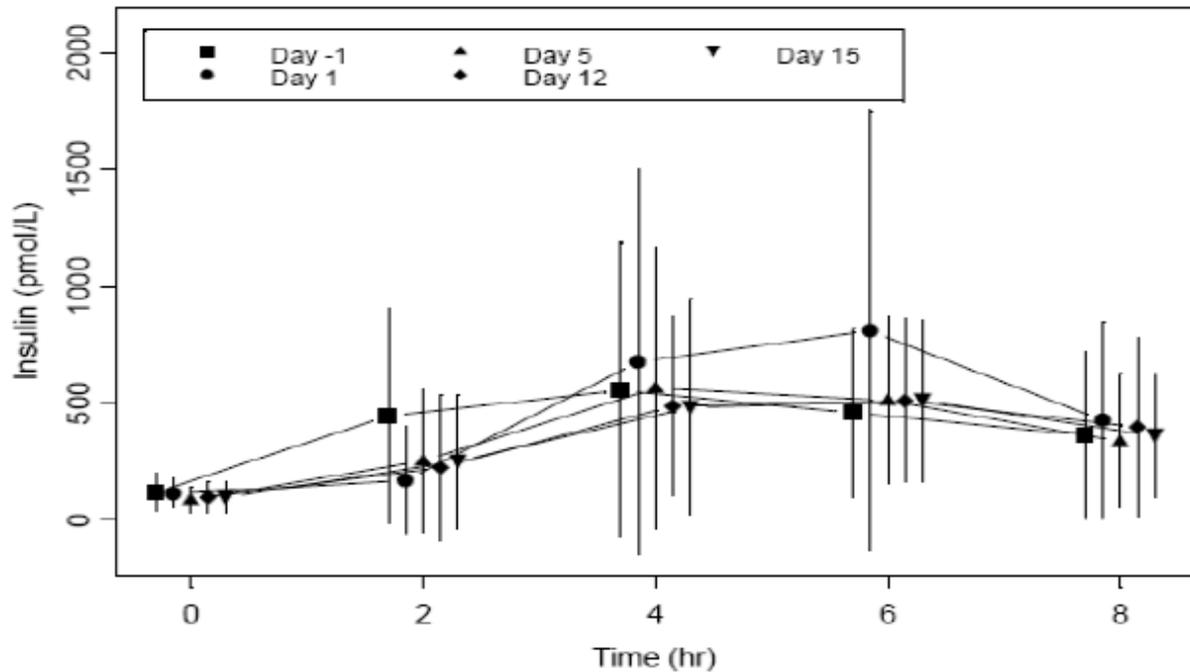
Glucose increased with the initial drug exposure and then decreased within 8 hours. The 4 and 6-hour mean glucose values were higher on Day 1 than the subsequent days. Compared to the Day -1 levels, insulin values were lower at 2 hours for all measured days. It is unclear they insulin was increased at certain timepoints, particularly on Day 1.

Figure 19 Mean (SD) blood glucose versus time profiles by day following pasireotide dosing (Safety population)



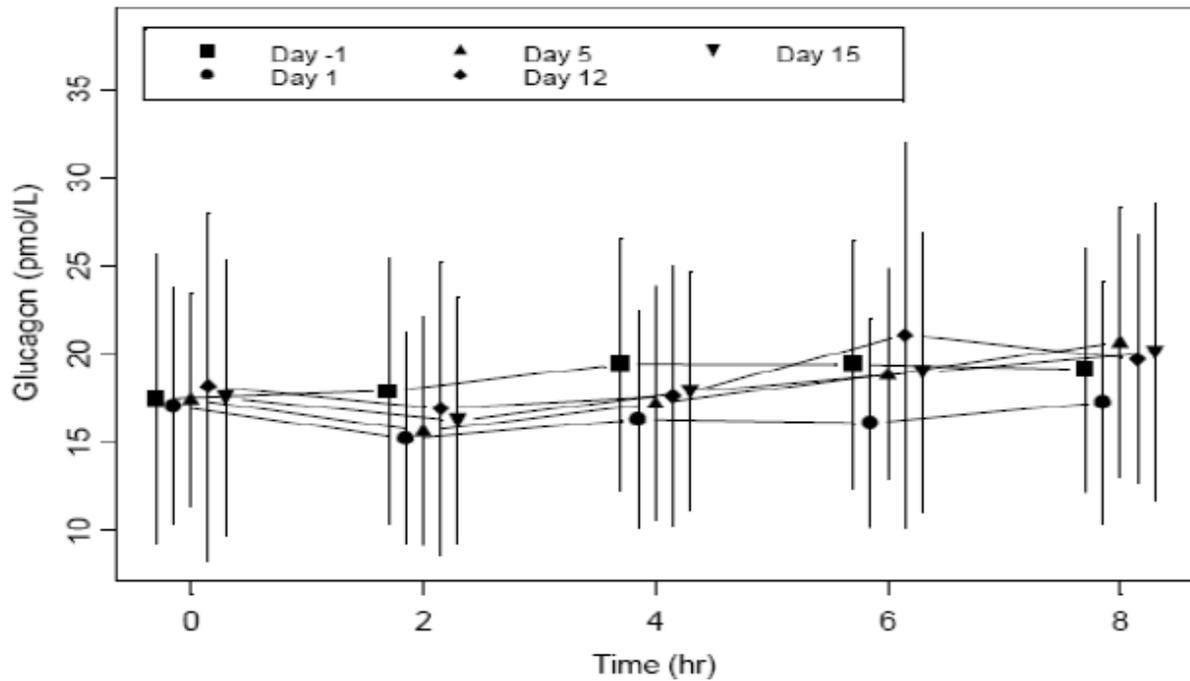
Clinical Study Report, Figure 12-1

Figure 20 Mean (SD) insulin versus time profile by day following pasireotide dosing (Safety population)



Clinical Study Report, Figure 12-2

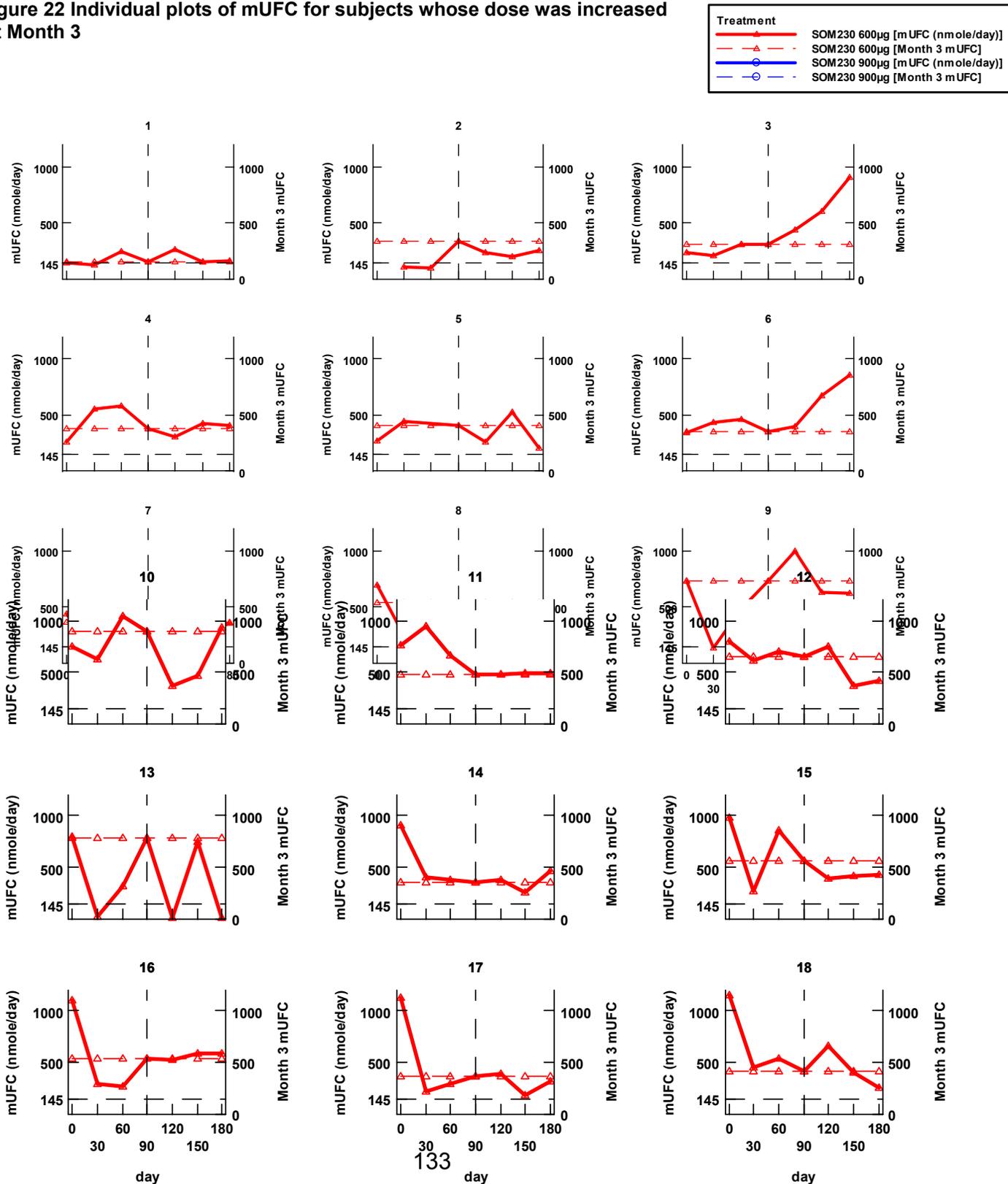
Figure 21 Mean (SD) glucagon versus time profile by day following pasireotide dosing (Safety population)

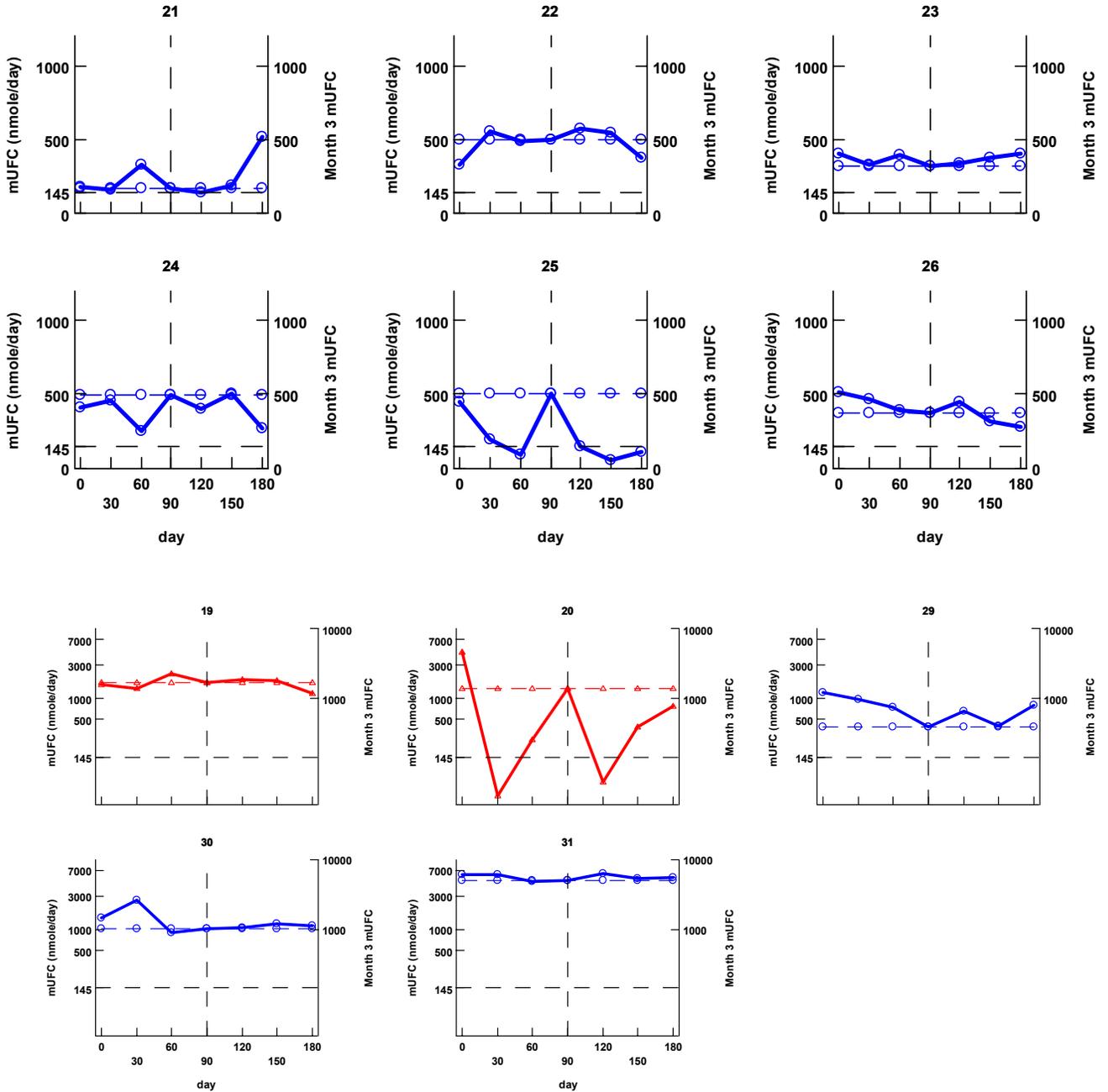


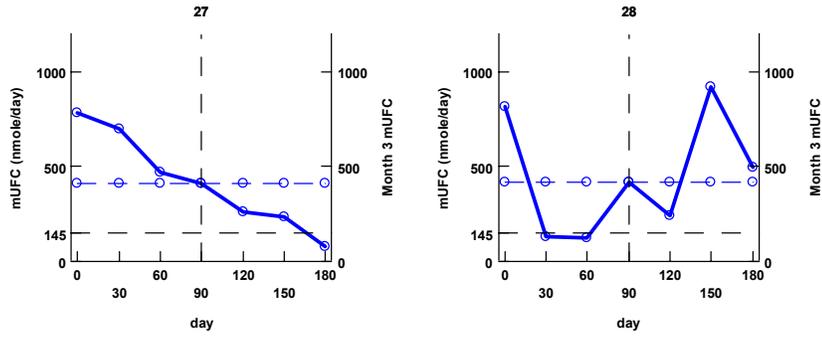
Clinical Study Report, Figure 12-3

Appendix 2 Individual Plot of mUFC for subjects whose dose was increased at Month 3

Figure 22 Individual plots of mUFC for subjects whose dose was increased at Month 3

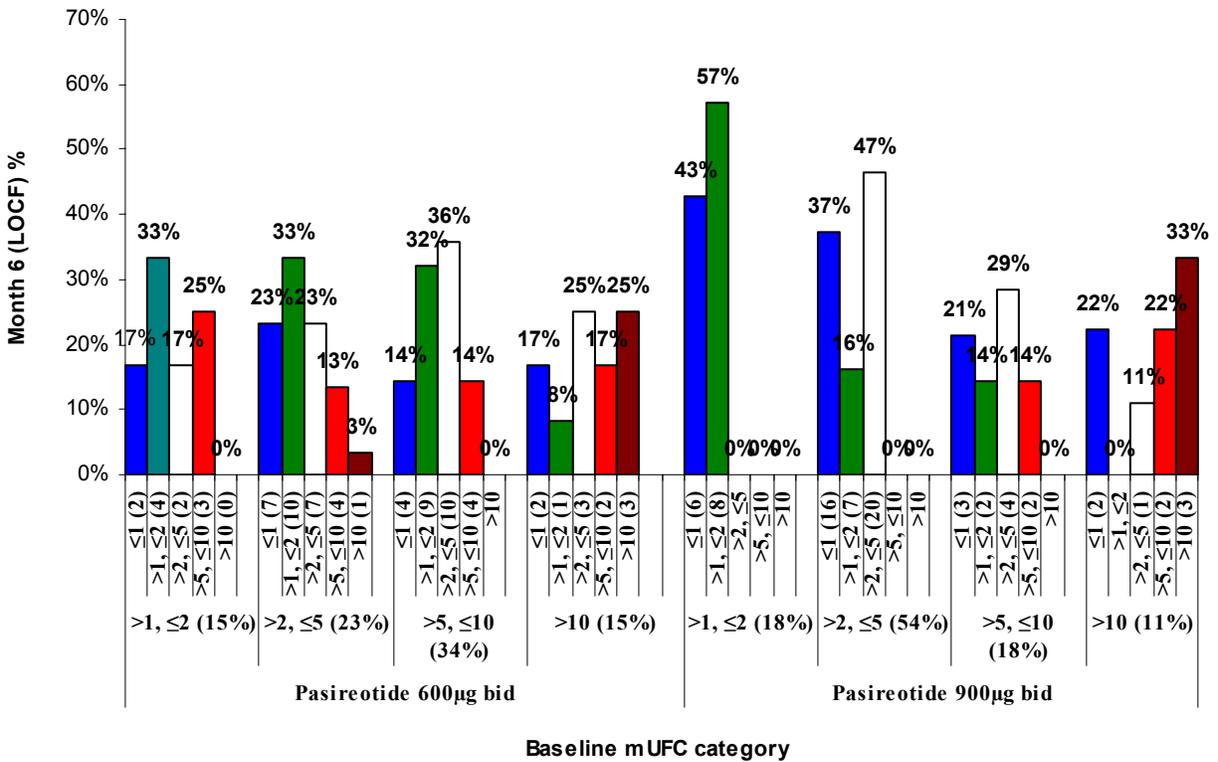






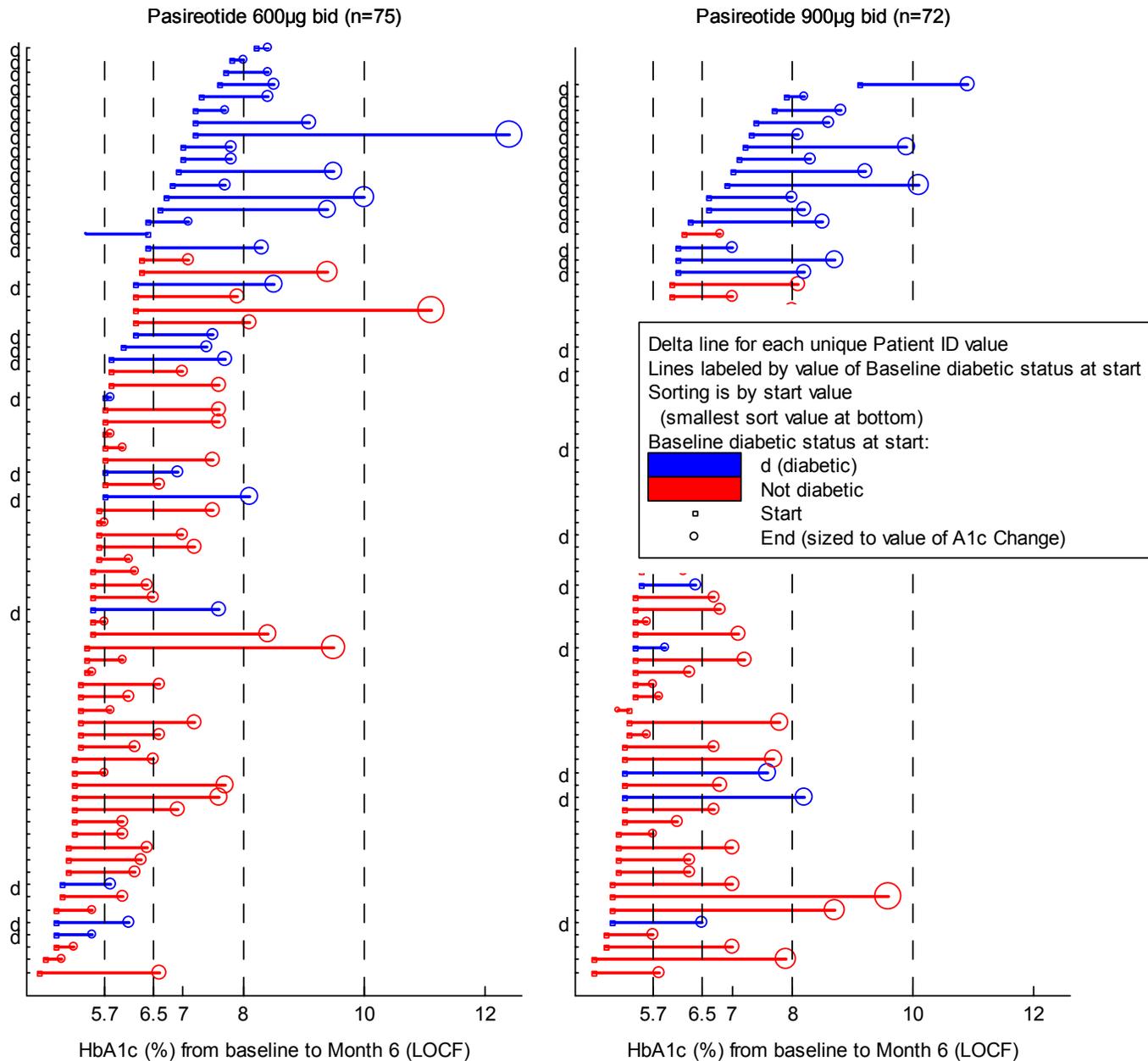
Appendix 3 Shifts in mUFC category during treatment to Month 6

Figure 23 Shifts on treatment from baseline UFC categories (1-2, 2-5, 5-10, > 10x ULN) to Month 6 (LOCF)



Appendix 4 Individual HbA1c changes by dose group

Figure 24: Individual HbA1c changes from baseline to Month 6 for the 600 µg bid and 900 µg bid dose groups; d=subject was diabetic at baseline



Appendix 5 Summary of Trials used in Safety Review

Study	Pasireotide s.c. doses	Duration of exposure to pasireotide s.c.	LFT Monitoring Study days
Healthy Volunteer Single Day Studies:			
N=153 subjects (pasireotide), N=18 subjects (placebo)			
B2101 Randomized, double-blind, placebo-controlled, ascending dose study in healthy volunteers to assess tolerability/safety, PK and PD (GHRH stimulation test)	Single dose pasireotide: 1µg, 2.5µg, 10µg, 30µg, 100µg, 200µg, 300µg, 600µg, or 1200µg	1 day	Screening, Baseline (Day -1), 24 hrs post-dose, 48 hours post-dose, study completion (>144 hours post-dose)
72 subjects:			
-18 on placebo			
-54 on pasireotide			
B2106 Open-label, ascending dose study in healthy volunteers	Ascending dose Pasireotide 900µg, 1200µg, 1500µg qd.	1 day	Screening, Baseline (Day -1), 24 hrs post-dose, 48 hours post-

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

Study	Pasireotide s.c. doses	Duration of exposure to pasireotide s.c.	LFT Monitoring Study days
to assess tolerability/safety, PK and PD (glucose, insulin and glucagon profiles) 17 subjects	Or Pasireotide 450µg, 600µg, 750µg bid.		dose, study completion (>144 hours post-dose)
B2112 Human ADME study 4 subjects	Single dose pasireotide 600µg ¹⁴ C	1 day	Screening, pre-dose, Baseline, an 24 hrs post-dose (Day 2)
C2101 Open-label, ascending single LAR dose in healthy volunteers to assess tolerability/safety, PK and PD (glucose, insulin and glucagon profiles) 78 subjects	Single dose pasireotide 300µg	1 day	Screening, Study Days 13, 21, 27, and Study completion
Healthy Volunteer Multiple Day Studies: N= 465 subjects (pasireotide), N=38 subjects (other treatment)			
B2102 Randomized, double-blind, placebo-controlled crossover study in healthy volunteers to assess tolerability/safety, PK and PD (blood glucose, insulin, glucagon, GHRH stimulation test) 33 subjects	Pasireotide crossover 50µg, 200µg, 600µg once daily	Crossover; 14 days placebo and 14 days pasireotide with two week washout	Screening and Baseline of periods 1 and 2
B2107 Open-label, ascending dose study in healthy volunteers to assess tolerability/safety and PD (glucose, insulin and glucagon profiles) 66 subjects	Pasireotide dose escalation 150, 300, 600, 900, 1200, 1500µg qd. 150µg, 300µg, 450µg, 600µg, 750µg bid.	8 days	Screening, pre-dose, and at study completion (>Day 6)
B2108 Open-label escalating dose levels in healthy volunteers to assess tolerability/safety and PD (glucose, insulin and glucagon profiles) in a continuous s.c. infusion 44 subjects	Pasireotide s.c. continuous infusion 450µg, 900µg, 1350µg, 1800µg, 2025µg, 2250µg	7 days	Screening and Study Completion (Day 10). ALT, AST, GGT daily on Study Days 1-9 for doses >1800ug/day

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

Study	Pasireotide s.c. doses	Duration of exposure to pasireotide s.c.	LFT Monitoring Study days
B2113 Part 1: Ascending dose study in healthy volunteers to assess the maximally tolerated dose (MTD). Part 2: Thorough QT study. Randomized, double-blind, crossover study to assess effects on QTc intervals Part 1= 55 subjects -18 on placebo -37 on pasireotide Part 2= 103 subjects -88 received pasireotide -15 did not receive pasireotide dose	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	Part 1: 7 days Part 2: 38 days 3-way crossover with pasireotide, moxifloxacin and placebo 3 treatment periods of 5 days separated by 10 day washout period	Screening, Baseline, and End of Study (Day 38).
B2124 Randomized, open-label, single-center, Phase I study to evaluate the effects of concomitant administration of antihyperglycemic drugs and pasireotide and pasireotide alone on glucose metabolism in healthy male volunteers 90 subjects	<i>Pasireotide monotherapy:</i> 600µg bid <i>Pasireotide combination therapy:</i> 600µg bid. + one of the following agents -metformin -nateglinide -vildagliptin -liraglutide	7 days	Screening, Baseline, and end of treatment period (Day 7)
B2125 Randomized, placebo and active controlled, blinded thorough QT/QTc study with a 4-way treatment crossover in healthy volunteers 112 subjects - 107 subjects received pasireotide - 5 subjects did not receive pasireotide dose	Pasireotide with active and placebo controlled cross-over 600µg bid, 1950µg bid, moxifloxacin (active control) and placebo	51 days 4-way crossover with pasireotide (2 doses), moxifloxacin and placebo 4 treatment periods of 5 days separated by 10 day washout period	Screening, Baseline, and End of study (Day 51)
Hepatic Impairment: N=34 subjects and patients (pasireotide)			
B2114	Pasireotide 600µg	1 day	Screening, Study Day 2, Completion

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

Study	Pasireotide s.c. doses	Duration of exposure to pasireotide s.c.	LFT Monitoring Study days
Open-label study to assess effect of hepatic impairment on PK and safety -15 healthy volunteers -19 patients with hepatic insufficiency Degrees of hepatic dysfunction (19 patients): 6 patients – mild 7 patients – moderate 6 patients - severe	single dose		(Day 7)
Investigator initiated trial (IIT): N=45 subjects (pasireotide)			
B2216¹ Randomized double-blind study to assess the effects of pasireotide on insulin secretion and glucose metabolism in healthy male volunteers. 45 subjects	Pasireotide 600µg bid, 900µg bid, 1200µg bid	8 days	Screening, End of study (Day 8), Follow-up (Day 15)
Cushing's Disease: N=201 patients (pasireotide)			
B2208 Open-label, non-randomized study in patients with Cushing's disease to assess efficacy, safety and PK 39 patients	Pasireotide 600µg bid	15 days	Screening, Baseline, Day 5, Day 8, Day 12 and Day 15
B2208E1² Open-label extension to assess long-term safety, efficacy and PK 19 patients	Pasireotide 600µg bid 900µg bid	Up to 58 months	Every 3 months
B2305² Double-blind randomized study of 2 dose levels in patients with Cushing's disease to assess efficacy, safety, QoL, PK and PK/PD relationship 162 patients	Pasireotide Randomized: 600µg or 900µg bid Up or down titration to 300µg or 1200µg bid.	Core = 12 months Extension = Up to 39 months	Screening, baseline and every 30 days (30, 60, 90, 120, 150, 180), and 30 days after last dose.
Acromegaly, N=72 patients (pasireotide)			
B2103 Double-blind randomized 3-way crossover to compare the efficacy of single doses	Pasireotide single dose cross-over: 100µg, 250µg Octreotide 100µg	1 day	Screening, Day 0, pre-dose, 24 days after each dose, and End of study

Study	Pasireotide s.c. doses	Duration of exposure to pasireotide s.c.	LFT Monitoring Study days
of SOM230 and Sandostatin 12 patients			
B2201 Open-label, randomized, crossover study in acromegaly patients to assess efficacy biochemical response, tumor volume, symptoms), safety, PK/PD relationship 60 patients	Pasireotide 200µg, 400µg, 600µg bid Octreotide 100µg tid	4 months	Screening, Day 0, 28, 56, 84, 112.
B2201E² Open-label extension to assess long-term safety, efficacy and PK 30 patients	Pasireotide 600µg or 900µg bid	Up to 64 months	First visit, then every 3 months, and last visit; gallbladder ultrasound at last visit or every six months, whichever is first.
Carcinoid Syndrome, N=45 patients (pasireotide)			
B2202 Open-label, non-randomized study in inadequately controlled carcinoid syndrome patients to assess efficacy (symptoms, tumor size), safety, QoL and PK 45 patients	Pasireotide 300µg, 600µg, 900µg, 1200µg Total daily dose range from 300µg-2400µg/day	Up to 104 weeks	Screening, Washout, Visit 1, Visit 2, every four weeks, and end of study

qd= once daily, bid= twice daily, tid= three times daily
 From Sponsor's Hepatic Report, Table 3-1

Appendix 6: Summary of Antihypertensive Use Before and During Pasireotide Treatment

Table 76 Use of antihypertensive medications at baseline and after start of pasireotide in Trial 2305 (FAS)

	Prior to start of pasireotide			After start of pasireotide		
	Pasireotide 600 µg bid N=82	Pasireotide 900 µg bid N=80	Overall N=162	Pasireotide 600 µg bid N=82	Pasireotide 900 µg bid N=80	Overall N=162
Ace Inhibitors and Diuretics	5 (6.1)	5 (6.3)	10 (6.2)	5 (6.1)	5 (6.3)	10 (6.2)

Clinical Review
Naomi Lowy, MD
NDA 200,677
Pasireotide (Signifor®, SOM230)

Ace Inhibitors, Plain	20 (24.4)	19 (23.8)	39 (24.1)	20 (24.4)	22 (27.5)	42 (25.9)
Aldosterone Antagonists	6 (7.3)	3 (3.8)	9 (5.6)	11 (13.4)	4 (5.0)	15 (9.3)
Alpha and Beta Blocking Agents	1 (1.2)	2 (2.5)	3 (1.9)	2 (2.4)	2 (2.5)	4 (2.5)
Angiotensin II Antagonists and Diuretics	4 (4.9)	5 (6.3)	9 (5.6)	4 (4.9)	6 (7.5)	10 (6.2)
Angiotensin II Antagonists, Combinations	0 (0.0)	1 (1.3)	1 (0.6)	0 (0.0)	1 (1.3)	1 (0.6)
Angiotensin II Antagonists, Plain	7 (8.5)	11 (13.8)	18 (11.1)	7 (8.5)	14 (17.5)	21 (13.0)
Beta Block, Selective and Other Antihypertensives	0 (0.0)	1 (1.3)	1 (0.6)	0 (0.0)	1 (1.3)	1 (0.6)
Beta Blocking Agents	0 (0.0)	4 (5.0)	4 (2.5)	0 (0.0)	4 (5.0)	4 (2.5)
Beta Blocking Agents, Non-Selective	0 (0.0)	3 (3.8)	3 (1.9)	0 (0.0)	3 (3.8)	3 (1.9)
Beta Blocking Agents, Selective	12 (14.6)	12 (15.0)	24 (14.8)	14 (17.1)	12 (15.0)	26 (16.0)
Dihydropyridine Derivatives	20 (24.4)	12 (15.0)	32 (19.8)	23 (28.0)	18 (22.5)	41 (25.3)
Other Antihypertensives	0 (0.0)	1 (1.3)	1 (0.6)	0 (0.0)	1 (1.3)	1 (0.6)

Adapted from Sponsor's Clinical Study Report

ⁱ He YL et al 2007, Hirose et al 2002, Kalbag et al 2001, Vilsboll et al 2008.

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/s/

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11/01/2012

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