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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 200-677
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This is a joint clinical and statistical briefing document served as a statistical review for NDA 200677.

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JOINT CLINICAL AND STATISTICAL REVIEW
SIGNIFOR (pasireotide injection)

NDA 200677

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1. Introduction

1.1 Drug substance and drug product

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

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

1.2 Indication

Novartis is proposing the following indication for Signifor:

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

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

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1.3 Pasireotide Clinical Program

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

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

Table 1: Overview of Phase 2/3 Trials

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

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

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

1.3.1 Study B2305 – Trial Design and Patient Population

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

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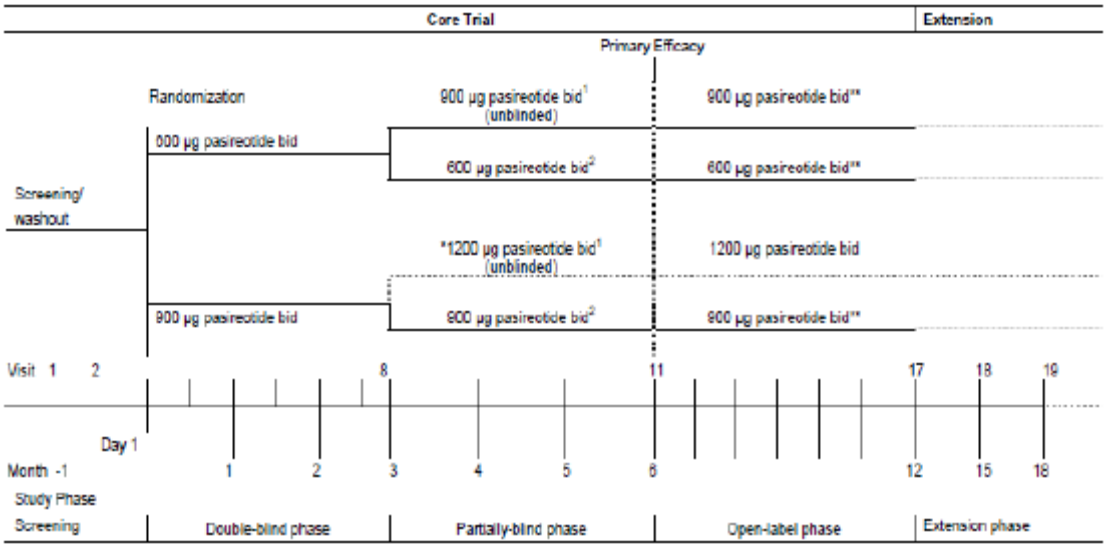
to continue the same double-blind treatment as long as their mean urinary free cortisol[1] (mUFC) was reduced relative to baseline and, in addition, reached a level that was below twice the upper limit of normal (2 x ULN). Patients who did not meet these criteria were considered non-responders for the purpose of the primary efficacy analysis, were unblinded, and their doses increased by 300 µg bid to no more than 1200 µg bid daily; if they could not or did not undergo dose escalation they were discontinued from the trial. Patients who remained blinded continued treatment until Month 6 when they were unblinded and analyzed in the primary efficacy analysis. The primary efficacy analysis was a responder analysis, with a responder being defined as any subject who attained mUFC ≤ULN at the Month 6 time point and whose dose was not increased after Month 3. Any patient who completed 6 months of treatment was allowed participation in a 6-month open-label phase which could be further extended. During the open-label/extension phase patients were continued on the same dose or had their daily dosage further escalated to a maximum of 1200 µg bid in most sites, depending on their individual responses.[2] At any time during the trial, a subject's dose could be decreased for tolerability reasons.

Figure 1: Study Design for Study B2305



Applicant's Clinical Study Report

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

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

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

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

Patients who received medical treatment for Cushing's disease prior to enrollment had to be washed out of such medications; wash out periods varied between drugs and depended on the half-life of each drug. Patients with evidence of glucose intolerance or diabetes mellitus were allowed enrollment as long as they were stable on diet and/or medication, but they were closely monitored with daily fasting blood glucose by fingerstick. Subjects with diabetes on antidiabetic drugs with an HbA1c over 8% were excluded. Criteria were in place for referral to a diabetes specialist for evidence of poor glycemic control.[3] Initiation or adjustment of antihyperglycemic medications was allowed as needed.

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

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

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

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

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

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

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

Baseline characteristics

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

Table 2: Baseline demographics by randomized dose group

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

Applicant's Clinical Study Report, Table 11-2

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

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

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

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

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

Applicant's Clinical Study Report, Table 11-3

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

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

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that, while 41% of patients had a baseline mUFC in the > 2xULN to ≤ 5xULN range, a sizeable proportion (38%) also had mUFC > 5xULN, and a smaller proportion (16%) had baseline levels between 1.5 and 2X ULN. When comparing the two randomization groups, a larger proportion of patients in the 600 µg bid group had mUFC > 5XULN (48% vs 28%), which may have contributed to the numerical imbalance in baseline mUFC levels between the 600 µg and the 900 µg arms.

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

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

From Sponsor's Response to Information Request, Table 2-1
*Although these 9 subjects were considered to have "missing" baseline mUFC values in this table because they did not have the required 3 baseline 24 UFC urine collections, they were used in the primary efficacy analysis because they had two 24 hour urine collections in addition to other evidence supporting the diagnosis of Cushing's disease.

Patient Disposition

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

Table 5: Subject disposition by randomized dose group

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

*Three subjects were screening failures but investigator mistakenly chose the IVRS randomization option.
[#]Subjects who completed Month 12 and did not enter extension phase are not counted as discontinuations

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From Applicant's Clinical Study Report Tables 10-1 and 14.1-1.3a

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

Protocol Deviations

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

1.3.3 Statistical Analysis Plan

Primary efficacy analysis

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

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

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

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

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

Longitudinal analysis of mUFC

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The applicant pre-specified a mixed model repeated measures (MMRM) statistical model for the purpose of analyzing mUFC as a continuous variable. The MMRM model used mUFC change from baseline on the natural log scale as the dependent variable with randomized dose and month as fixed effects and log(baseline mUFC) as a covariate.

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2. Review of Efficacy

2.1 Primary efficacy analysis

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

Table 6: Primary efficacy analysis (Month 6)

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

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

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

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

From Statistical Reviewer Lee Ping Pian

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

2.2 Exploratory analysis using alternate definition of responder

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

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

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

2.3 Additional efficacy analyses of changes in mUFC

2.31 Changes in mUFC over time by randomization group

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

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

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

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

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

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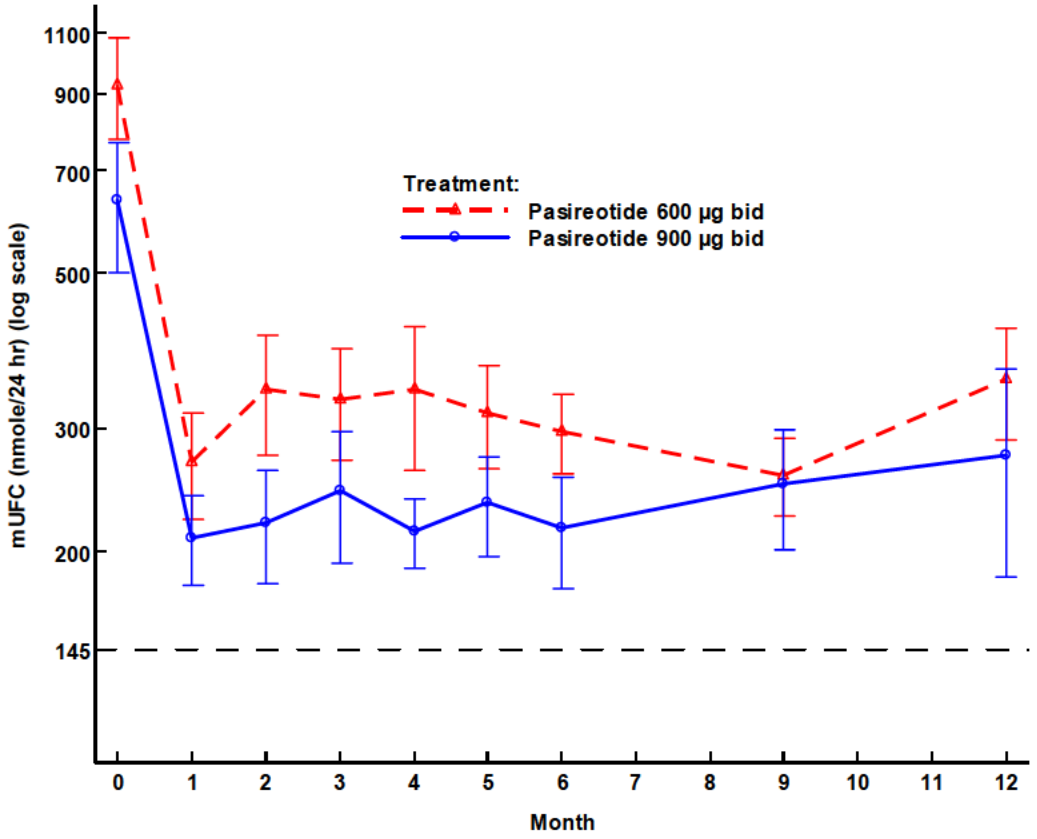
Figure 2: Mean (±SE) Urinary Free Cortisol (nmol/24h) at all Time Points up to Month 12 by Randomized Dose Group (Completers, n=39/group)



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

Table 10: Longitudinal analysis of mUFC % change from baseline

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

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

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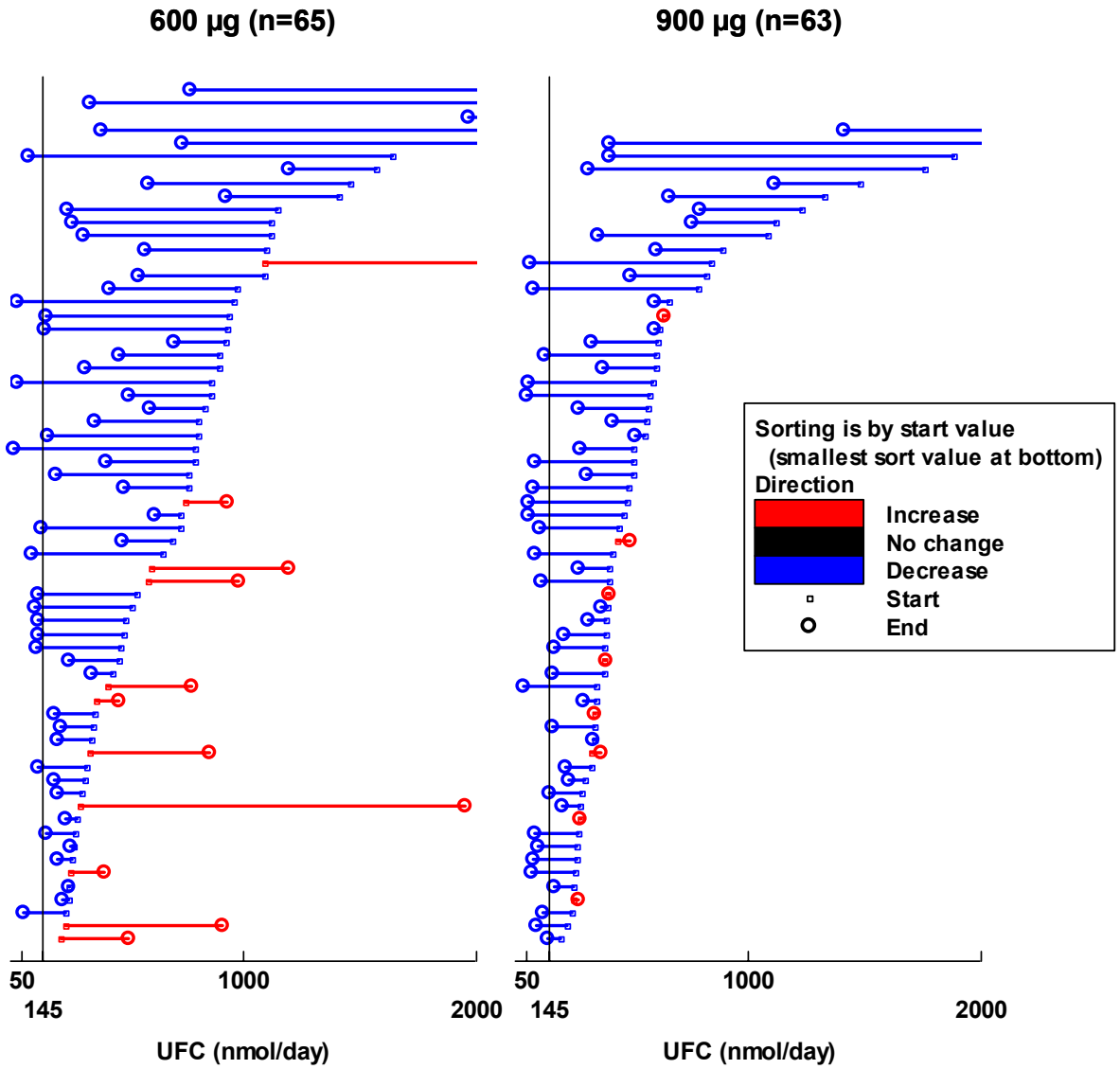
2.32 Individual UFC changes

Individual changes in mUFC from baseline are presented by randomized group in the figure below. Red lines represent increases from baseline, black lines (noticeable for the vast majority of patients) represent reductions. The upper limit of normal for urinary free cortisol (145 nmol/day) is indicated. In this graph individual values were calculated from a minimum of 3 measurements.

Figure 3: Individual UFC Changes from baseline to Month 6 in Study 2305



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2.33 Categorical efficacy analyses

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

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

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

*95% CI from exact method

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

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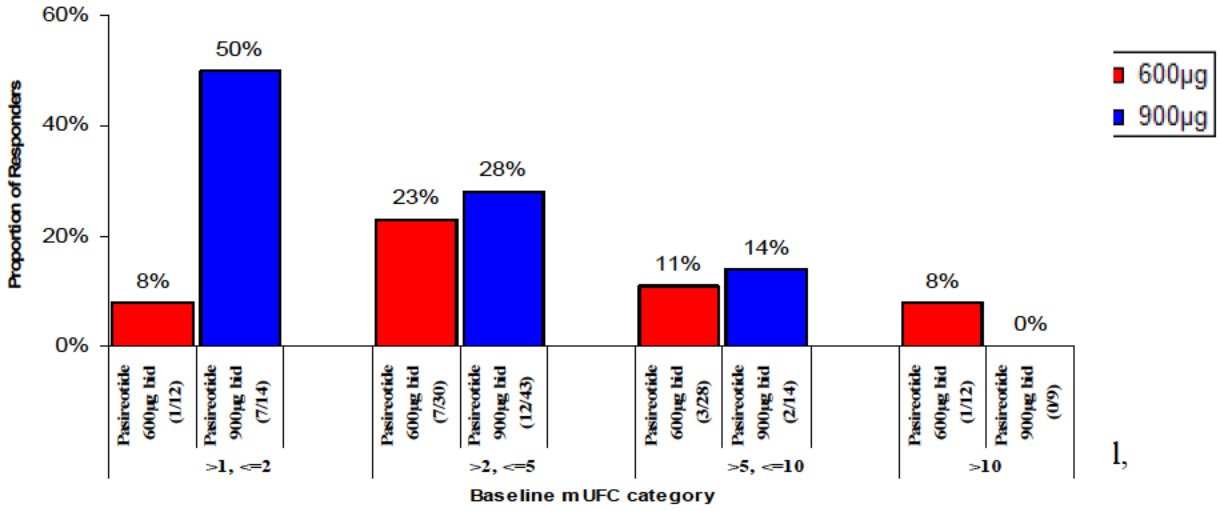
Figure 4: Percentages of mUFC primary responders by baseline mUFC category.



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

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

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

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

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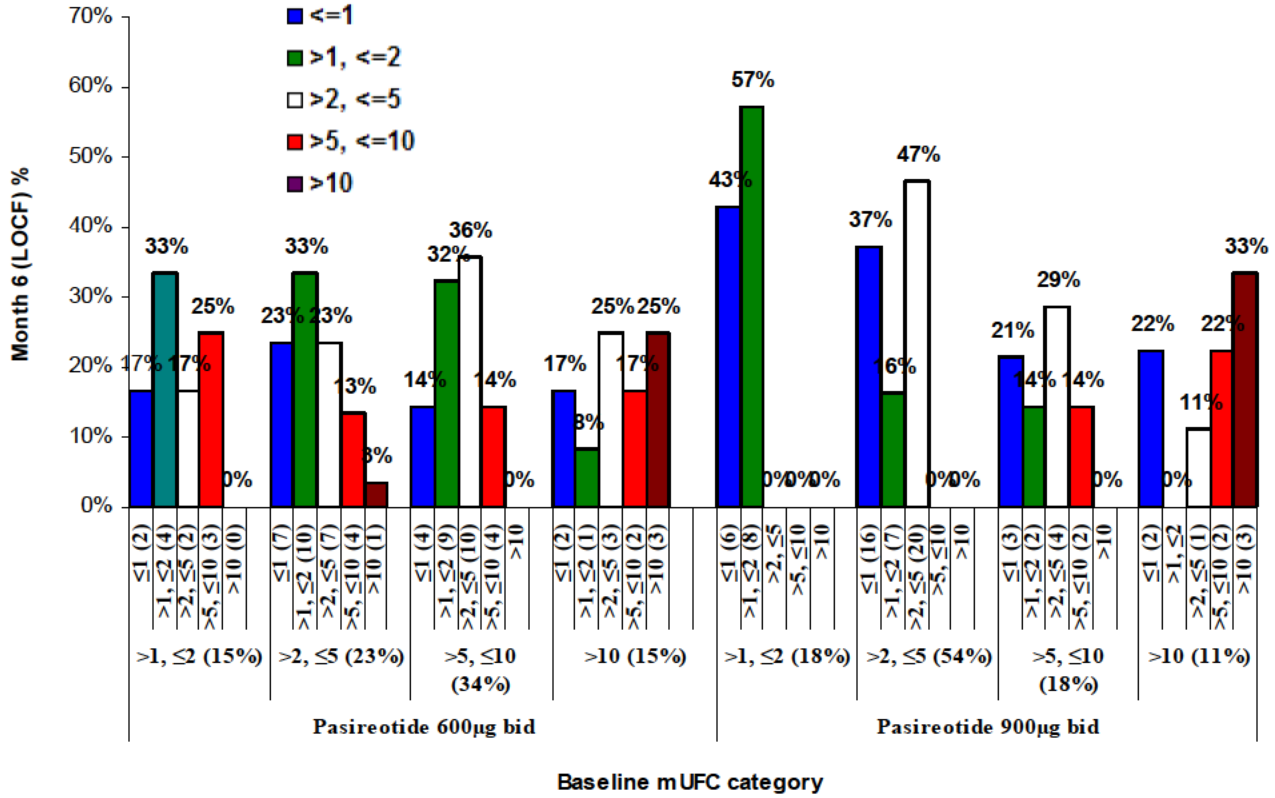
Figure 5: Shifts on treatment from baseline UFC categories (1-2, 2-5, 5-10, > 10x ULN) to Month 6 (LOCF)



2.34 Additional analyses of dose

Mean dose

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

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

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

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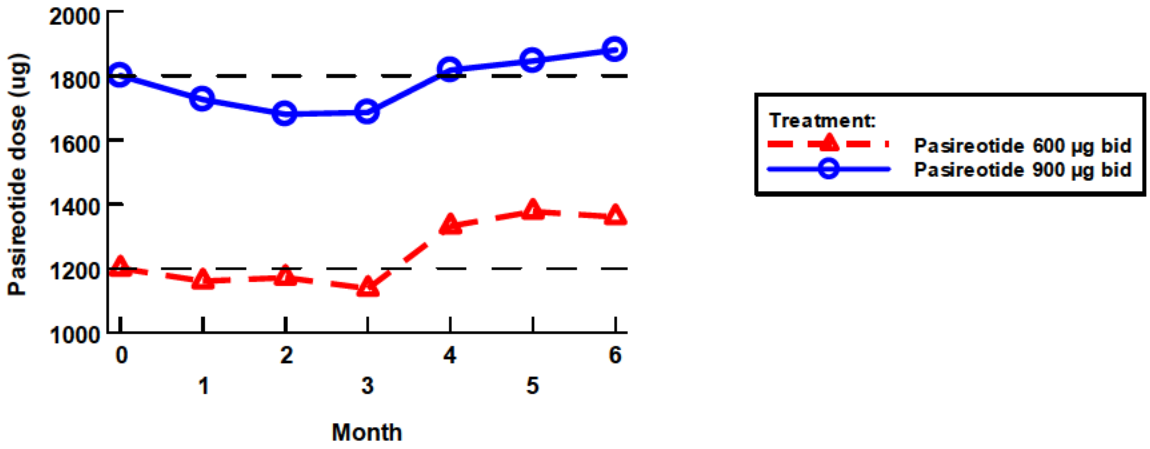
Figure 6: Mean total daily dose (prior to visit day) over time – Month 6 completers



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

Effect of dose change on responder status

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

Dose-clinical response correlations

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

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

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

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

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

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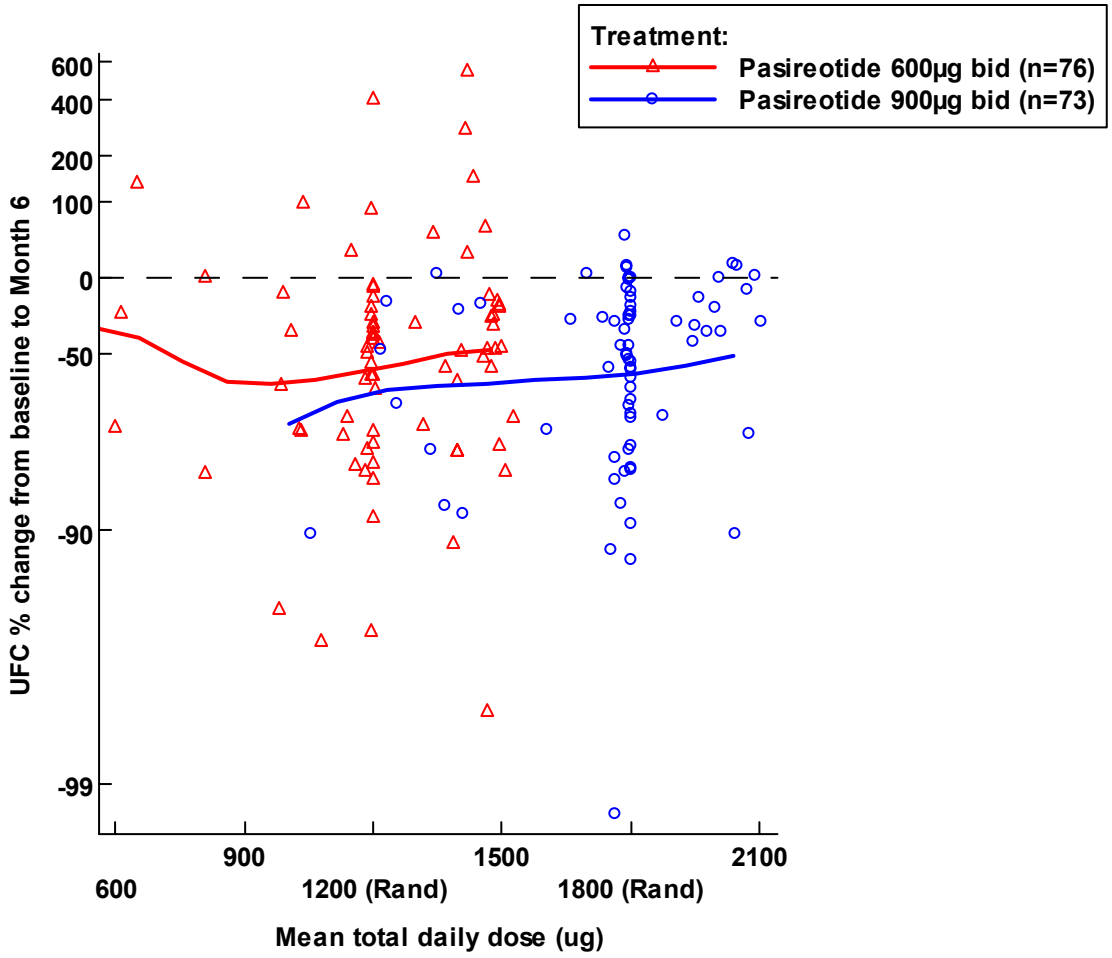
Figure 7: Percent change in mUFC as a function of mean total daily dose



2.4 Secondary and exploratory endpoints

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

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

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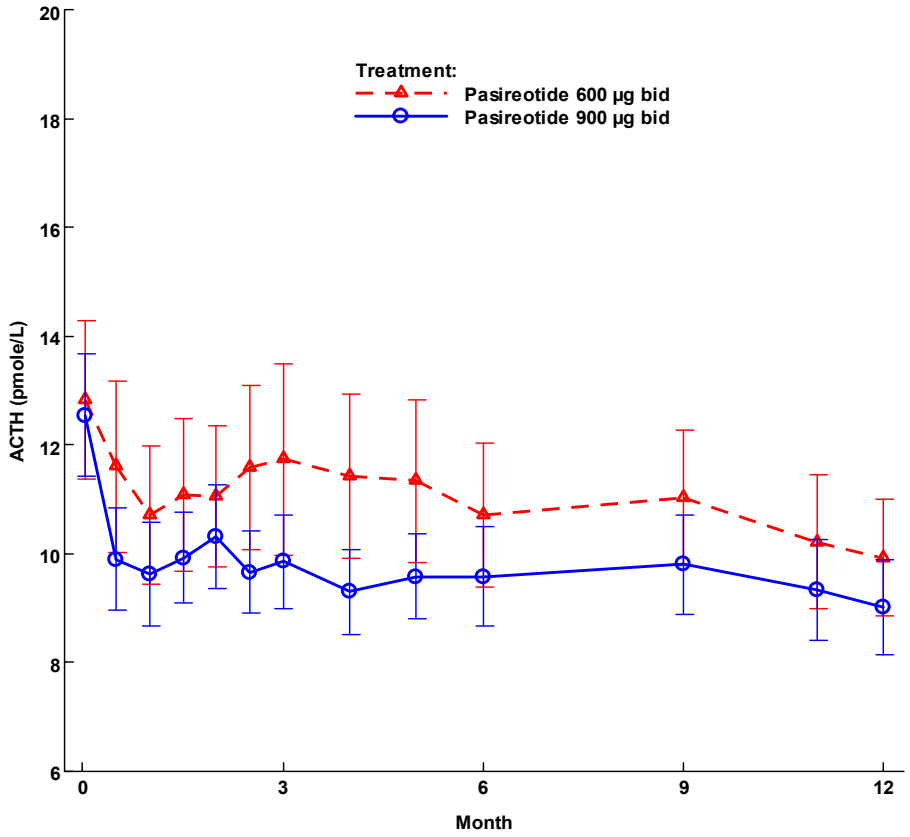
ACTH

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

Figure 8: Mean ACTH plasma concentrations



Blood pressure changes

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

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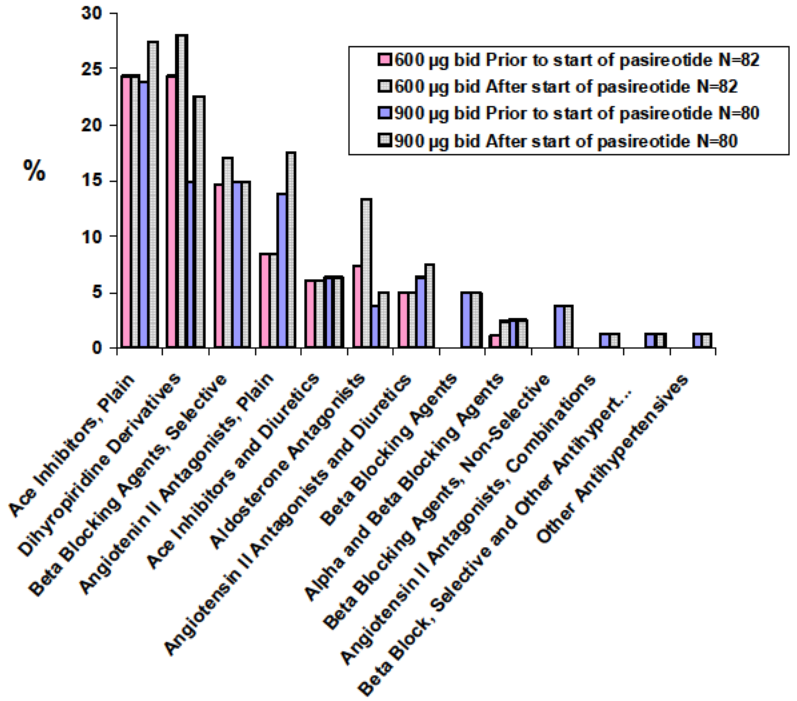
Table 15: Mean change from baseline in blood pressure by randomized dose group at Month 6

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

Applicant's 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. Information regarding the use of such drugs, including dose and duration, was not specifically collected. The general use of antihypertensives was, however, recorded in the same way as any concomitant medication. A general comparison of antihypertensives used at baseline versus during the trial is presented in Figure 9, which indicates that there was an increase in use in some categories of antihypertensives. Unfortunately, in the absence of a comparator group, the exact contribution of these changes in medication to the overall reductions in systolic and diastolic blood pressure cannot be accurately assessed.

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



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Quality of life

A Cushing's syndrome health related quality of life (HRQL) questionnaire was used in this trial.[4] A critical assessment is provided in the Study Endpoints and Labeling Development (SEALD) review, attached to this briefing document.

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

Items in the questionnaire are:

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

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

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

[4] 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.

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

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

Sponsor's Clinical Study Report, Table 11-11

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

Tumor volume

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

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

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

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

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

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

2.5 *Efficacy conclusions*

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

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

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

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

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

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

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

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3. Review of Safety

3.1 Drug Exposure

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

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

3.2 Deaths

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

3.3 Non-fatal serious adverse events

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

The most common reported SAE across dose groups were, in descending order, pituitary-dependent Cushing's syndrome (3.7%)[5], diabetes mellitus (2.5%), hyperglycemia (2.5%),

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

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

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

3.4 Trial discontinuations due to adverse events

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

3.5. Treatment-emergent adverse events

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

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Most frequent treatment-emergent adverse events (i.e. TEAEs present in > 50% of patients) were in the gastrointestinal disorders (80.9%), metabolism and nutrition disorders (74.7%), and general disorders and administration site conditions (54.3%) system organ class. Regardless of the overall frequency, the percentage of TEAEs was generally comparable between dose groups with the exception of psychiatric disorders, injury, poisoning & procedural complications, blood and lymphatic system disorders, ear and labyrinth disorders (however, the number of the patients contributing events in some of these groups was relatively small and therefore such group imbalances may simply reflect variability due to small numbers).

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

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

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

Adverse events that triggered dose adjustment or study interruption

Dose adjustment or temporary interruption of study drug because of an adverse event was seen in almost one-third of patients (55/162). The most common adverse events responsible for this course of action were nausea, diarrhea, hyperglycemia and adrenal insufficiency[6].

Finally, the most common AEs requiring additional therapy were (in the 600 µg vs. 900 µg bid groups) hyperglycemia (26.8% vs. 30.0% of patients), headache (17.1% vs. 21.3%

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

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of patients), nausea (8.5% vs. 22.2% of patients), diabetes mellitus (13.4% vs. 18.8%), and diarrhea (14.6% vs. 7.5% of patients).

3.6 Adverse events of special interest

The Sponsor categorized these AEs as follows:

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

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

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

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

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

The remainder of the discussion in this document focuses on the adverse events considered to be most vital in the safety assessment of this novel somatostatin analogue:

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hyperglycemia, liver test elevations, gastrointestinal events, hypocortisolism, bradycardia and QT prolongation, pancreatitis, and PTT/PT-INR elevations.

3.7. Glucose metabolism

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

3.71 Fasting Plasma Glucose

Mean fasting plasma glucose values by randomization group and time on trial are presented in Table 19, below. Baseline mean FPG values were in the normal range (i.e < 100 mg/dl); specifically they were 98.6 and 97.0 mg/dL, respectively for the 600 and 900 µg bid groups. A distinct elevation of mean FPG values was noticeable at the first post-baseline assessment at two weeks, and the FPG remained elevated throughout the trial. At early timepoints (primarily through Month 2) the mean FPG reached the diabetic range, and even though mean FPG decreased somewhat with time they did not normalize and remained at least in the pre-diabetic range throughout Month 12.[7]. Of note, one cannot support the conclusion that there was a decline in mean FPG between Month 3 and Month 12 because a significant number of patients discontinued the trial for a variety of reasons, including hyperglycemia and diabetes.

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

	Pasireotide 600 µg bid		**Pasireotide 900 µg bid**	
Visit	N	Mean (SD)	N	Mean (SD)
Baseline	79	98.6 (23.6)	79	97.0 (18.7)
Month 0.5	78	136.0 (57.0)	76	149.2 (68.1)
Month 1	76	138.8 (68.6)	72	153.4 (71.5)
Month 1.5	74	131.4 (57.0)	69	143.6 (57.0)
Month 2	70	133.7 (51.4)	67	138.4 (60.3)
Month 3	69	122.0 (41.5)	66	124.7 (52.1)
Month 4	68	122.1 (41.8)	61	124.9 (43.1)
Month 5	62	121.3 (33.9)	57	128.5 (46.3)

[7] The 2013 American Diabetic Association definitions:

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

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Month 6	57	125.1 (34.6)	55	128.0 (54.6)
Month 9	46	126.9 (35.9)	48	119.4 (33.1)
Month 12	39	120.9 (40.5)	38	114.4 (36.3)

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

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

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

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

3.7.2 Hemoglobin A1 c

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

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

	Pasireotide 600 µg bid		Pasireotide 900 µg bid	
Visit	n	Mean (SD)	N	Mean (SD)
Baseline	78	5.83 (0.78)	76	5.76 (0.79)
Month 2	73	7.24 (1.65)	66	7.41 (1.50)
Month 4	68	7.23 (1.49)	61	7.15 (1.17)
Month 6	59	7.24 (1.42)	56	7.34 (1.18)

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Month 8	49	7.31 (1.46)	46	7.36 (1.38)
Month 10	43	7.37 (1.35)	47	7.15 (1.33)
Month 12	40	7.25 (1.32)	38	7.21 (1.60)

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

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

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

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

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

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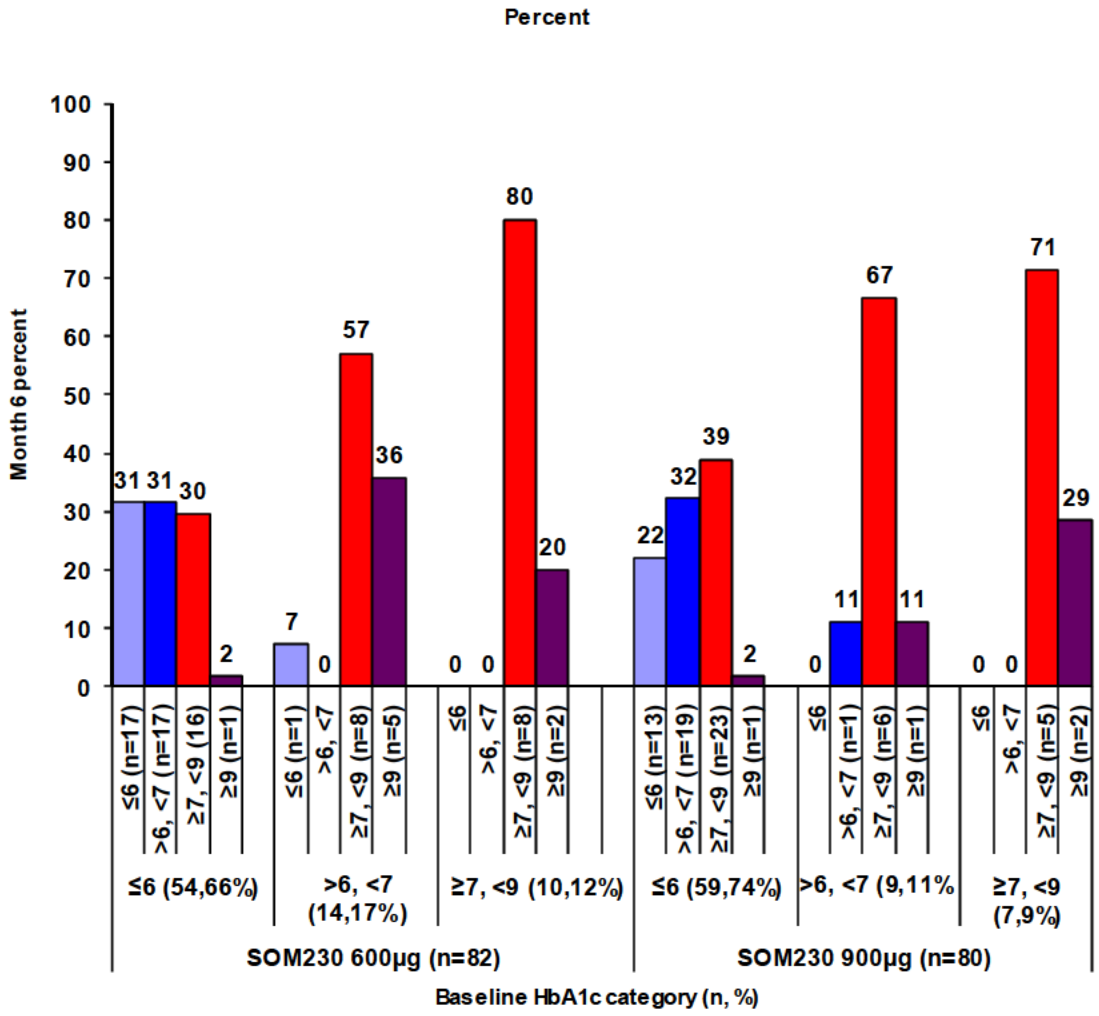
Figure 10: Shift in HbA1c from baseline to last value up to Month 6 by randomized dose group



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

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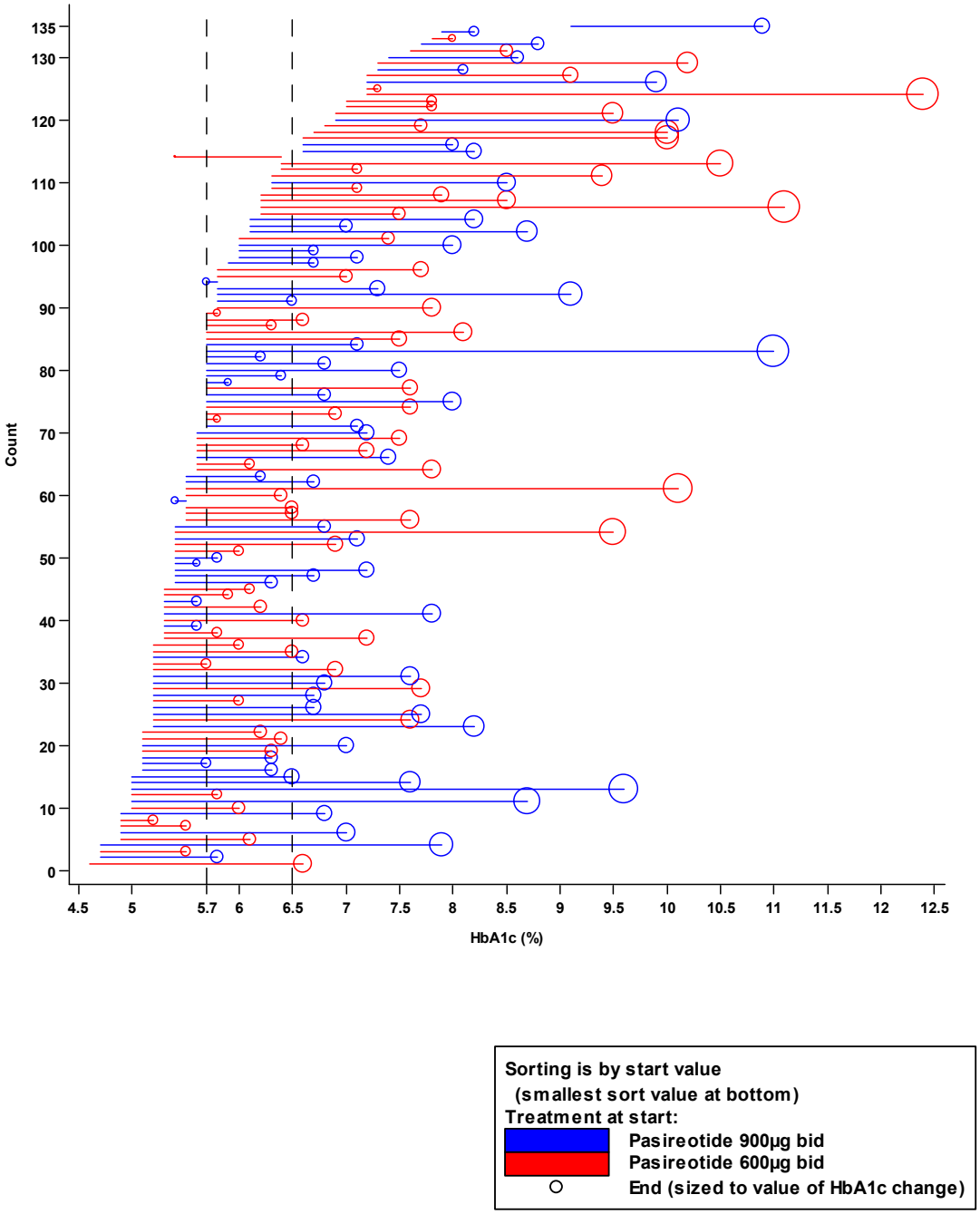
Figure 11: Individual changes in HbA1c from baseline to Month 6



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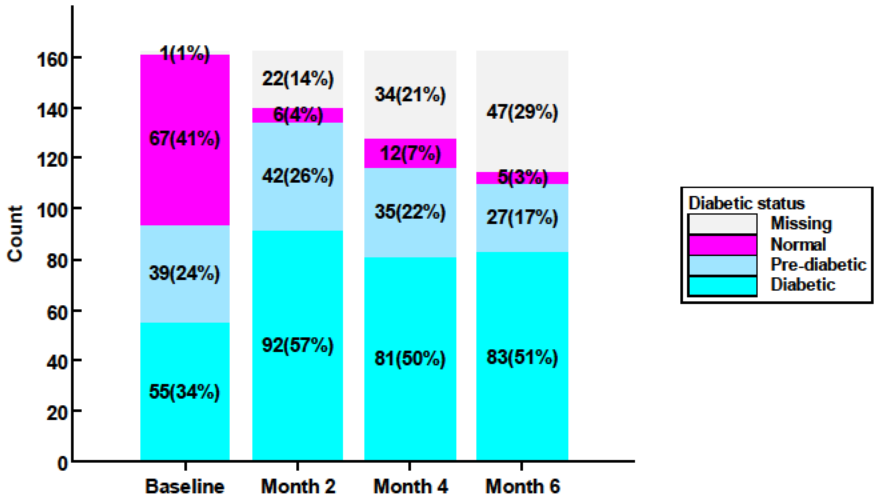
3.7.3 Shifts in diabetes status during the trial

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

Figure 12: Changes in pre-diabetes and diabetes status



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

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

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

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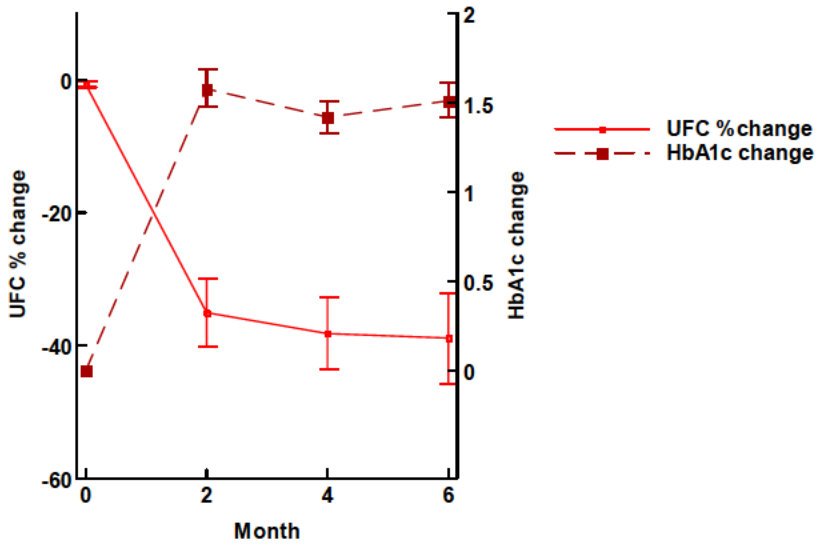
Figure 13: mUFC and HbA1c changes from Baseline (Completers)



3.7.4 Changes in antidiabetic medications

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

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

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

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

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

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

3.7.5 Measures of glycemia after treatment discontinuation

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

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

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

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

3.8 Liver and Gallbladder Events

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

3.8.1 Elevations in liver enzymes

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

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

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

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

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

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

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

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

Reference ID: 3212809

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[8]

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

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

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

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

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

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

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

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

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

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

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Table 28: Liver laboratory values—Subject PHHO2010AU13717

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

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

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

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

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

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

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

Reference ID: 3212809

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

3.8.2 Gallbladder and biliary-related adverse events

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

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

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

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

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

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

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

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

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

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

3.9 Gastrointestinal adverse events

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

3.10 Hypocortisolism

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

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

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

3.11 Bradycardia and QT prolongation

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

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

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

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

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

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

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

3.12 Changes in coagulation parameters

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

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

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

3.13 Safety Conclusions

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

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

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

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

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

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

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Appendix 1: Listing of Clinical Trials

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

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

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

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

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

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

From Sponsor's Summary of Clinical Safety

Reference ID: 3212809

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

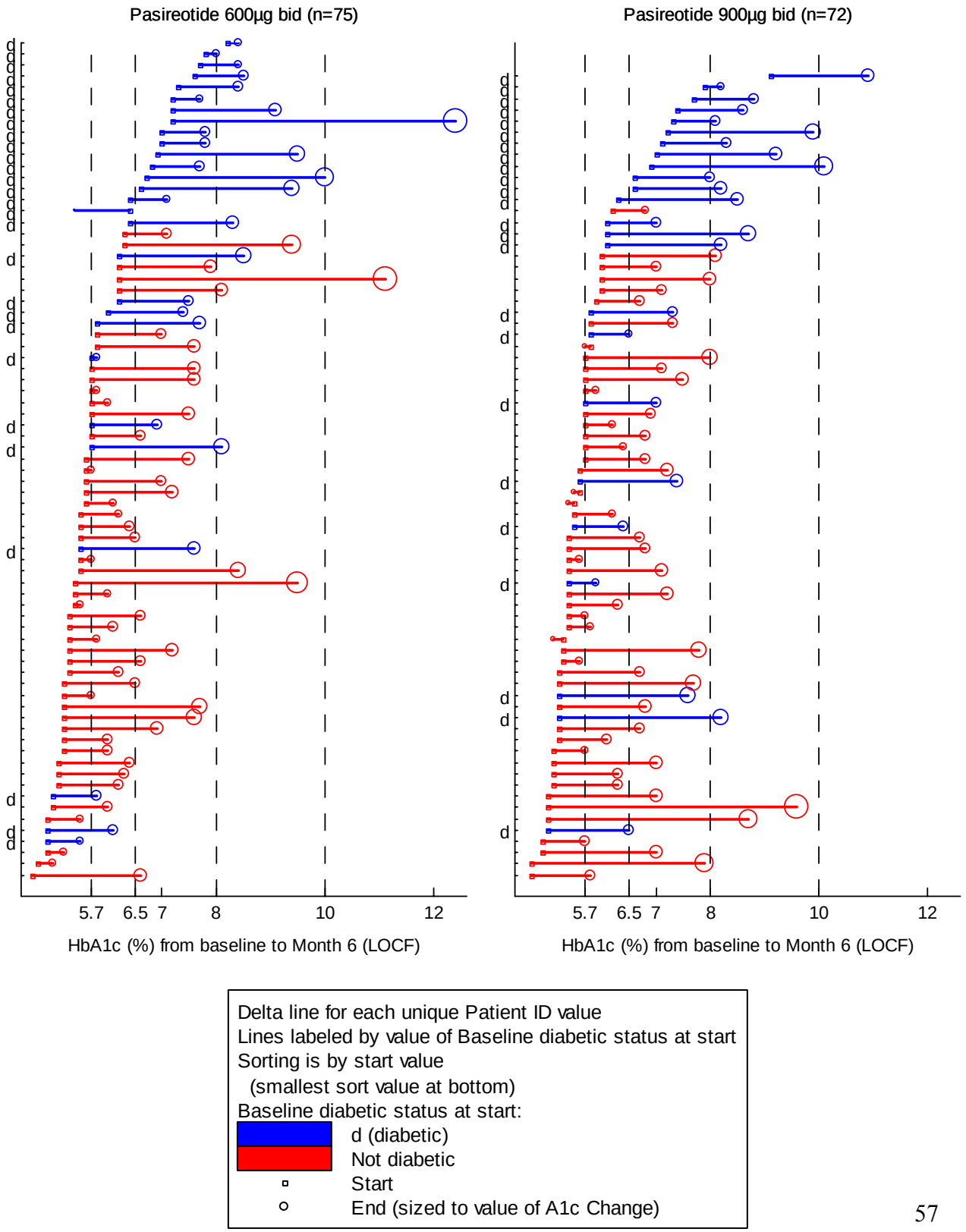
Study	Study objective	# of patients	Treatment duration	Dosage
Acromegaly				
B2103	Double-blind randomized 3-way crossover to compare efficacy of single doses of SOM230 and sandostatin	12	Single doses with 6 day washout	octreotide 100 µg pasireotide 100 µg and 250 µg
B2201	Open-label, randomized, crossover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

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

Reference ID: 3212809

Appendix 2: Individual HbA1c changes

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



Appendix 3: Additional Efficacy Analyses

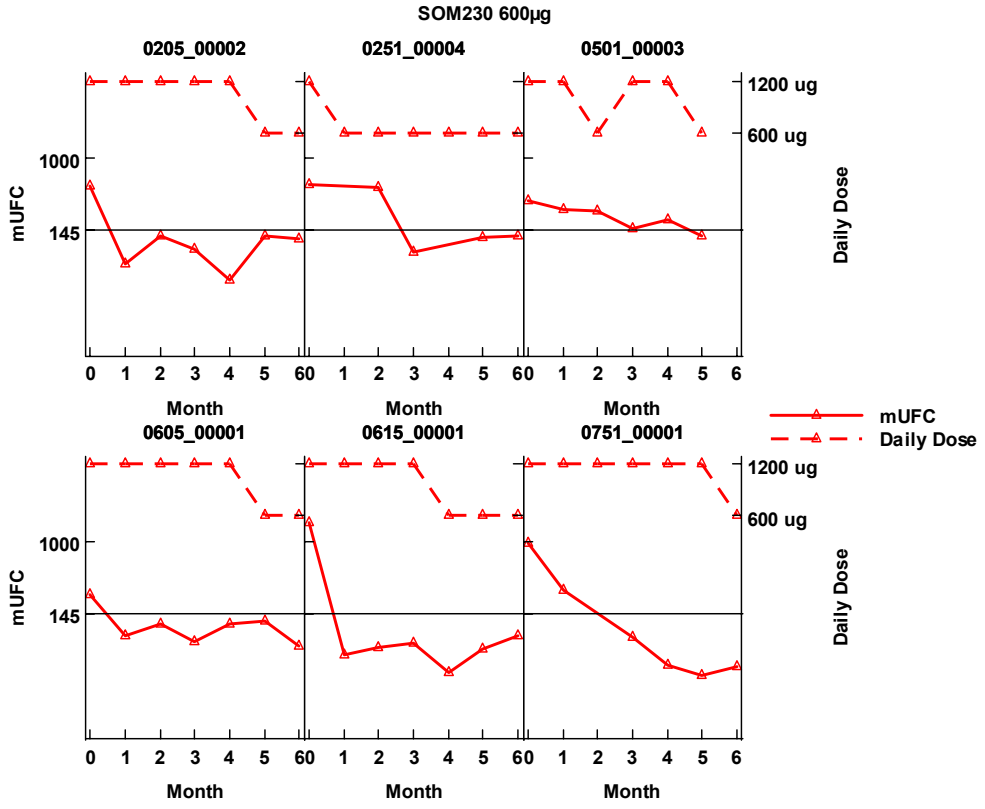
Dose reduction in responders

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

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

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

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



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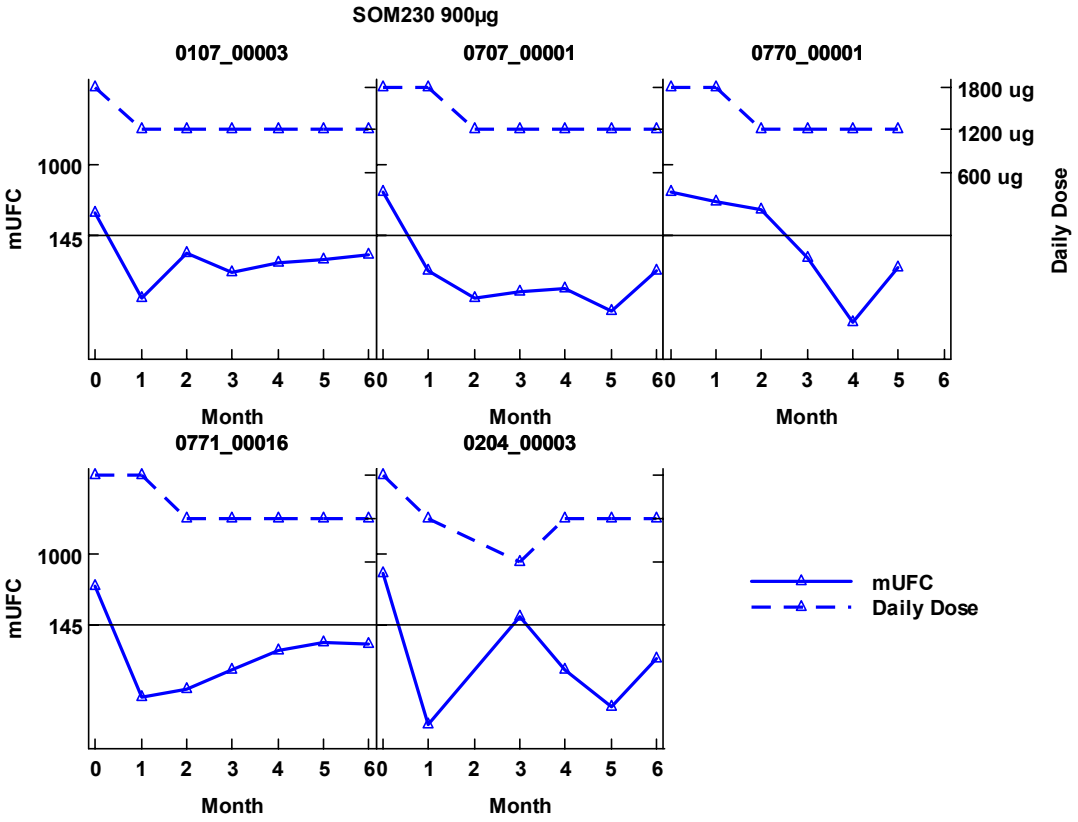
SOM230 900µg
0107_00003
0707_00001
0770_00001
0771_00016
0204_00003
mUFC
1000
145
1800 ug
1200 ug
600 ug
Daily Dose
0 1 2 3 4 5 6
Month
mUFC
Daily Dose

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

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

From Sponsor's Clinical Study Report

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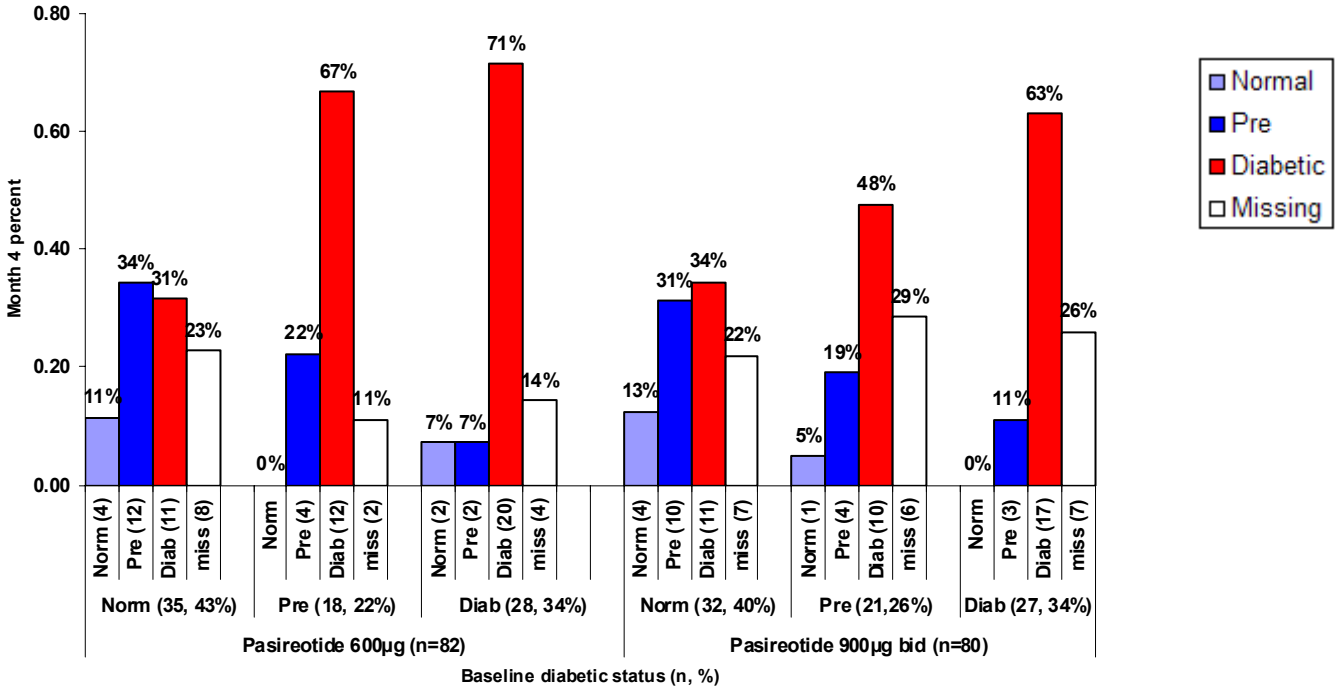
Appendix 4: Shift tables for diabetic status at Month 4

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

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

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



Sponsor's Glucose Metabolism Report, Table 5-35

Reference ID: 3212809

Appendix 5: Additional Hepatic Safety Analyses

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

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

Results for studies in healthy volunteers are presented first.

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

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

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

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

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

From Sponsor's Hepatic Report, Table 4-1
[1]AxT=AST or ALT
[2]=moxifloxacin (active control used in B2113 and B2125 thorough QT studies)
[3]=One additional subject had a concomitant elevation of ALT>3xULN and TB≥2xULN, but the ALP was not measured and therefore this subjects is not captured in this table.

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

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

Patient trials

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

Table 39: Liver enzyme and total bilirubin in patient trials

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

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

From Sponsor's Hepatic Report, Table 4-2
[1]=AST or ALT
[2]Percentages based on number of patients who had a non-missing post-baseline assessment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

From Sponsor's Hepatic Report, Table 4-17

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

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

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

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

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

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

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

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

Applicant's Glucose Metabolism Report

Study 2124

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

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

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

The reductions seem to be consistent with studies in which these drugs were administered to patients with type 2 diabetes or healthy subjects.[9] The greatest effect was seen with

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

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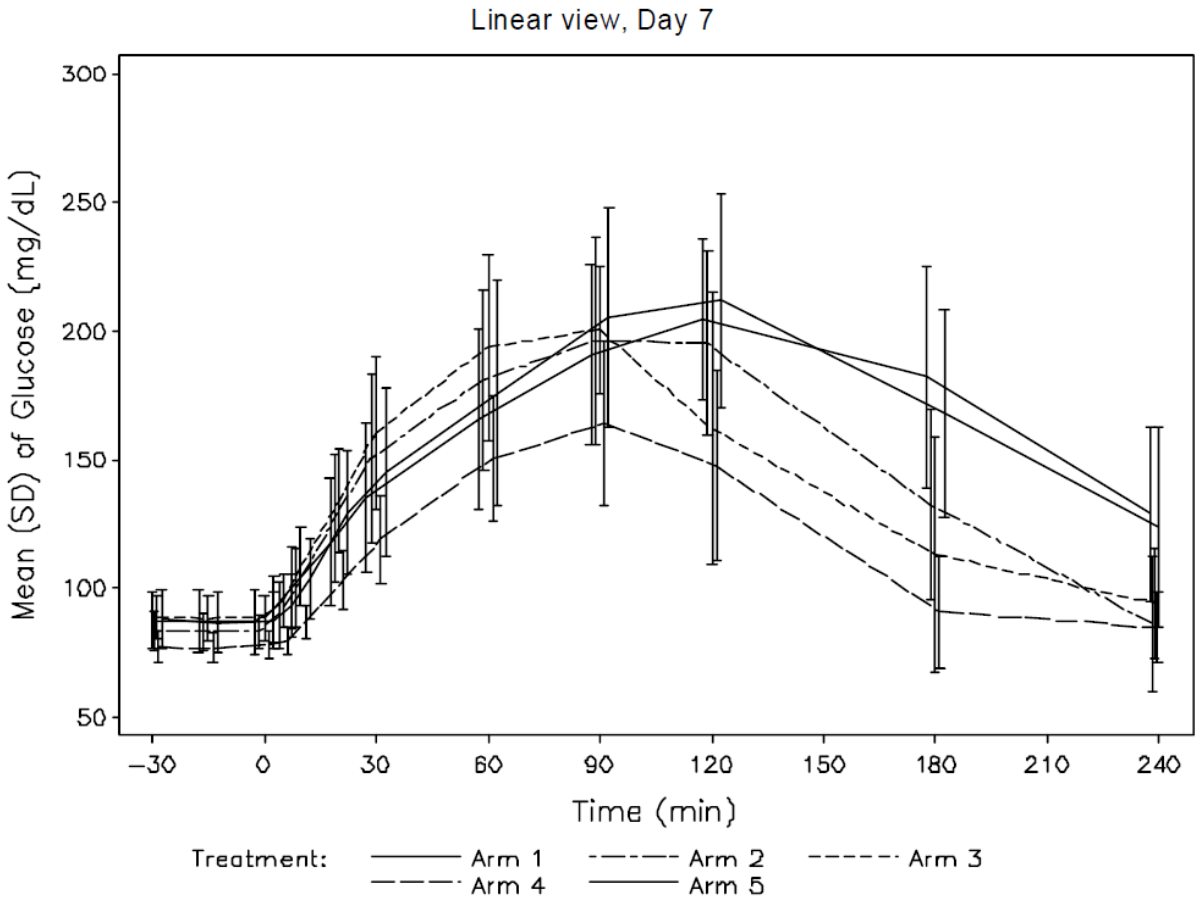
liraglutide. No antihyperglycemic effect was observed with metformin. However, the Sponsor hypothesizes that the lack of effect is consistent with metformin's mechanism of action to decrease hepatic glucose production and to improve insulin sensitivity by increasing peripheral glucose uptake, which are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

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



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

From Applicant's Glucose Metabolism Report

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

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

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

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

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

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

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

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

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

Reference ID: 3212809

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11/05/2012

JON T SAHLROOT
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Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 200677
Drug name:	SOM230
Indication(s):	Cushing's Disease
Applicant:	Novartis Pharmaceuticals Corporation
Documents Reviewed:	Electronic submission Electronically submitted dataset Dated: 2011-08-01
Review Priority:	
Biometrics Division:	Division of Biometrics 6
Statistical Reviewer:	Matthew Jackson, PhD
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Medical Division:	Division of metabolism and endocrinology products
Reviewing Pharmacologist:	Miyun Tsai-Turton, Ph.D.
Project Manager:	Jennifer Johnson
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Background

In this submission the sponsor included reports of two animal carcinogenicity studies, in mice and rats, to assess the carcinogenic potential of SOM230 when administered by injection, once daily at appropriate drug levels for about 26 weeks (in the mouse study) or 104 weeks (in the rat study). Results of this review have been discussed with the reviewing pharmacologist, Miyun Tsai-Turton, Ph.D..

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Chapter 1

Summary of findings

1.1 Mouse study

The mouse study is problematic. While there are no positive findings to report, it is notable that animals in the low and mid dose groups were not, in general, fully examined, and so have been excluded from analysis. On the other hand, the numbers of tumors reported in the high dose group are so low that it is unlikely that there could have been enough unobserved tumors in the low and mid dose groups to generate a positive finding. Furthermore, given the ECAC's current view that a significant finding in the pairwise comparison of the control and high dose groups is a prerequisite for a positive finding, we can conclude that regardless of the results in the intermediate groups, it would not have been possible to achieve statistical significance.

In addition, the sponsor has failed to submit data from the positive control group, and the concurrent wild type arms.

As in most studies of transgenic mice, the mortality rates were very low, suggesting that the dose levels were not excessive. However, the fact that there does appear to be a dose related reduction in weight gain suggests that the dose levels were reasonably close to the MTD.

Ultimately, there does appear to be sufficient evidence to consider this a negative study, rather than ultimately inconclusive.

1.2 Rat study

The rat study is a negative study. The only potentially significant finding is for fibromas in male rats, but when combined with fibrosarcomas, the result ceases to be significant. The overall levels of mortality were low, but the reductions in observed weight gain suggest that the dose levels were nonetheless adequate.

Chapter 2

Mouse Study

2.1 Experimental design

The study was conducted on a mixture of CB6F1 wild type and CB6F1/TgrasH2 hemizygous mice. The study comprised two separate groups of experiments; one in male mice and one in female mice. Each experiment comprised five groups of hemizygous mice (with twenty five animals per group) and two groups of wild type mice (twenty five animals per group).

One group of wild type mice and one group of hemizygous mice were designated the control groups; animals in these groups received daily doses of the acetate buffer solution (sodium acetate trihydrate (1234 mg/L), acetic acid, (956.6 mg/L), mannitol (43.5 g/L) and sterile Water) by subcutaneous injection, for a dose volume of 10 mL per kilogram of bodyweight.

Three groups of hemizygous mice, and the remaining group of wild type mice, received the test article, SOM230 , with this same vehicle, for daily doses of 0.5, 1, and 2.5 mg/kg (hemizygous mice), and 2.5 mg/kg (wild type mice). In addition, the remaining group of hemizygous mice received a single dose (75 mg/kg) of N-methyl-N-nitrosourea by intraperitoneal injection.

The study was conducted conducted for 26 weeks. During this period, the animals were checked for mortality twice a day, and for clinical signs weekly. In additional, animals underwent palpation exams weekly from the second week. The sponsor reports that all animals underwent a full necroscopy after death (regardless of the cause of death):

> Complete necropsies, including macroscopic observations, were performed on all main study animals. Protocol-specified organs were weighed and tissues were collected and microscopically examined.

However, the organs of the animals in the 0.5 mg/kg and 1 mg/kg dose groups have not, in general, been microscopically analyzed.

2.2 Sponsor's analysis

The sponsor does not appear to have conducted statistical analyses of either tumor incidence rates or mortality.

Regarding survival data, the sponsor concludes that "There was no treatment-related mortality or moribundity with SOM230 based on the animal survival data at the end of the study." Given the very low rates of mortality reported in the study, the decision to omit statistical analyses of mortality is reasonable.

Regarding tumor findings, the sponsor reports that "[t]here were no SOM230-related neoplastic observations."

2.3 Data analysis

This is a study in transgenic mice. In addition to the control group and the three treated groups, three additional groups of mice were included in the study: a positive control group, and two groups of wildtype mice; one receiving the control vehicle and one receiving the test article at a daily dose level of 2.5mg/kg (a level equal to the high dose group). Unfortunately, at time of writing, the sponsor has not submitted electronic datasets for additional groups, and so these groups have not been analyzed. The only analyses conducted are a comparison of the treated hemizygous mice with the control hemizygous mice.

As noted above, the animals in the low and mid dose groups appear not to have undergone full necroscopies. This means that these groups are of little use for our analysis: in those cases where organs have been microscopically analyzed and tumors found, the data can not be compared with tumor findings in the control and high dose groups. This is because the endpoint in the low or mid dose group is " a possible tumor was found, either through palpation or visual inspection, and which was subsequently identified microscopically". The numbers of such findings can clearly not be compared with the numbers of cases of "a tumor was found through routine microscopic investigation", which is the endpoint of interest in the control and high dose groups. For this reason, the decision has been made to exclude the low and mid dose groups from the analysis, and treat the mice experiments as two group experiments.

2.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 2.1 and 2.2. The numbers and proportions of animals surviving to various times are presented in table A.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table A.2, and the results of log-rank survival tests comparing the treated groups with the control group are presented in table A.3.

As is often the case in studies of transgenic mice, the mortality rates are extremely low in both sexes. There is no indication of any dose related increase in mortality.

2.3.2 Tumor analysis

Endpoints

Analyses have been conducted using the sponsor's submitted dataset, and the sponsor's chosen nomenclature. In this dataset, organs or tissue types are described as being either tumorous, examined but found unusable due to autolysis, or unexamined. An organ that has been examined but was not found to be tumorous is not mentioned in the dataset.

From these data, we can infer the numbers of animals for which each organ or tissue type was examined, but only in those cases where at least one anomalous finding (i.e., a tumor was found, or a sample that was planned to be analyzed could not be, either because no sample was taken or because the sample was unusable due to autolysis) was reported. Organs which can thus be deduced to have been successfully analyzed in the majority of animals are, for the purposes of this review, considered *primary*. The lists of primary organs in the experiments on female and male mice respectively are presented in tables A.4 and A.5.

Organ or tissue types which were examined in only a few animals are considered *secondary*.

Secondary organs in the male and female mouse experiments are presented in tables A.6 and A.7 respectively.

Each tumor type found in a primary organ of at least one animal is considered a primary endpoint. In addition, in consultation with Miyun Tsai-Turton, Ph.D., a list of combination endpoints has been drawn up. This list is presented in table A.8.

Statistical procedure

The tumor data were analyzed for pairwise comparisons of tumor incidence in the high dose group versus the vehicle control group. These comparisons were performed using the poly-k method

Figure 2.1: Survival curves for female mice

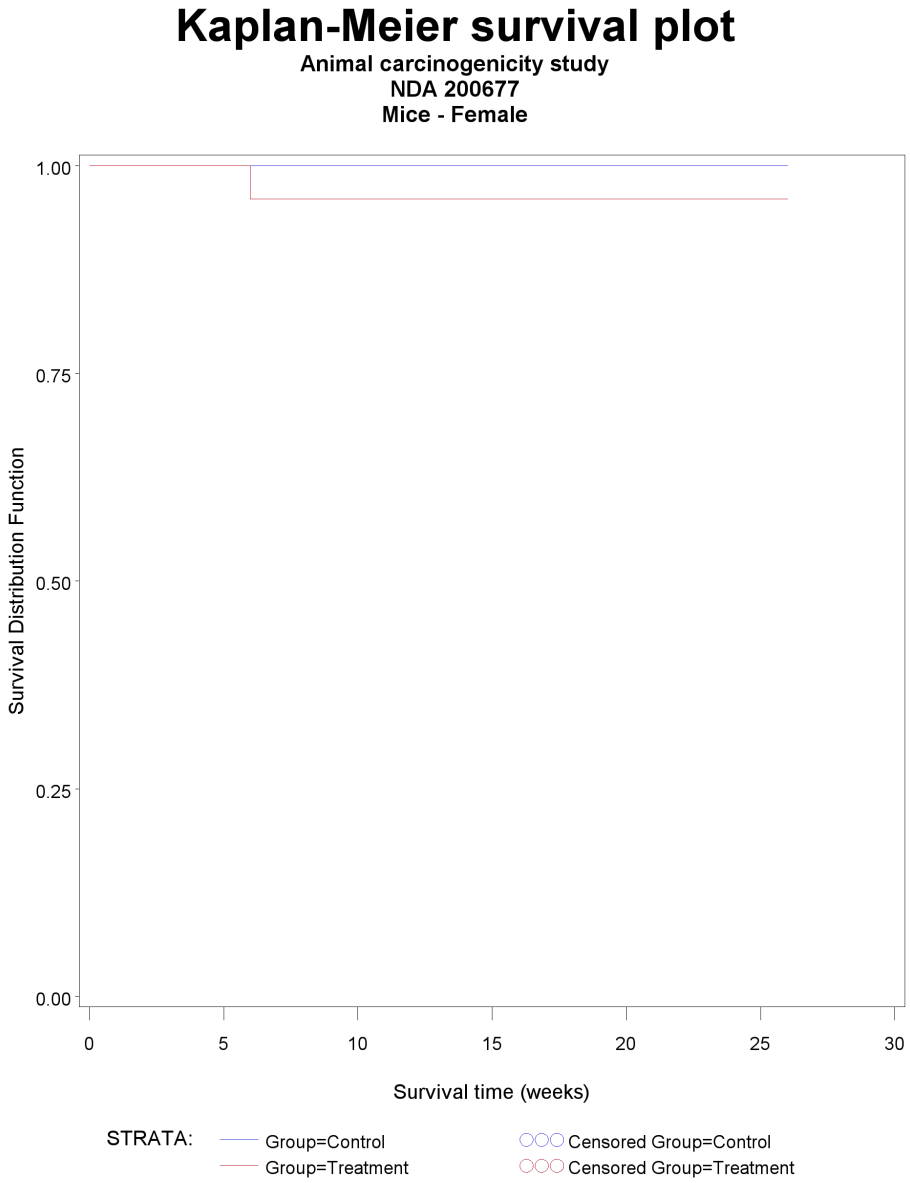
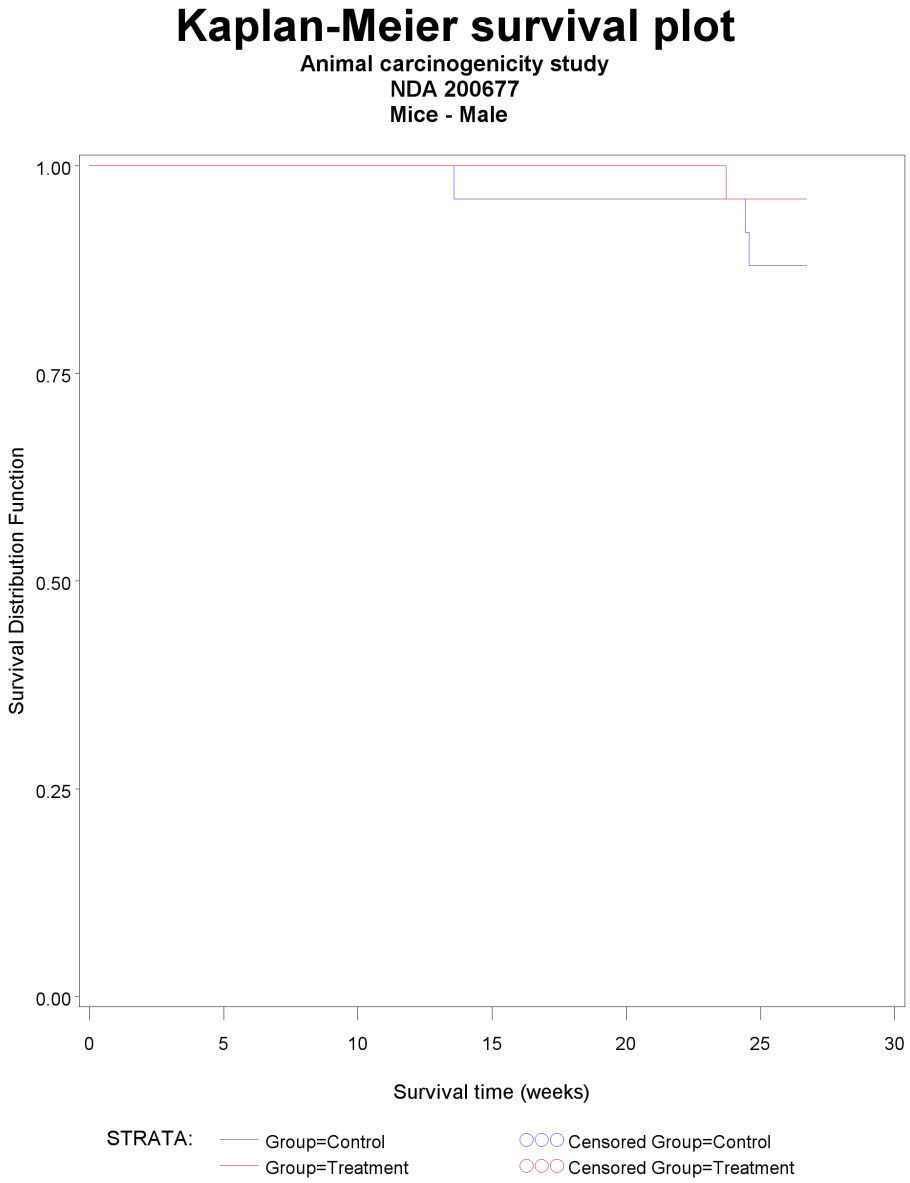


Figure 2.2: Survival curves for male mice



described in the paper of Bailer and Portier[1] and developed in the paper of Bieler and Williams[2]. In this method, given a tumor type T, an animal h that lives the full study period (w_m) or dies before the terminal sacrifice with at least one tumor of type T gets a score of $s_h = 1$. An animal that dies at week w_h before the end of the study without such a tumor gets a score of

$$s_h = \left(\frac{w_h}{w_m}\right)^k < 1.$$

The adjusted group size is defined as $\sum_h s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops at least one tumor of type T, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. The test is repeated for each tumor type T.

One critical point to consider in the application of the poly-k test is the choice of the appropriate value of k, which depends on the relationship between tumor onset time and increased dose. There is no consensus for the correct value to use for studies of transgenic mice. In the absence of such a consensus, this review uses the value $k = 1$, a value which is consistent with the assumption of constant hazard over the twenty six week period of the study. In any event, when there is little premature mortality (as is typically the case with transgenic mouse studies — see section 2.3.1), the analyses are not very sensitive to variations in the value of k.

For the calculation of p-values, the exact permutation method was used.

Under normal circumstances, since so many end points are being tested, it is appropriate to make some sort of multiplicity adjustment in order to control type I error. However, in the case of transgenic mice there is no guidance specifying how this should be done. Furthermore, in light of the fact that exact tests tend to be very conservative when considering rare events, the fact that there are only twenty five animals in each group, and the fact that tumorigenesis is very rare over the twenty six weeks that transgenic mouse studies typically run, it seems reasonable to consider each test as having yielded positive findings whenever the p-value is below 0.05.

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables A.9 (female mice) and A.10 (male mice). The results of analyses of customized endpoints (see table A.8) are presented in tables A.11 and A.12.

Noteworthy results

No statistical tests were conducted in either sex for which the reported p-value was below 0.05. No tumors were reported in any secondary organs.

2.3.3 Analysis of unexamined and autolytic organs

As noted above, the animals from the low and mid dose groups have generally not had most of their organs analyzed, and so have been excluded from the analysis.

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

The numbers of organs found in female mice to be autolytic to the extent that analysis of collected tissue was not possible are presented in table A.13. No organs in male mice were found to be autolyzed to this extent.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables A.14 and A.15. The only noteworthy finding is that the male mice have generally not had their mammary glands examined.

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Chapter 3

Rat Study

3.1 Experimental design

The study was conducted on a Wistar Hannover rats. The study comprised two separate experiments; one in male rats and one in female rats. Each experiment comprised four groups of rats (with fifty animals per group).

One group was designated the control groups; animals in these groups received daily doses of the acetate buffer solution (sodium acetate trihydrate (1234 mg/L), acetic acid, (956.6 mg/L), mannitol (43.5 g/L) and sterile Water) by subcutaneous injection, for a dose volume of 1 mL per kilogram of bodyweight. The remaining three groups received the test article, SOM230 , with this same vehicle, for daily doses of 0.01, 0.05, and 0.3 mg/kg. These groups were denoted the *low dose*, *mid dose*, and *high dose* groups, respectively.

The study was conducted conducted for 104 weeks. During this period, the animals were checked for mortality twice a day, and for clinical signs weekly. In additional, animals underwent palpation exams weekly from the twenty sixth week. Upon death, all animals underwent a full necroscopy.

3.2 Sponsor's analysis

3.2.1 Survival analysis

A two tailed log rank test of homogeneity of survival was conducted, with no significant results ($p = 0.3965$ for the male rats, and $p = 0.0944$ for the female rats) being recorded.

3.2.2 Tumor analysis

A list of tumor types and tumor combinations eligible for analysis was determined before analysis began. Some individual endpoints (tumors of the sub cutaneous tissue, for example) were not planned for individual analysis, but only in combination with other endpoints. Analyses were conducted using the Peto method [6].

Among male rats, a possibly significant finding for fibromas (whole body) was found, but was not present when fibromas and fibrosarcomas were combined. The sponsor concludes that there is no evidence of a test article effect.

3.3 Data analysis

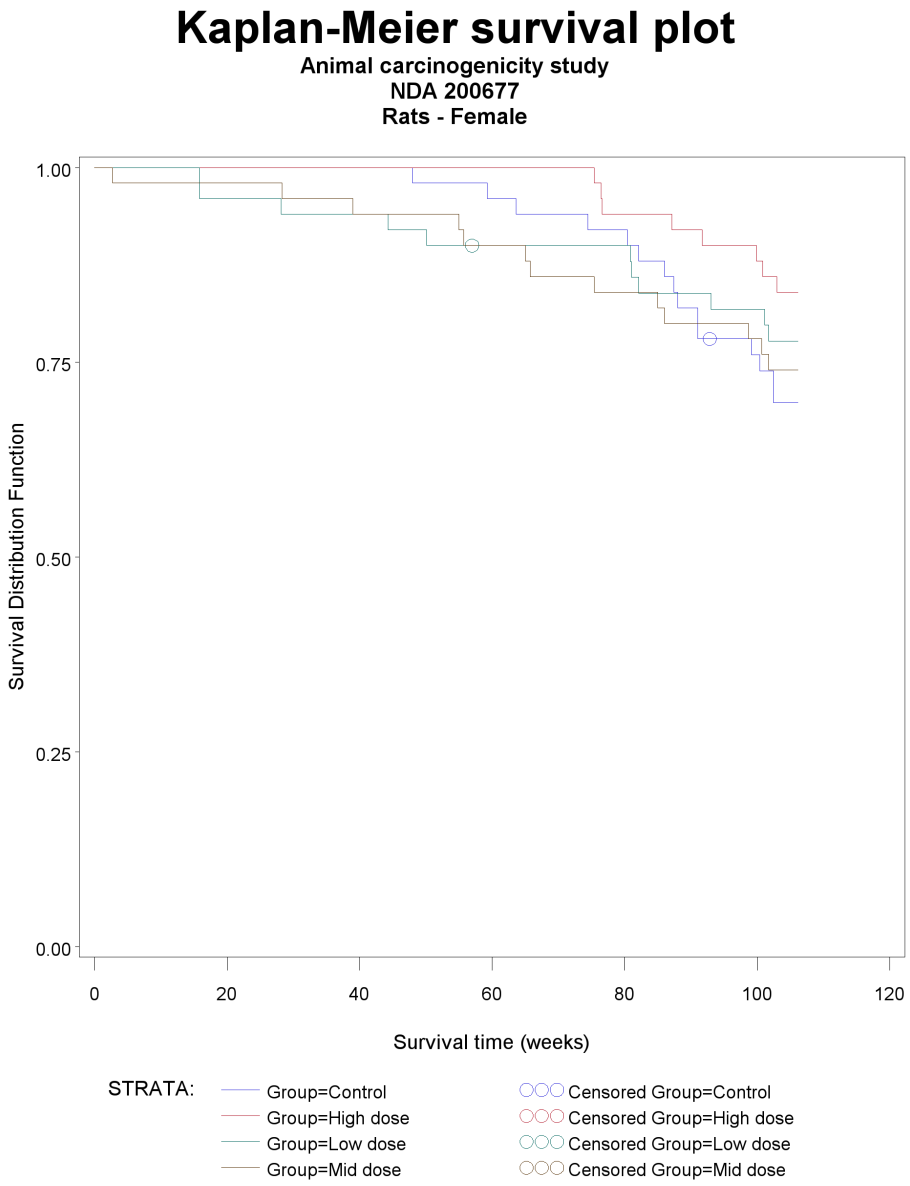
3.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 3.1 and 3.2. The numbers and proportions of animals surviving to various times are presented in table B.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table B.2, and the

results of log-rank survival tests comparing the treated groups with the control group are presented in table B.3.

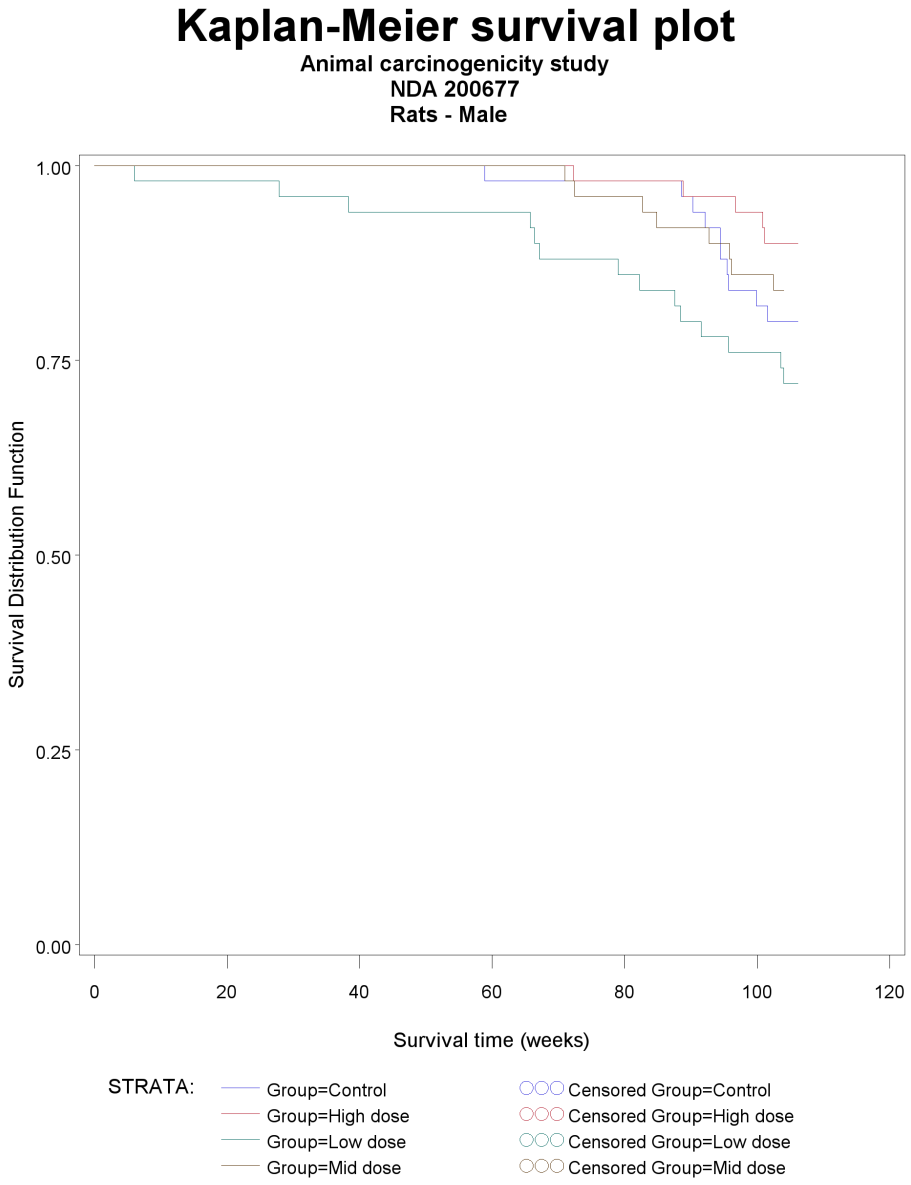
Survival was generally very good in both male and female rats. Visual inspection of figure 3.2 suggests that the low dose male rats experienced higher mortality than the other groups, but neither the contrast of the low dose group with the control group ($p = 0.2420$), nor the test of heterogeneity across all four groups ($p = 0.1154$) yielded significant results. There is thus no evidence of a dose related effect on mortality.

Figure 3.1



Commentry

Figure 3.2


Kaplan-Meier survival plot
Animal carcinogenicity study
NDA 200677
Rats - Male
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
120
Survival time (weeks)
STRATA:
Group=Control
Group=High dose
Group=Low dose
Group=Mid dose
Censored Group=Control
Censored Group=High dose
Censored Group=Low dose
Censored Group=Mid dose

3.3.2 Tumor analysis

Endpoints

As in the mouse study, organs have been classed as either primary or secondary (see Section 2.3.2). The lists of organs adduced to be primary are presented in tables B.4 and B.5. Secondary organs in the male and female rat experiments are presented in tables B.6 and B.7 respectively.

The same customized endpoints have been analyzed as were considered in the mouse study (see table A.8).

Statistical procedure

As with the mouse study (see Section 2.3.2), the tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the control group, using the poly-k method described in the paper of Bailer and Portier[1] and developed in the paper of Bieler and Williams[2].

Again, it is critical consider the choice of the appropriate value of k, which depends on the relationship between tumor onset time and increased dose. For long term 104 week standard rat and mouse studies, a value of $k = 3$ is suggested in the literature, and so has been used in this review. For the calculation of p-values, the exact permutation method was used.

For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of significance levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for a submission with two species, and a significance level $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control, the FDA guidance suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors, for both submissions with one or two species, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman [5]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin [7] showed that this rule for multiple testing for dose response relationship is also suitable for poly-k tests.

Since this is a study involving two species, it follows that for the comparisons of SOM230 with control, we use the thresholds for significance presented in table 3.1.

Table 3.1: Critical p-values used to determine statistical significance

Type of test	Rare tumor	Common tumor
Trend	0.025	0.005
Pairwise test between placebo and high dose	0.05	0.01

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables B.8 (female rats) and B.9 (male rats). The results of analyses of customized endpoints (see table A.8) are presented in tables B.10 and B.11.

Noteworthy results

No statistical tests were conducted in the female rat experiment which resulted in p-values below 0.05. Individual tumor types in male rats for which tests yielding p-values below 0.05 were conducted are presented in table B.12, which is excerpted from table B.9. No tests of customized or combination tumor types were conducted that yielded p-values below 0.05.

Incidence rates for tumors found in secondary organs have not been analyzed statistically. Count data for such tumors are presented in table B.13.

Fibromas in male rats The only findings for which any tests have yielded p-values below 0.05 are for fibromas in male rats. In the case of fibromas at the injection site, the test of trend yields a p-value of 0.0219 (with four such tumors being detected; three among the high dose animals and one in a mid dose animal). The pairwise test between the high dose and control group does not yield a significant p-value ($p = 0.1250$), so is not normally be an especially worrying finding. Furthermore, when fibrosarcomas are included in the analysis, there is no indication of any dose related response (the only reported injection site fibrosarcoma was in a control animal).

The test of trend for subcutaneous fibromas also yields a p-value below 0.05 ($p = 0.0455$). However, this result fails to be significant, even by the standards of rare tumors (and there is no reason to consider this an especially rare outcome), so this should be considered a negative finding.

3.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

No rats were reported as having any organs autolyzed to the extent that a usable sample was not obtainable.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables B.14 and B.15. Some skin sites are noted as being frequently unexamined: SKIN MISC and SUBCUT. TISSUE. The sponsor claims that although microscopic examinations were not conducted on many animals, it was nonetheless assumed that all neoplasia in these sites would nonetheless have been detected at necropsy.

Chapter 4

Assessment of the validity of a negative study

4.1 Issues of concern when selecting the dose levels

The selection of an appropriate dose level for the high dose group is made difficult by the need to satisfy two competing imperatives: on the one hand, if the dose level is insufficiently high, then genuine carcinogenicity effects may not be apparent, but on the other hand, if the dose level is too high, then there is a risk of non-carcinogenic toxic effects killing the animals before they have a chance to demonstrate a carcinogenicity effect.

Haseman [4] suggested that a satisfactory balance between these two imperatives has been found when the following two conditions are both satisfied:

1. Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?

2. Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman [4] has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80—90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward [3], suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80–90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward [3], the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met:

1. A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls.

2. The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.

3. In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls.

4.2 Assessment of the validity of the mouse study

The general rules of thumb are not applicable for transgenic mouse studies. However, it should be noted (see table A.16) that although there was no indication of a dose related increase in mortality, there is clear evidence that the high dose group experienced considerably less weight gain than the other groups, and hence that the does levels were close to, and possibly in excess of, the MTD.

However, in this case the validity of the study is called into question by the experimental design; the fact that the low and mid dose animals were not analyzed according to the same protocol as the control and high dose animals means that they cannot be included in this analysis. Consequently, this must be considered a two group study. Accordingly, the mouse experiments convey less information than is normally the case, and care must be taken when making negative inferences from the data.

On the other hand, given the negative findings in the comparisons between the control and high dose groups, it seems extremely unlikely that any positive findings are being obscured by the unobserved data from the low and mid dose groups. Furthermore, given the ECAC's current posture – that significant results in both the trend and pairwise test are necessary to conclude a positive finding – the absence of significant results in the pairwise test is itself sufficient to conclude that no finding that met the ECAC's criteria could be present.

4.3 Assessment of the validity of the rat study

In the case of the rat study, survival rates are good, with at least 34 animals in each group surviving the full 104 weeks. Accordingly there is no concern that excessive toxicity has been a problem in this study. There is no indication of a dose related effect on survival in either sex. However, there is clear evidence of a dose related reduction in weight gain, so we can be reasonably confident that the dose levels were satisfactory without being excessive.

Appendix A

Tables from mouse study

A.1 Survival analysis

Table A.1

Survival rates at key times
NDA 200677
Animal carcinogenicity study
Mice

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 12 weeks*	*Percentage alive after 12 weeks*	*Number alive after 19 weeks*	*Percentage alive after 19 weeks*	*Number alive after 22 weeks*	*Percentage alive after 22 weeks*	*Number sacrificed*	*Percentage sacrificed*	*Maximum surivial (weeks)*
Mice - Female	Control	0	25	25	100%	25	100%	25	100%	24	96%	27
	Treatment	2.5	25	24	96%	24	96%	24	96%	23	92%	27
Mice - Male	Control	0	25	25	100%	24	96%	24	96%	22	88%	27
	Treatment	2.5	25	25	100%	25	100%	25	100%	24	96%	27

Table A.2

Log-rank tests of survival
NDA 200677
Animal carcinogenicity study
Mice

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	0.3388	1	2	0.5605	0.5605	0.2802
Male	1.0423	1	2	0.3073	0.3073	0.8464

Table A.3

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 200677
Animal carcinogenicity study
Mice

Species and Sex	*Quantity*	*Treatment*
Mice - Female	Chi squared test statistic	0.3388
	p-value of comparison with control	0.5605
Mice - Male	Chi squared test statistic	1.0423
	p-value of comparison with control	0.3073

A.2 Tumor analysis

Table A.4

Primary organs in study of female mice
NDA 200677
Animal carcinogenicity study

Organ or tissue name
CECUM
ESOPHAGUS
HARDERIAN GL
ILEUM
JEJUNUM
KIDNEYS
LUNGS
SKIN
SPLEEN
STOMACH
UTERUS

Reference ID: 3207508

Table A.5

Primary organs in study of male mice
NDA 200677
Animal carcinogenicity study

Organ or tissue name
LUNGS
SPLEEN
THYMUS

Reference ID: 3207508

Table A.6

Secondary organs in study of female mice
NDA 200677
Animal carcinogenicity study

Organ or tissue name
GUMS/GINGIVA

Reference ID: 3207508

Table A.7

Secondary organs in study of male mice
NDA 200677
Animal carcinogenicity study

Organ or tissue name
GUMS/GINGIVA
MAMMARY

Reference ID: 3207508

Table A.8

Customized and combination endpoints analyzed
NDA 200677
Animal carcinogenicity study

Composite endpoint
Adenomas and adenocarcinomas of the stomach
Adenomas and carcinomas of the stomach and small intestine
All fibromas and fibrosarcomas
All hemangiomas and hemangiosarcomas
Endometrial stromal polyps and sarcomas of the uterus
Fibromas and fibrosarcomas (injection site)
Fibromas and fibrosarcomas (subcutaneous tissue)
Hemangiomas and hemangiosarcomas (injection site)
vaginal polyps and endometrial stromal polyps and sarcomas of the uterus

Reference ID: 3207508

Table A.9

Table of reported tumors in Mouse Study
NDA 200677
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 25*	*Treatment Size = 25*
HARDERIAN GL	ADENOMA, SINGLE	P-value of test of comparison		.4898
		Number of animals reported with tumor	0	1
KIDNEYS	ADENOMA RENAL TUBULE, cystic, multi	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
LUNGS	ADENOMA BRONCHIOALVEOLAR, SINGLE	P-value of test of comparison		.7449
		Number of animals reported with tumor	1	1
SKIN	HEMANGIOSARCOMA	P-value of test of comparison		.4898
		Number of animals reported with tumor	0	1
SPLEEN	HEMANGIOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
STOMACH	HEMANGIOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
UTERUS	POLYP ENDOMETRIAL STROMAL	P-value of test of comparison		.7449
		Number of animals reported with tumor	1	1

Reference ID: 3207508

Table A.10

Table of reported tumors in Mouse Study
NDA 200677
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 25*	*Treatment Size = 25*
LUNGS	ADENOMA BRONCHIOALVEOLAR, MULTIPLE	P-value of test of comparison		.5106
		Number of animals reported with tumor	0	1
	ADENOMA BRONCHIOALVEOLAR, SINGLE	P-value of test of comparison		.9781
		Number of animals reported with tumor	4	1
	CARCINOMA BRONCHIOALVEOLAR	P-value of test of comparison		.5208
		Number of animals reported with tumor	0	1
SPLEEN	HEMANGIOSARCOMA	P-value of test of comparison		.7660
		Number of animals reported with tumor	1	1

Table A.11

Table of reported tumors in Mouse Study
NDA 200677
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 25*	*Treatment Size = 25*
All hemangiomas and hemangiosarcomas	P-value of test of comparison		.8752
	Number of animals reported with tumor	2	1
Endometrial stromal polyps and sarcomas of the uterus	P-value of test of comparison		.7449
	Number of animals reported with tumor	1	1
vaginal polyps and endometrial stromal polyps and sarcomas of the uterus	P-value of test of comparison		.7449
	Number of animals reported with tumor	1	1

Reference ID: 3207508

Table A.12

Table of reported tumors in Mouse Study
NDA 200677
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 25*	*Treatment Size = 25*
All hemangiomas and hemangiosarcomas	P-value of test of comparison		.7660
	Number of animals reported with tumor	1	1

A.3 Unexamined and autolytic organs

Table A.13

Organs reported as autolytic
NDA 200677
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Treatment(count)*	*Treatment(%)*	*Total(count)*	*Total(%)*
CECUM	.	.	1	4.0%	1	2.0%
ILEUM	.	.	1	4.0%	1	2.0%
JEJUNUM	.	.	2	8.0%	2	4.0%

Reference ID: 3207508

Table A.14

Organs reported as unexamined
NDA 200677
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Treatment(count)*	*Treatment(%)*	*Total(count)*	*Total(%)*
ESOPHAGUS	.	.	1	4.0%	1	2.0%
GUMS/GINGIVA	25	100%	25	100%	50	100%

Table A.15

Organs reported as unexamined
NDA 200677
Animal carcinogenicity study
Male Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Treatment(count)*	*Treatment(%)*	*Total(count)*	*Total(%)*
GUMS/GINGIVA	25	100%	25	100%	50	100%
MAMMARY	24	96%	24	96%	48	96%
THYMUS	1	4.0%	2	8.0%	3	6.0%

Reference ID: 3207508

A.4 Bodyweight changes

Table A.16: Weight changes by group (mice)

Sex	Control	SOM230					
	Δ_{C_P}	Δ_L	$\frac{\Delta_L}{\Delta_{C_P}} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_{C_P}} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_{C_P}} - 1$
Female	6.2	4.5	-27%	4.7	-24%	4.2	-32%
Male	10.3	7.3	-29%	6.3	-39%	6.9	-33%

Appendix B

Tables from rat study

B.1 Survival analysis

Table B.1

Survival rates at key times
NDA 200677
Animal carcinogenicity study
Rats

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 52 weeks*	*Percentage alive after 52 weeks*	*Number alive after 78 weeks*	*Percentage alive after 78 weeks*	*Number alive after 90 weeks*	*Percentage alive after 90 weeks*	*Number sacrificed*	*Percentage sacrificed*	*Maximum surivial (weeks)*
Rats - Female	Control	0	50	49	98%	46	92%	41	82%	34	68%	106
	Low dose	0.01	50	45	90%	44	88%	41	82%	38	76%	106
	Mid dose	0.05	50	47	94%	42	84%	40	80%	37	74%	106
	High dose	0.3	50	50	100%	47	94%	46	92%	42	84%	106
Rats - Male	Control	0	50	50	100%	49	98%	48	96%	40	80%	106
	Low dose	0.01	50	47	94%	44	88%	40	80%	36	72%	106
	Mid dose	0.05	50	50	100%	48	96%	46	92%	40	80%	106
	High dose	0.3	50	50	100%	49	98%	48	96%	45	90%	106

Table B.2

Log-rank tests of survival
NDA 200677
Animal carcinogenicity study
Rats

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	2.9683	3	4	0.3965	0.1276	0.9362
Male	5.9241	3	4	0.1154	0.0439	0.9781

Table B.3

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 200677
Animal carcinogenicity study
Rats

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Rats - Female	Chi squared test statistic	0.6412	0.1275	2.6679
	p-value of comparison with control	0.4233	0.7210	0.1024
Rats - Male	Chi squared test statistic	1.3691	0.0006	1.5469
	p-value of comparison with control	0.2420	0.9802	0.2136

B.2 Tumor analysis

Table B.4

Primary organs in study of female rats
NDA 200677
Animal carcinogenicity study

Organ or tissue name
ADRENAL
BRA N
CECUM
CLITORAL GL
EYE
HEMOLYM. TISSUE
INJECTION SITE
JEJUNUM
KIDNEY
L N. MESENTERIC
L N.TRACHEO.
LIVER
LUNG
MAMMARY GL
OVARY
PANCREAS
PITUITARY
SKIN
THYMUS
THYRO D
UTERUS
VAGINA

Reference ID: 3207508

Table B.5

Primary organs in study of male rats
NDA 200677
Animal carcinogenicity study

Organ or tissue name
ADRENAL
BRA N
HEMOLYM. TISSUE
INJECTION SITE
JEJUNUM
L N. MESENTERIC
L N.TRACHEO.
LIVER
LUNG
PANCREAS
PITUITARY
PROSTATE
SKIN
SPLEEN
STOMACH
TESTIS
THYMUS
THYRO D

Reference ID: 3207508

Table B.6

Secondary organs in study of female rats
NDA 200677
Animal carcinogenicity study

Organ or tissue name
ABDOMEN
BONE MISC.
FAT
LYMPH NODE
MUSC.SKEL MISC.
SK N MISC.
SUBCUT. TISSUE
THORAX

Reference ID: 3207508

Table B.7

Secondary organs in study of male rats
NDA 200677
Animal carcinogenicity study

Organ or tissue name
ABDOMEN
BONE MISC.
FAT
LYMPH NODE
MAMMARY GL
MUSC.SKEL MISC.
SK N MISC.
SUBCUT. TISSUE
THORAX
VAS DEFERENS

Reference ID: 3207508

Table B.8

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
ADRENAL	Adenoma: cortical	P-value of test of trend or comparison	.4189	1	1	.8519
		Number of animals reported with tumor	3	0	0	2
	Benign pheochromocytoma	P-value of test of trend or comparison	.5256		.2412	
		Number of animals reported with tumor	0	0	2	0
BRAIN	Benign granular cell tumor	P-value of test of trend or comparison	.5940	1	.8751	.8950
		Number of animals reported with tumor	2	0	1	1
	Benign mixed glioma	P-value of test of trend or comparison	.2701			.5222
		Number of animals reported with tumor	0	0	0	1
	Malignant astrocytoma	P-value of test of trend or comparison	.5115		.4941	
		Number of animals reported with tumor	0	0	1	0
	Malignant oligodendroglioma	P-value of test of trend or comparison	.7543	.5000		
		Number of animals reported with tumor	0	1	0	0
CECUM	Adenocarcinoma	P-value of test of trend or comparison	.2701			.5222
		Number of animals reported with tumor	0	0	0	1
CLITORAL GL	Adenoma	P-value of test of trend or comparison	.7469	.4875		
		Number of animals reported with tumor	0	1	0	0
EYE	Leiomyoma: uvea	P-value of test of trend or comparison	.7529	.4941		
		Number of animals reported with tumor	0	1	0	0
HEMOLYM. TISSUE	Histiocytic sarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Malignant lymphoma	P-value of test of trend or comparison	.2701			.5222
		Number of animals reported with tumor	0	0	0	1
INJECTION SITE	Hemangioma	P-value of test of trend or comparison	.7529	.4941		
		Number of animals reported with tumor	0	1	0	0
	Keratoacanthoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
JEJUNUM	Leiomyoma	P-value of test of trend or comparison	.5115		.4941	

Reference ID: 3207508

Table B.8

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
		Number of animals reported with tumor	0	0	1	0
KIDNEY	Liposarcoma	P-value of test of trend or comparison	.7529	.4941		
		Number of animals reported with tumor	0	1	0	0
L.N. MESENTERIC	Hemangioma	P-value of test of trend or comparison	.5256		.2412	
		Number of animals reported with tumor	0	0	2	0
L.N.TRACHEO.	Sarcoma (not otherwise specified)	P-value of test of trend or comparison	.5000		.5000	
		Number of animals reported with tumor	0	0	1	0
LIVER	Adenoma: hepatocellular	P-value of test of trend or comparison	.8446	.8126	.6507	.9517
		Number of animals reported with tumor	3	2	3	1
	Carcinoma: hepatocellular	P-value of test of trend or comparison	.7529	.4941		
		Number of animals reported with tumor	0	1	0	0
LUNG	Adenoma: alveolar/bronchiolar	P-value of test of trend or comparison	.7529	.4941		
		Number of animals reported with tumor	0	1	0	0
MAMMARY GL	Adenocarcinoma	P-value of test of trend or comparison	.8797	.3431	.2298	.8461
		Number of animals reported with tumor	3	5	6	2
	Adenoma	P-value of test of trend or comparison	.7927	.9391	1	.9517
		Number of animals reported with tumor	3	1	0	1
	Fibroadenoma	P-value of test of trend or comparison	.8273	.3748	.0635	.6799
		Number of animals reported with tumor	8	10	15	8
OVARY	Adenoma: sertoliform tubular	P-value of test of trend or comparison	.9263	.2991	.7471	1
		Number of animals reported with tumor	1	3	1	0
	Benign granulosa-theca cell tumor	P-value of test of trend or comparison	.7529	.4941		
		Number of animals reported with tumor	0	1	0	0
	Cystadenoma	P-value of test of trend or comparison	.7537	.2412	.4941	
		Number of animals reported with tumor	0	2	1	0
	Malignant granulosa-theca cell tumo	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0

Table B.8

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
PANCREAS	Adenoma: islet cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Carcinoma: acinar cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
PITUITARY	Adenoma: pars distalis	P-value of test of trend or comparison	.9351	.9572	.6714	.9808
		Number of animals reported with tumor	32	22	29	23
	Carcinoma: pars distalis	P-value of test of trend or comparison	.9400	.7471	1	1
		Number of animals reported with tumor	1	1	0	0
SKIN	Fibroma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
THYMUS	Benign thymoma	P-value of test of trend or comparison	.8131	.1873	.5288	.7883
		Number of animals reported with tumor	1	4	2	1
	Malignant thymoma	P-value of test of trend or comparison	.8534	.7597	.7718	1
		Number of animals reported with tumor	1	1	1	0
THYROID	Adenoma: C-cell	P-value of test of trend or comparison	.6668	.1250	.6831	.5426
		Number of animals reported with tumor	2	6	2	3
	Adenoma: follicular cell	P-value of test of trend or comparison	.9911	.5000	.9391	1
		Number of animals reported with tumor	3	4	1	0
	Carcinoma: C-cell	P-value of test of trend or comparison	.8976	.8751	.6831	1
		Number of animals reported with tumor	2	1	2	0
UTERUS	Adenocarcinoma: endometrial	P-value of test of trend or comparison	.1227	1	1	.5426
		Number of animals reported with tumor	2	0	0	3
	Adenoma: endometrial	P-value of test of trend or comparison	.5115		.4941	
		Number of animals reported with tumor	0	0	1	0
	Benign granular cell tumor	P-value of test of trend or comparison	.5645	.7471	1	.7745
		Number of animals reported with tumor	1	1	0	1
	Hemangioma	P-value of test of trend or comparison	1	1	1	1

Table B.8

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
		Number of animals reported with tumor	1	0	0	0
	Leiomyoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Polyp: endometrial stromal	P-value of test of trend or comparison	.2907	.2298	.6507	.2891
		Number of animals reported with tumor	3	6	3	6
	Sarcoma: endometrial stromal	P-value of test of trend or comparison	.7441	.2991	1	.7745
		Number of animals reported with tumor	1	3	0	1
VAGINA	Benign granular cell tumor	P-value of test of trend or comparison	.5256		.2412	
		Number of animals reported with tumor	0	0	2	0
	Leiomyosarcoma	P-value of test of trend or comparison	.2701			.5222
		Number of animals reported with tumor	0	0	0	1
	Polyp	P-value of test of trend or comparison	.2701			.5222
		Number of animals reported with tumor	0	0	0	1

Table B.9

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
ADRENAL	Adenoma: cortical	P-value of test of trend or comparison	.6612	.9909	.8420	.9256
		Number of animals reported with tumor	6	1	4	3
	Malignant pheochromocytoma	P-value of test of trend or comparison	.9351	.7240	1	1
		Number of animals reported with tumor	1	1	0	0
BRAIN	Benign granular cell tumor	P-value of test of trend or comparison	.6593	.4719	.2419	
		Number of animals reported with tumor	0	1	2	0
	Benign mixed glioma	P-value of test of trend or comparison	.2623			.5053
		Number of animals reported with tumor	0	0	0	1
	Malignant astrocytoma	P-value of test of trend or comparison	.5137		.4946	
		Number of animals reported with tumor	0	0	1	0
	Malignant meningioma	P-value of test of trend or comparison	.6362	.4719	.5000	
		Number of animals reported with tumor	0	1	1	0
HEMOLYM. TISSUE	Histiocytic sarcoma	P-value of test of trend or comparison	.5137		.4946	
		Number of animals reported with tumor	0	0	1	0
	Malignant lymphoma	P-value of test of trend or comparison	.9472	1	.9415	1
		Number of animals reported with tumor	3	0	1	0
INJECTION SITE	Adenoma: sebaceous	P-value of test of trend or comparison	.9351	.7240	1	1
		Number of animals reported with tumor	1	1	0	0
	Carcinoma: squamous cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Fibroma	P-value of test of trend or comparison	.0219		.4946	.1250
		Number of animals reported with tumor	0	0	1	3
	Fibrosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Hemangiosarcoma	P-value of test of trend or comparison	.5137		.4946	
		Number of animals reported with tumor	0	0	1	0
	Keratoacanthoma	P-value of test of trend or comparison	.7408	1	.3002	1

Table B.9

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
		Number of animals reported with tumor	1	0	3	0
	Sarcoma (not otherwise specified)	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
JEJUNUM	Leiomyoma	P-value of test of trend or comparison	.5137		.4946	
		Number of animals reported with tumor	0	0	1	0
	Malignant teratoma	P-value of test of trend or comparison	.7432	.4719		
		Number of animals reported with tumor	0	1	0	0
L.N. MESENTERIC	Hemangioma	P-value of test of trend or comparison	.2623			.5053
		Number of animals reported with tumor	0	0	0	1
	Hemangiosarcoma	P-value of test of trend or comparison	.4138	1	.7473	.7579
		Number of animals reported with tumor	1	0	1	1
LIVER	Adenoma: hepatocellular	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
LUNG	Adenoma: alveolar/bronchiolar	P-value of test of trend or comparison	.7648	1	.7473	1
		Number of animals reported with tumor	1	0	1	0
	Sarcoma: metastasis	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
PANCREAS	Adenoma: islet cell	P-value of test of trend or comparison	.6941	1	.8126	.9440
		Number of animals reported with tumor	3	0	2	1
	Carcinoma: acinar cell	P-value of test of trend or comparison	.5165		.4946	
		Number of animals reported with tumor	0	0	1	0
PITUITARY	Adenoma: pars distalis	P-value of test of trend or comparison	.9891	.9635	.9948	.9992
		Number of animals reported with tumor	21	12	10	8
	Adenoma: pars intermedia	P-value of test of trend or comparison	.7627	.2142	.2419	
		Number of animals reported with tumor	0	2	2	0
PROSTATE	Adenocarcinoma	P-value of test of trend or comparison	.5163		.5000	
		Number of animals reported with tumor	0	0	1	0

Table B.9

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
SKIN	Fibroma	P-value of test of trend or comparison	.5137		.4946	
		Number of animals reported with tumor	0	0	1	0
SPLEEN	Sarcoma (not otherwise specified)	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
STOMACH	Adenocarcinoma	P-value of test of trend or comparison	.5137		.4946	
		Number of animals reported with tumor	0	0	1	0
	Adenoma	P-value of test of trend or comparison	.2623			.5053
		Number of animals reported with tumor	0	0	0	1
	Fibrosarcoma	P-value of test of trend or comparison	.5137		.4946	
		Number of animals reported with tumor	0	0	1	0
	Leiomyosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
TESTIS	Adenoma: interstitial cell	P-value of test of trend or comparison	.9410	.2952	.9389	.9440
		Number of animals reported with tumor	3	5	1	1
THYMUS	Benign thymoma	P-value of test of trend or comparison	.7661	1	.7641	1
		Number of animals reported with tumor	1	0	1	0
THYROID	Adenoma: C-cell	P-value of test of trend or comparison	.8704	.7030	.9738	.9470
		Number of animals reported with tumor	11	9	5	6
	Adenoma: follicular cell	P-value of test of trend or comparison	.9684	.9269	.9389	1
		Number of animals reported with tumor	3	1	1	0

Table B.10

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
All fibromas and fibrosarcomas	P-value of test of trend or comparison	.7965	.4772	.0678	.6807
	Number of animals reported with tumor	9	10	16	9
All hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.8300	.7471	.2991	1
	Number of animals reported with tumor	1	1	3	0
Endometrial stromal polyps and sarcomas of the uterus	P-value of test of trend or comparison	.4060	.1050	.7737	.3152
	Number of animals reported with tumor	4	9	3	7
Fibromas and fibrosarcomas (subcutaneous tissue)	P-value of test of trend or comparison	.2857			
	Number of animals reported with tumor	0	0	1	2
Hemangiomas and hemangiosarcomas (injection site)	P-value of test of trend or comparison	.7529	.4941		
	Number of animals reported with tumor	0	1	0	0
vaginal polyps and endometrial stromal polyps and sarcomas of the uterus	P-value of test of trend or comparison	.4060	.1050	.7737	.3152
	Number of animals reported with tumor	4	9	3	7

Reference ID: 3207508

Table B.11

Table of reported tumors in Rat Study
NDA 200677
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 50*	*Low dose Size = 50*	*Mid dose Size = 50*	*High dose Size = 50*
Adenomas and adenocarcinomas of the stomach	P-value of test of trend or comparison	.2623			.5053
	Number of animals reported with tumor	0	0	0	1
Adenomas and carcinomas of the stomach and small intestine	P-value of test of trend or comparison	.2003		.4946	.5053
	Number of animals reported with tumor	0	0	1	1
All fibromas and fibrosarcomas	P-value of test of trend or comparison	.2633	.9269	.3449	.5119
	Number of animals reported with tumor	3	1	5	4
All hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.5648	1	.8933	.9029
	Number of animals reported with tumor	4	0	2	2
Fibromas and fibrosarcomas (injection site)	P-value of test of trend or comparison	.0721	1	.7473	.3165
	Number of animals reported with tumor	1	0	1	3
Fibromas and fibrosarcomas (subcutaneous tissue)	P-value of test of trend or comparison	.1472	.6429	.4048	.4286
	Number of animals reported with tumor	2	1	2	1
Hemangiomas and hemangiosarcomas (injection site)	P-value of test of trend or comparison	.5137		.4946	
	Number of animals reported with tumor	0	0	1	0

Reference ID: 3207508

Table B.12

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 200677
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
INJECTION SITE	Fibroma	P-value of test of trend or comparison	.0219		.4946	.1250
		Number of animals reported with tumor	0	0	1	3
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	6.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0,8.4)	(0.05,11.5)	(1.28,17.2)
		Poly-3 adjusted number of animals at risk	47.0	42.4	46.9	48.7
SUBCUT. TISSUE	Fibroma	P-value of test of trend or comparison	.0455		.3333	.1429
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	29%	75%
		95% CI for poly-3 adjusted incidence rate (%)	(0,45.9)	(0,84.2)	(0.63,90.6)	(1.26,100)
		Poly-3 adjusted number of animals at risk	6.8	2.6	3.5	1.3

Reference ID: 3207508

Tumor counts for organs reported widely unanalyzed
NDA 200677
Animal carcinogenicity study
Rats

Table B.13

Species and Sex	Organ or tissue name	Tumor name	Quantity	Control	Low dose	Mid dose	High dose
Rats - Female	ABDOMEN	Sarcoma (not otherwise specified)	Number of tumors found	0	0	1	0
			Number of animals examined	3	1	1	2
	BONE MISC.	Sarcoma: metastasis	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	2
	FAT	Hemangiosarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	7	11	9	7
		Mesothelioma(M)	Number of tumors found	0	0	0	1
			Number of animals examined	7	11	9	7
	SKIN MISC.	Carcinoma: basal cell	Number of tumors found	0	0	0	1
			Number of animals examined	10	10	11	5
	SUBCUT. TISSUE	Benign granular cell tumor	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	7	3
		Carcinoma (not otherwise specified)	Number of tumors found	0	0	1	0
			Number of animals examined	0	0	7	3
		Fibroma	Number of tumors found	0	0	1	0
			Number of animals examined	0	0	7	3
		Fibrosarcoma	Number of tumors found	0	0	0	2
			Number of animals examined	0	0	7	3
		Hemangiosarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	0	0	7	3
		Lipoma	Number of tumors found	0	0	2	0
			Number of animals examined	0	0	7	3
		Liposarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	0	0	7	3
	THORAX	Sarcoma (not otherwise specified)	Number of tumors found	0	1	0	0
			Number of animals examined	0	1	0	1
Rats - Male	ABDOMEN	Lipoma	Number of tumors found	1	0	0	0
			Number of animals examined	2	1	1	0
	LYMPH NODE	Hemangiosarcoma	Number of tumors found	2	0	0	0
			Number of animals examined	21	22	19	14
	MUSC.SKEL.MISC.	Benign granular cell tumor	Number of tumors found	0	0	0	1
			Number of animals examined	2	0	1	2
		Hemangiosarcoma	Number of tumors found	1	0	0	0
			Number of animals examined	2	0	1	2

Reference ID: 3207508

Tumor counts for organs reported widely unanalyzed
NDA 200677
Animal carcinogenicity study
Rats

Table B.13

Species and Sex	Organ or tissue name	Tumor name	Quantity	Control	Low dose	Mid dose	High dose
			Number of animals examined	26	22	21	15
		Carcinoma: basal cell	Number of tumors found	0	0	1	0
			Number of animals examined	26	22	21	15
		Carcinoma: sebaceous	Number of tumors found	0	1	0	0
			Number of animals examined	26	22	21	15
		Carcinoma: squamous cell	Number of tumors found	0	1	0	0
			Number of animals examined	26	22	21	15
		Keratoacanthoma	Number of tumors found	4	2	2	0
			Number of animals examined	26	22	21	15
		Papilloma: squamous cell	Number of tumors found	2	0	0	0
			Number of animals examined	26	22	21	15
	SUBCUT. TISSUE	Fibroma	Number of tumors found	0	0	1	1
			Number of animals examined	7	3	4	2
		Fibrosarcoma	Number of tumors found	2	1	1	0
			Number of animals examined	7	3	4	2
		Lipoma	Number of tumors found	3	1	0	0
			Number of animals examined	7	3	4	2
		Malignant schwannoma	Number of tumors found	0	1	0	1
			Number of animals examined	7	3	4	2
		Osteosarcoma	Number of tumors found	1	0	0	0
			Number of animals examined	7	3	4	2
	VAS DEFERENS	Fibrosarcoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	1

Reference ID: 3207508

B.3 Unexamined and autolytic organs

Table B.14

Organs reported as unexamined
NDA 200677
Animal carcinogenicity study
Female Rats

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ABDOMEN	47	94%	49	98%	49	98%	48	96%	193	97%
BONE MISC.	50	100%	50	100%	50	100%	48	96%	198	99%
CLITORAL GL	3	6.0%	4	8.0%	5	10%	4	8.0%	16	8.0%
FAT	43	86%	39	78%	41	82%	43	86%	166	83%
L.N.TRACHEO.	6	12%	4	8.0%	5	10%	7	14%	22	11%
LYMPH NODE	31	62%	31	62%	31	62%	38	76%	131	66%
MUSC.SKEL.MISC.	50	100%	49	98%	50	100%	50	100%	199	100%
SKIN MISC.	40	80%	40	80%	39	78%	45	90%	164	82%
SUBCUT. TISSUE	50	100%	50	100%	43	86%	47	94%	190	95%
THORAX	50	100%	49	98%	50	100%	49	98%	198	99%
THYMUS	7	14%	4	8.0%	2	4.0%	3	6.0%	16	8.0%

Reference ID: 3207508

Table B.15

Organs reported as unexamined
NDA 200677
Animal carcinogenicity study
Male Rats

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ABDOMEN	48	96%	49	98%	49	98%	50	100%	196	98%
BONE MISC.	49	98%	50	100%	50	100%	50	100%	199	100%
FAT	49	98%	48	96%	47	94%	48	96%	192	96%
L.N.TRACHEO.	4	8.0%	5	10%	6	12%	13	26%	28	14%
LYMPH NODE	29	58%	28	56%	31	62%	36	72%	124	62%
MAMMARY GL	50	100%	49	98%	50	100%	50	100%	199	100%
MUSC.SKEL.MISC.	48	96%	50	100%	49	98%	48	96%	195	98%
PANCREAS	.	.	1	2.0%	.	.	.	.	1	0.5%
PITUITARY	.	.	1	2.0%	.	.	.	.	1	0.5%
SKIN MISC.	24	48%	28	56%	29	58%	35	70%	116	58%
SUBCUT. TISSUE	43	86%	47	94%	46	92%	48	96%	184	92%
THORAX	49	98%	50	100%	49	98%	50	100%	198	99%
THYMUS	4	8.0%	4	8.0%	1	2.0%	6	12%	15	7.5%
THYROID	.	.	.	.	.	.	1	2.0%	1	0.5%
VAS DEFERENS	50	100%	50	100%	50	100%	49	98%	199	100%

Reference ID: 3207508

B.4 Weight changes

Table B.16: Weight changes by group (rats)

Sex	Control	SOM230					
	Δ_{C_P}	Δ_L	$\frac{\Delta_L}{\Delta_{C_P}} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_{C_P}} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_{C_P}} - 1$
Female	251.2	232.4	-7%	255.6	2%	206.5	-18%
Male	459.2	360	-22%	342.6	-25%	281.4	-39%

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[6] R Peto, M C Pike, N E Day, R G Gray, P N Lee, S Parish, J Peto, S Richards, and J Wahrendorf. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, NIL(2 Suppl):311–426, 1980.

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/s/

MATTHEW T JACKSON
10/23/2012

KARL K LIN
10/24/2012
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 200677 **Applicant: Novartis** **Stamp Date: June 21, 2011**

Drug Name: Signifor (pasireotide) injection **NDA/BLA Type: NDA** **Indication: Cushing's disease**

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			2 doses uncontrolled
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	1 trial
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

1. The NDA documents display Study B2305 lab-related values in SI units. You provided two lab-related Study B2305 datasets, one in SI units and a corresponding dataset in US units. Please include a column variable for lab unit in the dataset Aeffvis (SI unit e.g. LBSIUNIT) and Aeffvisu (US unit e.g. LBUSUNIT) to display their respective UFC unit.

2. Please indicate which variable in dataset Aeffsum to use in order to get the number of responders at Month 6 as listed in the Final Report Table 11-4 (12 in the 600 µg group and 21 primary endpoint responders in the 900 µg group).

3. For the analysis of response (primary efficacy endpoint) at Month 6 by baseline mUFC using logistic regression model, please send the SAS proc logistic program for Figure 14.2-2.10.

4. At the pre-NDA meeting, a delta graph was requested to present the change of HbA1c from baseline to the end of study by patient. Please indicate the location of the graph.

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
SOM230B 2305	**2-dose, uncontrolled, randomized, double-blind**	**600 µg bid, n=82** **900 µg bid, n=80**	**mean urinary free cortisol (mUFC)≤ULN at month 6 (patients with dose increase prior to month 6 as nonresponders)/ % responder as point estimator and 95% CI**	**600 µg bid, 12/82 (14.6%, 95% CI 7.0, 22.3)** **900 µg bid, 21/80 (26.3%, 95% CI 16.6, 35.9)** **prespecified lower bound of the 95% CI threshold: 15%**

Lee pian — August 8, 2011
Reviewing Statistician — Date

Todd Sahlroot — August 8, 2011
Supervisor/Team Leader — Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

LEE PING PIAN
08/11/2011

JON T SAHLROOT
08/11/2011