

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

Novartis is seeking approval for pasireotide for the treatment of patients with acromegaly. Approval for this treatment is being sought based on “biochemical control of IGF-1 and GH levels” (reduction of growth hormone and insulin-like growth factor-1) as a primary objective.

1.1 Conclusions and Recommendations

Efficacy results for the primary composite endpoint involving GH and IGF-1 were significant showing an increased response rate for pasireotide when compared with octreotide. However, these results were driven by differences seen in IGF-1 values (see Table 10 and Table 13); the observed GH values were fairly similar between arms. This anomaly does not necessarily preclude approvability based on efficacy (technically the study did not achieve an advantage in biochemical control as defined as reduction in GH and IGF-1). If an improvement in IGF-1 values over standard of care constitutes clinically meaningful progress, or the conditional interpretation of IGF-1 values given the GH response (see section 3.3) is sufficient, then the findings in this review indicate that pasireotide is effective for the treatment of acromegaly in the general population. There is also evidence that pasireotide could be efficacious in a population which has already failed on current standard of care medical treatment.

1.2 Brief Overview of Clinical Studies

There were two efficacy and safety studies submitted for the indication of acromegaly which had an active control comparator arm. Due to study design issues, only one study was useful for determining efficacy within a general population against standard of care controls. This study, C2305, was a blinded multicenter, parallel-group design with two arms. Main results for the composite primary endpoint are given in Table 1.

Table 1: Primary Endpoint Results for Study C2305

	Octreotide LAR	Pasireotide LAR	
	n (%)	n (%)	P
Non-Responder	147 (80.77)	121 (68.75)	
Responder	35 (19.23)	55 (31.25)	0.0075

Study C2402 used entry criteria which constituted having already failed on the standard of care medical therapy. Subjects were randomized between pasireotide LAR 40 mg, pasireotide LAR 65 mg and continuing that standard of care therapy that they were taking and to which their condition was not responding. The study was also not a truly blinded study as subjects knew whether they were receiving experimental treatment or standard of care control which they had previously failed on. This study design criterion means results based off of the findings from C2402 are not generalizable beyond a population who has already failed on standard of care medical treatment. Most of the analyses done on C2402 were kept to a descriptive level for the

purposes of this review. The proportion of patients who achieved the composite primary endpoint for this study can be seen in Table 2.

Table 2: Primary Endpoint Results for study C2402

	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg	Active Control
	N=65	N=65	N=68
	n (%)	n (%)	n (%)
Non-Responder	55 (84.6%)	52 (80%)	68 (100%)
Responder	10 (15.4%)	13 (20%)	0 (0%)

Analyses and conclusions for this review will be weighted largely on results from the C2305 clinical study. Further details on these studies can be seen in Table 3.

1.3 Statistical Issues and Concerns

The main statistical issue within this submission has to do with interpreting efficacy results wherein only one of the two components for the primary analysis was truly significant. While the composite primary endpoint was significant, this significance was driven through one of the two components within the endpoint. By conditioning on the non-significant component, I found that responders for the first non-significant factor were more likely to also have a response for the second component which was the significant component in the overall (non-conditioned) population. However, in the population that did not respond to the first component, both treatment options were equally likely to achieve a response for the second component.

2 INTRODUCTION

2.1 Overview

The stated treatment goals for acromegaly are “to control both GH and IGF-1 levels, to reduce and/or stabilize tumor size, to preserve pituitary function and to prevent recurrence.” Treatment options for acromegaly include surgery, radiotherapy, and medical treatment which involves somatostatin analogs (SSAs) octreotide and lanreotide as the first choice of medical therapy. This submission is for approval of a new option within medical therapy treatments.

The main study used for this review, C2305, is a multicenter, randomized, blinded study run to assess the safety and efficacy of pasireotide LAR when compared with an active control of octreotide LAR in patients with acromegaly. Study C2402 is a phase 3, multicenter, parallel-group, three-arm study of pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR 30 mg or lanreotide ATG 120 mg in a patient population which had inadequately controlled acromegaly. Details on these two studies are given below in Table 3.

Table 3: Efficacy and Safety Studies for NDA 203255

Study Number	Study Objectives	Study Design and Type of Control	Active Treatment	Active Control	Number of Subjects	Duration of Treatment
CSOM230C2305	Efficacy and Safety by comparing the proportion of patients between pasireotide LAR and octreotide LAR who achieved biochemical control	Phase 3, blinded, active controlled, randomized study	pasireotide LAR 40 mg	octreotide LAR 20 mg	Treatment=176, Control=182	12 months (with a 1 year extension)
SCSOM230C2402	Efficacy and Safety	Phase 3, multicenter, randomized, parallel-group, 3-arm study	double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg	open-label octreotide LAR 30 mg or lanreotide ATG 120 mg	pasireotide LAR 40 mg=65, pasireotide LAR 60 mg=65, Control=68	6 months

2.1.1 Class and Indication

Pasireotide (SOM 230) is a second generation somatostatin analog (SSA) designed to inhibit hormone secretion through somatostatin receptors (SSTR). It was developed with a broader binding profile typical of other SSAs. It is because of this broader profile that pasireotide LAR was expected to show better efficacy. The proposed indication for pasireotide is for treatment of acromegaly (b) (4)

2.1.2 History of Drug Development

Clinical development of pasireotide (b) (4)
 (b) (4) acromegaly and Cushing's disease with s.c. injection under IND 68635. In 2006 the LAR i.m. formulation with these indications was introduced under INDs 74642 (b) (4)

(b) (4) Pasireotide s.c. has been approved by the agency in December 2012 for treating adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. On August 25, 2009, pasireotide received an orphan designation for the treatment of acromegaly.

In October 2007 an end of phase II meeting was held to establish the approach for Study C2305. A pre-NDA meeting later occurred in November 2011 to discuss the submission package for pasireotide LAR for treatment of patients with acromegaly. A follow-up to this meeting

occurred in September 2013 wherein it was agreed that there would be no pooling of efficacy for the two registration studies but a pooling strategy was agreed upon for safety “to facilitate evaluation and comparison of data of similar populations from both studies.”

2.2 Data Sources

Data and final study report were submitted electronically and archived under the network path location < \\CDSESUB1\evsprod\NDA203255\203255.enx>. The information needed for this review was contained in Module 1 FDA Regional Information (cover letter, meeting correspondence, and labeling), Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Reports of Efficacy and Safety Studies. This review focuses on documents submitted to serial number 0000. Some code was provided in the application, but independent coding and verification was done for the purposes of this review.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This submission is in the electronic common technical document (eCTD) format with an xml backbone. A statistical analysis plan in section 10 of the protocol was submitted and reviewed for the main study. Primary and key secondary efficacy endpoints were reproduced from the submitted data. All required documents that are necessary for statistical review were submitted. Study datasets were provided as SAS XPORT transport files. No additional information request was made for the statistical review.

A true double-blind treatment was not feasible due to differences in appearance between the two treatments. An unblinded independent nurse/coordinator administered the LAR treatment and completed an Unblinded Dosage Administration Record case report form (CRF) so that blinding still remained intact for the patient, investigator, and sponsor in study C2305.

In C2402 subjects were unblinded to the treatment arm. Blinding for this study occurred with the dosage of the treatment as subjects did not know whether they were on a low dose (40 mg) or high dose (60 mg) of pasireotide LAR. The overarching goal of this study was to examine safety and efficacy of pasireotide LAR 40 mg and 60 mg versus active control on octreotide LAR 30 mg or lanreotide ATG 120 mg in patients with inadequately controlled acromegaly. Since part of the entry criteria into this study was to already have failed on current methods of treatment for acromegaly, the efficacy results from this study will not be generalizable. This limitation does not constrain analyses for safety, dose comparisons, or efficacy for those in which current standard medical therapy doesn't work, but it renders statistical analyses of efficacy in the typical acromegaly population, when compared with standard of care controls, moot. Since this is a review of treatment efficacy, results from this study should only be viewed in the context of treatment after failed standard of care medical treatment.

There were two Mexican sites which were identified by the applicant with critical GCP compliance issues on September 7, 2011 and September 8, 2011. A total of 22 (6%) patients were randomized in these sites before they were closed. There were also at least two Brazilian sites having 21 (6%) subjects in the C2305 study with partial unblinding by study coordinator within the sites. Within these sites, study activities that were to be conducted by a blinded individual were performed by unblinded coordinators. On May 7, 2014 the applicant sent a letter informing the agency of these protocol violations within the Brazilian sites in advance of a scheduled inspection to begin at one of the sites on May 12. Sensitivity analyses in section 3.2.6 were run to excluding the Mexican and Brazilian sites to assess if they had an effect on the results.

Data were collected over three phases of study C2305,

1. Core Phase, all the data from the core phase up to month 12 (used for the primary efficacy analysis)
2. Up to Crossover, including data from both core and extension up to the data cut-off collected for patients who continued the same treatment as in the core. For those who switched medication only the data collected before crossover is included (main safety analysis, long-term efficacy for first line therapy).
3. After crossover, this includes all data in the extension collected after the crossover time point for patients who crossed over (used for analyses on efficacy and safety for patients who did not respond to previous SSA treatment).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Objectives

Study C2305, is a multicenter, randomized, blinded study to assess the safety and efficacy of pasireotide LAR when compared with an active control of octreotide LAR in patients with acromegaly. The primary objective was to compare the proportion of patients who had a reduction in GH to $<2.5 \mu\text{g/L}$ and normalization of IGF-1 between the two treatment groups at 12 months. Patients were enrolled in 84 centers across 27 countries. This was the largest prospective randomized study conducted by the applicant with N=358 patients with active acromegaly who had not received previous medical treatment. Data from the initial 12-month core phase were used for efficacy purposes. The optional extension period was used for supportive and exploratory analyses. There were 358 patients enrolled with 176 receiving pasireotide and 182 receiving octreotide. Amendment 4 added the crossover extension to the study. The 34 patients who entered the study before the amendment were unblinded at month 12 and those who had been receiving octreotide received their next injections as pasireotide. For those entering the study after the amendment, blinding was maintained at the patient level. Those responding at month 12 to the treatment (meeting the primary endpoint) were randomized to remain on that treatment and those who were not responding crossed-in to the other treatment. This study was further extended with an ongoing open label extension phase.

1:1 Randomization occurred at visit 2 and was stratified by:

1. Patients who had undergone one or more pituitary surgeries and

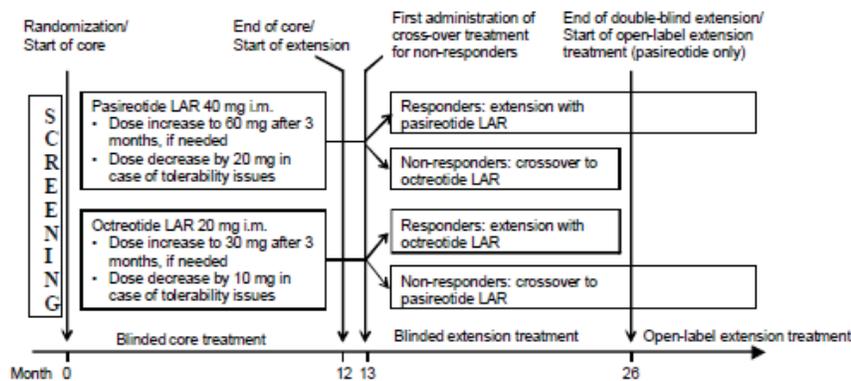
- De-novo patients presenting a visible pituitary adenoma on magnetic resonance imaging (MRI) and who refused pituitary surgery or for whom pituitary surgery was contraindicated.

An applicant created schematic of the study is shown in Figure 1.

Key secondary objectives included comparing the effect of pasireotide LAR vs. octreotide LAR on:

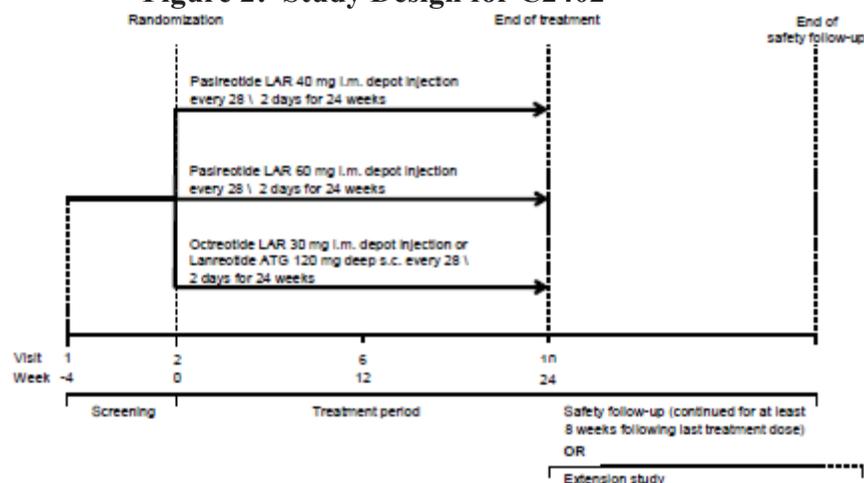
- The reduction of GH to $<2.5 \mu\text{g/L}$ at month 12
- Normalization of IGF-1 at 12 months
- Tumor volume at month 12

Figure 1: Study Design for C2305



The study design for C2402 was similar to that of C2305 with an initial four week screening period after which subjects were randomized with a ratio of 1:1:1 to low dose treatment, high dose treatment, or continue on same treatment as before randomization. The 24-week core phase was followed by an extension phase which allowed patients in the active control arm to receive pasireotide LAR if they were found to be uncontrolled at the end of the core phase. The applicant derived study diagram is given in Figure 2.

Figure 2: Study Design for C2402



There were a total of 198 patients randomized in this trial with 65 patients each in the 40 $\mu\text{g/L}$ and 60 $\mu\text{g/L}$ arms and 68 patients in the control arm.

3.2.2 Primary Endpoint

The primary objective in both studies was to compare the proportion of patients with a reduced GH <2.5 mg/L and normalized IGF-1 (age and sex related). These measurements were taken at 12 months for C2502 and 24 weeks for C2402. The primary efficacy variable was based on:

1. A reduction of GH to <2.5 mg/L (based on a 5-point 2-hour profile)
2. Normalized IGF-1 (ie, $\text{LLN} \leq \text{IGF-1} \leq \text{ULN}$, age and sex related) at month 12 or week 24 (study dependent). Those whose IGF-1 was below LLN were not considered normalized and therefore considered as non-responders.

For study C2305, this endpoint was taken at the first database lock which occurred at the end of the 12-month blinded core phase. However, there was no study report prepared from this lock and the blinding of the extension was kept at the patient level in order to not impact the analysis.

3.2.3 Key Secondary Endpoint

The three key secondary variables for study C2305 are:

1. The proportion of patients with GH <2.5 $\mu\text{g/L}$ at month 12
2. Proportion of patients with normalization of IGF-1
3. Change from baseline in tumor volume at month 12

The proportion of patients with normalization of IGF-1 at week 24 was the key secondary endpoint designated in Study C2402.

3.2.4 Statistical Methodologies

3.2.4.1 Populations

The full analysis set (FAS) consisted of all patients randomized into the study. The Per Protocol (PP) set was all those patients who did not have any major protocol deviations by month 12/week 24. The safety analysis set included all patients who received any study medication with a valid post-baseline assessment, analyzed according to treatment first received in the study. The second PP analysis set was a subset of the FAS population who did not have any major protocol deviations.

3.2.4.2 Missing Data Methods

Study C2305

The last observation at or after month 6 was carried forward for the primary efficacy variable when a month 12 assessment was not available (LOCF). The proportion of observed patients at each time point as I found is shown in Figure 3. Table 4 displays the reasons for discontinuation as given by the applicant.

For the primary efficacy variable there were several criteria for handling missing data in the different parts of the composite endpoint. If there were less than three samples in the GH assessment then the mean GH was considered missing. If the GH and IGF-1 measurements were taken more than 35 days after the LAR injection then the GH and IGF-1 measurements were considered missing for the corresponding visit and the LOCF method described above was used for imputation. If either mean GH or IGF-1 was missing at month 12 and the available value did not meet the aforementioned response criteria, then the patient was considered a non-responder.

When performing analyses based on the sponsor produced indicator of those who were imputed, I found results that were the same as those given in the study report. However, when looking at month 12 data and imputing based on what I could find during that time range, I found eight subjects that I imputed from month 9 results with six of them not having month 12 data in the efficacy set that I used, one missing IGH-1 value at month 12, and one missing GH value at month 12. There were two subjects on octreotide LAR who had visits that were not labelled as month 12 by the applicant but the number of days in the study seemed to have them fall closer to month 12. One subject had visits on day 329 and 342, labelled as month 12 and month 12.5, respectively. However, because day 342 is closer to the 12 month time point I used the observation from the latter visit. Similarly, another subject had a visit on day 353 which was classified as month 13 in the pre-crossover efficacy data. Since this occurred at roughly the 12 month time point, I used this as month 12 efficacy data. The primary endpoint results did not change from what was in the applicant's study report, but for the secondary endpoint involving mean GH one subject went from being a responder to not being a responder. This did not substantially affect the final results.

Study C2402

A non-responder imputation method was used for study C2402. Subjects needed at least three of the five samples for the 5-point mean GH assessment in order to not be considered missing. Those having missing values of mean GH or IGF-1 at the 24 week assessment were imputed as non-responders for analyses.

3.2.4.3 Primary Analysis

Study C2305

The results for the primary efficacy variable and key secondary variables are based on the full analysis set. The proportion of patients with a reduction of GH to $<2.5 \mu\text{g/L}$ and normalized IGF-1 at month 12 was used for the primary analysis. A two-sided null hypothesis of no difference in response rates between treatment groups was tested using a two-sided Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification with a significance level of 0.05. An adjusted response rate was calculated by treatment group using the two-sided 95% exact CI (Clopper-Pearson), presented as the OR in Table 9.

When a month 12 assessment was not available the LOCF method described in section 3.2.4.2 was used. If either mean GH or IGF-1 was missing and the available value did not meet response criteria at month 12, then the patient was considered a non-responder. If it did meet the response criteria then LOCF was implemented.

Given that the primary analysis was significant in favor of pasireotide LAR treatment, the three key secondary efficacy variables were tested using the closed multiple testing method based on the weighted version of Simes test to control the overall probability of type I error at a 0.05 level. The first endpoints were analyzed using the CMH testing procedure adjusting for stratifying randomization variables and implementing the same LOCF method as before. An ANCOVA model with treatment as the fixed effect and tumor volume at baseline and randomization stratum as covariates was used to compare the two treatment groups for the last endpoint, change in tumor volume at month 12.

Study C2402

The FAS was used for the main analysis with the following specified null hypotheses:

H_{01} : The response rate in the pasireotide LAR 40 mg group was at least as good as that of the control group

H_{02} : The response rate in the pasireotide LAR 60 mg group was at least as good as that of the control group

The applicant specified a gatekeeping procedure to control the type I error. This procedure combined the hierarchical nature of testing primary and secondary endpoints, along with simultaneous testing based on the Simes inequality for the multiple hypotheses (H_{01} and H_{02}). In total, there were four hypotheses which were tested using the gatekeeping procedures based on the graphical approach proposed by Bretz et al (2009); the trimmed version of the weighted Simes test was used to relax the positive regression dependent test statistics condition.

The protocol specified each hypothesis to be tested against a one-sided alternative that treatment was greater than active control. An exact logistic regression model adjusting for randomization stratification was used with exact two-sided 95% and 97.5% confidence intervals for the odds ratio. For the purposes of this review, though, most of the analyses will be of a descriptive nature rather than comparative with the control arm due to the reasons described in sections 1.2 and 3.1. When hypothesis tests are run they will be run against a two-sided alternative which will allow for the possibility that active control could be better than the experimental treatment.

3.2.4.4 Sensitivity Analysis

The applicant ran analyses for the primary endpoint on the per-population dataset as well as the FAS with patients having missing GH or IGF-1 at month 12 or who had discontinued prior to month 12 considered as non-responders. I also ran a month 12 non-responder sensitivity analysis based on my findings for those observed at month 12 (see section 3.2.4.2 on missing data for details). Additionally, I did an analysis based only on those subjects with measured values at month 12.

3.2.5 Patient Disposition, Demographic and Baseline Characteristics

When looking at the efficacy data over time for C2305, I found slightly more missing data than what the sponsor had indicated in the study report (see section 3.2.4.2 for more details). This, however, did not change the overall results of the analysis. Figure 3 below shows the proportion of observed responses I found at each measured time point in the study. It appears that the sharpest decline in observed number of subjects occurs after the 12 month core phase when transitioning into the crossover phase.

Figure 3: Observed Data

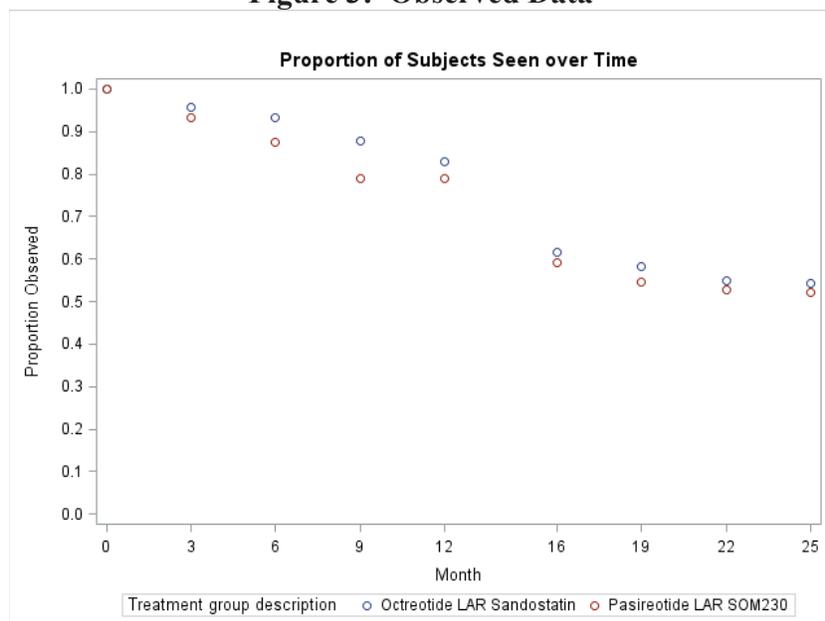


Table 4 below lists the reasons given by the applicant for discontinuation in the 61 subjects they had as unobserved at month 12. Based on these results, it seems that subjects were more likely to discontinue due to an adverse event if they were on pasireotide treatment, but were more likely to discontinue due to an unsatisfactory therapeutic effect if on the octreotide active control.

Table 4: Reasons for Discontinuation of Study Medication before Month 12

	Pasireotide LAR	Octreotide LAR	Total
Adverse Event(s)	14	6	20
Abnormal laboratory value(s)	1	0	1
Unsatisfactory therapeutic effect	5	8	13
Subject withdrew consent	5	3	8
Lost to follow-up	1	0	1
Administrative problems	2	0	2
Death	0	1	1
Protocol deviation	7	8	15
Total	35	26	61

Baseline characteristics looked balanced between the two treatment groups in C2305 as seen in Table 5.

Table 5: Descriptive Statistics for Baseline Characteristics

Characteristic	Category	Pasireotide LAR (N=176)	Octreotide LAR (N=182)	All
Age category	<65	168 (95.5%)	167 (91.8%)	335 (93.6%)
	≥65	8 (4.6%)	15 (8.2%)	23 (6.4%)
Sex	Male	85 (48.3%)	87 (47.8%)	172 (48.0%)
	Female	91 (51.7%)	95 (52.2%)	186 (52.0%)
Race	Caucasian	105 (59.7%)	111 (61.0%)	216 (60.3%)
	Black	3 (1.7%)	4 (2.2%)	7 (2.0%)
	Asian	39 (22.2%)	43 (23.6%)	82 (22.9%)
	Native American	6 (3.4%)	5 (2.8%)	11 (3.1%)
	Other	23 (13.1%)	19 (10.4%)	42 (11.7%)
Age at baseline	N	176	182	358
	Mean	45.12	45.62	45.37
	SD	12.37	12.97	12.67

Characteristic	Category	Pasireotide	Octreotide	All
		LAR (N=176)	LAR (N=182)	
	Median	46.00	45.00	46.00
	Min	18.00	19.00	18.00
	Max	80.00	85.00	85.00
Body Mass Index	N	175	181	356
	Mean	28.8	28.7	28.7
	SD	4.6	5.2	4.9
	Median	28.1	27.8	28.0
	Min	19.0	19.5	19.0
	Max	44.4	55.8	55.8

I ran descriptive statistics to compare the randomization stratification of those who were post-surgery versus de novo treatment at baseline. Table 6 provides the mean GH as well as standardized (for age and gender) IGF-1 levels at baseline for the post-surgery versus de novo stratification factor. Levels for all these variables do appear to be different between the two groups with those receiving de novo treatment having higher GH and IGF-1 values at baseline when compared with those post-surgery. Table 7 has similar results with the proportion of patients in lower, medium and higher level categories of mean GH at baseline. A majority of the post-surgery population has mean GH levels in the low or medium category (64%) while most of the de novo group has a mean GH greater than ten (58%).

Table 6: Baseline GH and IGF-1 by Stratification Groups

		Post-Surgery	De Novo	P
Mean GH (ug/L) at Baseline	N	143	202	
	Mean	14.6	24.3	
	Std. Dev.	23.9	31.8	
	Median	8.0	11.7	
	Min	0.6	1.5	
	Max	160.4	200.0	0.0021
Standardized IGF-1 (ug/L) at Baseline	N	149	209	
	Mean	2.7	3.3	
	Std. Dev.	1.1	1.3	
	Median	2.6	3.2	
	Min	0.8	0.9	
	Max	5.7	7.3	<.0001

P-values based on a pooled t test of equal variances

Table 7: Categorical Baseline GH by Stratification Groups

Baseline Mean GH	Post-Surgery	De Novo
≤ 2.5	19 (13.3%)	10 (5.0%)
2.5-10	73 (51.1%)	75 (37.1%)
>10	51 (35.7%)	117 (57.9%)

Table 8 given below shows similar results given in Table 6 but with results further broken down between treatment arms.

Table 8: Descriptive Statistics by treatment group and stratification

		Pasireotide LAR		Octreotide LAR	
		Post-Surgery	De Novo	Post-Surgery	De Novo
Mean GH (ug/L) at Baseline	N	68	99	75	103
	Mean	16.1	25.9	13.3	22.9
	Std. Dev.	27.1	34.8	20.6	28.6
	Median	5.9	10.8	8.7	12.9
	Min	0.8	1.6	0.6	1.5
	Max	160	200	160.4	169.6
Standardized IGF-1 (ug/L) at Baseline	N	71	105	78	104
	Mean	2.6	3.3	2.8	3.3
	Std. Dev.	1.1	1.4	1.2	1.2
	Median	2.4	3.3	2.6	3.1
	Min	0.9	0.9	0.8	0.9
	Max	5	6.9	5.7	7.3

In Study C2403 there were a total of 16 patients (8%) who were unobserved at week 24. The number of subjects in each treatment arm which were unobserved were 6 (9%) in the low dose treatment group (40 mg), 8 (12%) in the high dose (60 mg) group, and 3 (4%) in the active control group. All dropouts due to adverse events were in the pasireotide arms with 2 (3%) in low dose and 4 (6%) in high dose. Dropouts in the active control group were due either to withdrawal of consent or protocol deviations.

3.2.6 Results and Conclusions

Sensitivity analyses were run excluding sites with protocol violations. One analysis was based solely on observed data, and another imputing all unobserved subjects at month 12 as non-responders. The applicant missing data indicator (AMI) results are based on what was indicated as imputed values at month 12 by the applicant. The missing in month 12 data (MID) show similar results based on data and LOCF imputation described in section 3.2.4.2.

Table 9: Primary Endpoint Results for study C2305

		Pasireotide LAR		Octreotide LAR		P	
		N=176		N=182			
		n (%)	Exact 95% CI	n (%)	Exact 95% CI	OR (95% CI)	
Applicant LOCF	Non-Responder	121 (68.8)	(24.5, 38.7)	147 (80.8)	(13.8, 25.7)	1.9* (1.2, 3.2)	0.0075*
	Responder	55 (31.3)		35 (19.2)			
Removing 4 Sites with Violations	Non-Responder	105 (68.2)	(24.6, 39.8)	133 (82.6)	(11.9, 24.1)	2.3 (1.3, 3.9)	0.0024
	Responder	49 (31.8)		28 (17.4)			
Non-Responder Imputation, MID	Non-Responder	125 (71.0)	(22.4, 36.3)	149 (81.9)	(13.8, 25.7)	1.9 (1.1, 3.1)	0.0138
	Responder	51 (29.0)		33 (18.1)			
Observed (No Imputation), MID	Non-Responder	86 (62.8)	(29.1, 45.9)	119 (78.3)	(15.4, 29.1)	2.2 (1.3, 3.7)	0.0031
	Responder	51 (37.2)		33 (21.7)			
Non-Responder Imputation, AMI	Non-Responder	123 (69.9)	(23.4, 37.5)	148 (81.3)	(13.3, 25.1)	1.9 (1.2, 3.1)	0.0099
	Responder	53 (30.1)		34 (18.7)			
Observed (No Imputation), AMI	Non-Responder	88 (62.4)	(29.6, 45.6)	122 (78.2)	(15.6, 29.1)	2.2 (1.3, 3.7)	0.0022
	Responder	53 (37.6)		34 (21.8)			

*Indicates results used by sponsor in the study report

P-value results based on Cochran-Mantel-Haenszel Test

Exact 95% CI based on Exact CI calculations for each treatment group

Adjustments made in OR and P-values for possible confounding effects for surgery vs. de novo

Stratified hypotheses tests that there is no association between treatment and response in any strata

MID = Missing (month 12) in Data

AMI = Applicant Missing (month 12) Indicator

With a difference in response rates of around 12% and a 95% CI of (3.1%, 21%) in favor of pasireotide, there does seem to be some improvements in efficacy when compared with octreotide for this composite endpoint.

The first secondary endpoint of reduction of growth hormone levels under 2.5 µg/L was not found to be statistically significant when comparing pasireotide LAR to octreotide LAR. Sensitivity analyses were run in a manner similar to the primary analysis. Under the MID population I had one fewer responder on octreotide than the sponsor had, but this did not make much difference in the response rate or statistical significance. Table 10 shows response rates for having GH < 2.5 µg/L for the different scenarios and testing procedures.

Table 10: Results for GH < 2.5 µg /L in study C2305

		Pasireotide	Octreotide	OR (95% CI)
		LAR N=176	LAR N=182	
		n (%)	n (%)	
Applicant LOCF for GH<2.5	Non-Responder	91 (51.7%)	88 (48.4%)	0.87 (0.58, 1.13)
	Responder	85 (48.3%)	94 (51.7%)	
Removing 4 Sites with Violations	Non-Responder	78 (50.7)	80 (45.7)	0.96 (0.62, 1.50)
	Responder	76 (49.4)	81 (50.3)	
LOCF for GH<2.5, MID	Non-Responder	91 (51.7%)	89 (48.9%)	0.89 (0.59, 1.35)
	Responder	85 (48.3%)	93 (51.1%)	
Non-Responder Imputation GH<2.5, MID	Non-Responder	98 (56.3%)	96 (52.8%)	0.87 (0.57, 1.31)
	Responder	76 (43.7%)	86 (47.3%)	
Observed (No Imputation) GH<2.5, MID	Non-Responder	60 (44.1%)	66 (43.4%)	0.97 (0.61, 1.55)
	Responder	76 (55.9%)	86 (56.6%)	

It was also of interest to look at response rates for the mean growth hormone to be under 1 µg/L. Table 11 shows results for the response rate of those with GH < 1 µg/L and also for the composite primary endpoint changing the proportion of patients with GH < 2.5 µg/L at month 12 to be GH < 1 µg/L. Results using this more restrictive criterion remained non-significant for GH and the primary endpoint can only be viewed, at best, as borderline significant.

Table 11: Results for Endpoints using GH < 1 ug/L in study C2305

		Pasireotide	Octreotide	OR (95% CI)	CMH P
		LAR N=176	LAR N=182		
		n (%)	n (%)		
LOCF Response Rate for Mean GH<1	Non-Responder	132 (75.0%)	140 (76.9%)	1.1 (0.7, 1.8)	0.6701
	Responder	44 (25.0%)	42 (23.1%)		
LOCF for Primary Endpoint with Mean GH<1	Non-Responder	147 (83.5%)	164 (90.1%)	1.8 (1.0, 3.4)	0.0626
	Responder	29 (16.5%)	18 (9.9%)		

Table 12 below shows results for mean GH values taken at the end of treatment time period on which this secondary endpoint was based. Although there does appear to be a bigger decrease from baseline in growth hormone for the pasireotide group, it does not appear to be a significant difference.

Table 12: Results for Mean Growth Hormone at End of Treatment for study C2305

	Pasireotide LAR (N=154)		Octreotide LAR (N=171)		P
	Mean (SD)	(Min, Max)	Mean (SD)	(Min, Max)	
Growth Hormone (ug/L) at Month 12	5.13 (12.32)	(0.16, 108.8)	4.92 (11.62)	(0.08, 130.2)	0.872
Decrease From Baseline	16.04 (27.18)	(-8.96, 193.6)	13.24 (20.69)	(-9.32, 159.6)	0.302
% Decrease From Baseline	70.11 (25.75)	(-23.53, 98.24)	65.0 (32.14)	(-69.44, 99.5)	0.195

Results for the next secondary endpoint of normalization of IGF-1 at month 12 can be seen below in Table 13. Even though there were slight differences in the MID population versus the AMI, the outcome values here for these subjects were the same using the pre-specified LOCF methodology. The results for normal IGF-1 values are significant under all scenarios and testing procedures shown in Table 13. Since we did not find significant results for growth hormone in this study, it is exceptionally important that we have full confidence in the results for IGF-1 as it appears that this is driving all the significance that we saw in the composite primary endpoint in Table 9. We may want to consider disregarding the primary endpoint and basing conclusions and labeling on results from IGF-1 findings since growth hormone was found to be non-significant.

Table 13: Results for Normal IGF-1 Response in study C2305

		Pasireotide LAR	Octreotide LAR	OR (95% CI)	CMH P
		N=176	N=182		
		n (%)	n (%)		
LOCF for IGF-1	Non-Normal	108 (61.4)	139 (76.4)	2.0 (1.3, 3.2)	0.0016
	Normal	68 (38.6)	43 (23.6)		
Removing 4 Sites with Violations	Non-Normal	92 (59.7)	125 (77.6)	2.3 (1.4, 3.8)	0.0004
	Normal	62 (40.3)	36 (22.4)		
Non-Responder Imputation for IGF-1, MID	Non-Normal	113 (64.2%)	141 (77.5%)	1.9 (1.2, 3.1)	0.0047
	Normal	63 (35.8%)	41 (22.5%)		
Observed (No Imputation) IGF-1, MID	Non-Normal	75 (54.4%)	111 (73%)	2.3 (1.4, 3.7)	0.0007
	Normal	63 (45.7%)	41 (27%)		

Table 14: Results Comparing IGF-1 Values in study C2305

	Pasireotide LAR		Octreotide LAR		P		
	Mean (SD)	(Min, Max)	Mean (SD)	(Min, Max)			
Standardized IGF-1 (ug/L) at Baseline	176	3.1 (1.3)	(0.9, 6.9)	182	3.1 (1.2)	(0.8, 7.3)	
Standardized IGF-1 (ug/L) at Month 12	155	1.4 (1.1)	(0.2, 5.9)	172	1.6 (1.0)	(0, 5.3)	0.0733
Standardized Change in IGF-1	155	1.7 (1.2)	(-2.3, 5)	172	1.5 (1.3)	(-4, 5.2)	0.093
Standardized Percent Change in IGF-1	155	53.6 (28.7)	(-63.9, 92.8)	172	44.3 (39.4)	(-319.1, 100)	0.0136

P-values based on ANCOVA adjusting for age and sex

Results for the last key secondary endpoint, change in tumor volume by month 12, were similar to those found by the sponsor. Looking at results using both the end of treatment measurements and the pre-specified month 12 measurements we see a non-significant change when comparing the two treatment arms. Table 15 has results for this endpoint.

Table 15: Analysis Results for Change in Tumor Volume in study C2305

	Pasireotide LAR N=176			Octreotide LAR N=182			P
	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	
Baseline Values	166	2420.67 (4159.2)	1041.05 (0, 35095)	169	2259.25 (3390.2)	1052.9 (0, 25473)	
End of Treatment (EOT)	148	1502.3 (2369.8)	642.2 (0, 12038)	163	1590 (2519.9)	622.6 (0, 13539)	
Change at EOT	144	-894.5 (2261.7)	-314.7 (-23917, 1044.9)	153	-700.8 (1586.7)	-263.9 (-12355.4, 3036)	0.28
% Change at EOT	142	-38.7 (23.3)	-38.8 (-100, 16.9)	149	-34.7 (25.8)	-35.4 (-96.2, 29.1)	
Month 12 Values	129	1466.43 (2367.61)	607.9 (0, 12038)	142	1381.76 (2152.5)	629.9 (0, 13539)	
Change at Month 12	125	-970.033 (2412.28)	-320.4 (-23917, 1044.9)	132	-800.906 (1652.4)	-306.9 (-12355.4, 778.6)	0.86
% Change at Month 12	123	-39.91 (21.8)	-39.91 (-97.6, 16.9)	128	-38.26 (24.4)	-38.42 (-96.3, 27.9)	

P-value based on ANCOVA model adjusted for baseline tumor volume and strata (post-surgery and de novo)

Efficacy results for study C2402 are given in Table 16. When running two-sided, exact testing procedures on these results I found both of the hypotheses for the primary endpoint to be statistically significant. Low dose versus active control yielded a p-value of 0.001, and high dose versus active control showed $p < 0.0001$. These results remained significant level when testing under a sensitivity analysis which imputed those missing at week 24 to be responders in the active control arm and non-responders in the two experimental treatment arms.

Results for the key secondary endpoint of normalized IGF-1 are also given in the table. This was also statistically significant indicating improved efficacy in IGF-1 in the population for which current standard of care medical treatment has already failed. The active control arm, however, does not take into account other alternative forms of therapy, briefly mentioned in section 2.1, that could be used in lieu of medical therapy.

Table 16: Results for Study C2402

		Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active Control N=68
		n (%)	n (%)	n (%)
Composite Primary Endpoint	Non-Responder	55 (84.6%)	52 (80%)	68 (100%)
	Responder	10 (15.4%)	13 (20%)	0 (0%)
Normalized IGF-1	Non-Responder	49 (75.4%)	48 (73.9%)	68 (100%)
	Responder	16 (24.6%)	17 (26.2%)	0 (0%)

3.3 Conditional Interpretation of IGF-1 Results

Given the unusual results for the composite primary endpoint involving GH and IGF-1, additional analysis seemed reasonable based on findings from section 3.2.6. The significant outcome for IGF-1 but not for GH may be further interpreted as a conditional probability; given that a patient has a GH response $< 2.5 \mu\text{g/L}$, this individual is more likely to have a normal IGF-1 measurement if he is on pasireotide versus octreotide. Table 17 shows results for the IGF-1 endpoint stratified by GH $< 2.5 \mu\text{g/L}$ in both the LOCF and observed at month 12 populations. These results indicate that secondary endpoint of IGF-1 is only significant in the population with decreased GH. The odds ratio for this increased from around 2 (1.3, 3.2) in the combined population (see Table 13) to approximately 3 (1.6, 5.6) in the low GH population. Conversely, we may also say that normal IGF-1 levels are equally as likely for both treatments given that GH is not controlled ($\geq 2.5 \mu\text{g/L}$).

Table 17: IGF-1 Results Stratified by GH $< 2.5 \mu\text{g/L}$

			Pasireotide LAR	Octreotide LAR	OR (95% CI)	Exact P
			N=176	N=182		
			n (%)	n (%)		
LOCF	GH $< 2.5 \mu\text{g/L}$	Non-Normal	30 (35.3%)	58 (62.4%)	3.0 (1.6, 5.6)	0.0003
		Normal	55 (64.7%)	35 (37.6%)		
	GH $\geq 2.5 \mu\text{g/L}$	Non-Normal	78 (85.7%)	81 (91.0%)	1.7 (0.7, 4.3)	0.3541
		Normal	13 (14.3%)	8 (9.0%)		
Observed at month 12	GH $< 2.5 \mu\text{g/L}$	Non-Normal	24 (31.6%)	53 (61.6%)	3.5 (1.8, 6.7)	0.0002
		Normal	52 (68.4%)	33 (38.4%)		
	GH $\geq 2.5 \mu\text{g/L}$	Non-Normal	49 (81.7%)	58 (87.9%)	1.6 (0.6, 4.4)	0.4555
		Normal	11 (18.3%)	8 (12.1%)		

3.3.1 Prognostic Characteristics for GH levels

There are likely certain underlying characteristics within these subpopulations which make some subjects more disposed to attaining a lower GH when given medical treatment. Knowing what these characteristics are would be beyond the capacity of the current study and is not necessary for our use of the conditional interpretation, although for completeness, it should be addressed. This section details results from a superficial analysis on certain characteristics within the realm of the study to give a more comprehensive picture of these populations. Table 20 in the appendix contains descriptive statistics for baseline variables which were measured in this study for both low and high GH at month 12. This table is no way a comprehensive assessment of all possible prognostic features, additional forethought and studies for these populations would be necessary to better understand how they differ. We do, however, see some variables that are suggestive of a stronger disposition towards lower GH levels with medical treatment. Factors such as age indicate the odds of having lower GH levels are 3.1 times greater for those who are

older. Country also may be a factor as those in the USA had 2.1 greater odds of having lower GH at the end of medical treatment than those outside of the USA. It should be emphasized, however, that these prognostic findings are strictly exploratory.

4 FINDINGS IN SUBGROUP POPULATIONS

The treatment effect for the primary efficacy variable was pre-specified to be analyzed across race, ethnicity, and age (<65, ≥ 65) in the FAS for study C2305. Since significance for efficacy seemed to be driven by findings on the secondary IGF-1 endpoint, I also ran subgroup analyses for this endpoint.

4.1 Gender, Race, Age, and Geographic Region

Table 18, given below, shows subgroup analysis results for the primary endpoint, and Table 19 shows results for the IGF-1 secondary endpoint. Only limited conclusions should be drawn from these results as the study was neither geared nor powered for any specific subpopulation or testing for interaction effects. The results are fairly consistent across subgroups.

Table 18: Subgroup Analyses for the Primary Endpoint

		Pasireotide LAR	Octreotide LAR
		N=176	N=182
Age	<65	50/168 (29.8%)	32/167 (19.2%)
	≥65	5/8 (62.5%)	3/15 (20%)
Gender	Male	25/85 (29.4%)	17/87 (19.5%)
	Female	30/91 (33.0%)	18/95 (19.0%)
Race	Caucasian	33/105 (31.4%)	20/111 (18.0%)
	Other	22/71 (31.0%)	15/71 (21.1%)
Geography	USA	11/20 (55.0%)	3/21 (14.3%)
	Outside USA	44/156 (28.2%)	32/161 (19.9%)

Table 19: Subgroup Analyses for IGF-1 Secondary Endpoint

		Pasireotide LAR	Octreotide LAR
		N=176	N=182
Age	<65	63/168 (37.5%)	39/167 (23.4%)
	≥65	5/8 (62.5%)	4/15 (26.7%)
Gender	Male	31/85 (36.5%)	21/87 (24.1%)
	Female	37/91 (40.7%)	22/95 (23.2%)
Race	Caucasian	42/105 (40.0%)	27/111 (24.3%)
	Other	26/71 (36.6%)	16/71 (22.5%)
Geography	USA	15/20 (75%)	3/21 (14.3%)
	Outside USA	53/156 (54%)	40/161 (24.8%)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There was only one study designed to demonstrate efficacy results comparing pasireotide to active standard of care treatment in the general acromegaly population. Due to the design and entry criteria of the supportive study C2402, results comparing pasireotide LAR to standard of care, although valid to consider in certain populations, should not be used for efficacy in the general acromegaly population.

Ultimately, the data do not support any differences in GH between pasireotide LAR and standard of care octreotide LAR. This could be considered an approvability issue if it is necessary for the applicant to demonstrate improved biochemical control of both IGF-1 and GH levels for the entire patient population. Currently, treatment with either pasireotide LAR or octreotide LAR has around 50% of patients achieving GH < 2.5 µg/L and approximately 25% with GH < 1 µg/L. Given that this level of response for GH along with better responses for normal IGF-1 values is considered an improvement, then pasireotide could be considered as progress over the current medical therapy. An alternative way to look at the results is by first conditioning on the treatment results for GH. When a patient does not have GH levels that will be well controlled after medication therapy, then both treatments seem to be equally likely of achieving normal IGF-1 levels. In the patient population that does see some benefit in their GH levels, there does appear to be an improvement in attaining normal IGF-1 levels with pasireotide over octreotide. This could also be viewed as efficacy within a patient subpopulation for which medical therapy is effective in reducing GH levels.

5.2 Collective Evidence

While pasireotide did show statistically significant results for the composite IGF-1/GH endpoint when compared with octreotide, further breakdown of this endpoint revealed the substance of this result was driven through normal IGF-1 values and not with growth hormone levels. IGF-1 results (see Table 13) from the main study are supportive of the applicant's efficacy claim while GH showed no significant difference (see Table 10). When conditioning the IGF-1 results by GH levels, I did find that when medical therapy was effective for lowering GH levels, pasireotide also seemed more effective than the active control for having normal IGF-1 responses (see section 3.3). This analysis also indicated that when medical therapy was not effective in controlling GH, there did not appear to be any difference in normal IGF-1 responses when comparing pasireotide to octreotide.

5.3 Conclusions and Recommendations

From a statistical perspective, the information supplied in this package from study C2305 supports the efficacy claim for using pasireotide as an alternative treatment for acromegaly in achieving normal IGF-1. However, these results are limited to efficacy claims on IGF-1 as there is no evidence of improved efficacy for growth hormone levels in the general acromegaly

population. There is also evidence from C2402 that this therapy works well in a population which has already failed on standard of care medical treatment.

5.4 Labeling Recommendations

Results in the labeling section based on the composite primary endpoint for study C2305 are suggestive of an increased response in both GH and IGF-1. Since this study provided no evidence of improvement for GH, my recommendation is that this section be rewritten based more on results from the secondary IGF-1 endpoint.

There is also mention of [REDACTED] (b) (4)
[REDACTED] should be removed from the label.

In the supportive C2402 study, [REDACTED] (b) (4)
[REDACTED]

APPENDICES

Table 20: Descriptive Statistics based on GH Levels

Characteristic	Category	GH < 2.5 mg/L (N=178)	GH ≥ 2.5 mg/L (N=180)	P Value
Age category	<65	161 (90.45%)	174 (96.67%)	0.0164
	≥65	17 (9.55%)	6 (3.33%)	
Sex	Male	83 (46.63%)	89 (49.44%)	0.5940
	Female	95 (53.37%)	91 (50.56%)	
Race	Caucasian	109 (61.24%)	107 (59.44%)	0.8303
	Black	2 (1.12%)	5 (2.78%)	
	Asian	41 (23.03%)	41 (22.78%)	
	Native American	6 (3.37%)	5 (2.78%)	
	Other	20 (11.24%)	22 (12.22%)	
Country	USA	27 (15.17%)	14 (7.78%)	0.0281
	Not USA	151 (84.83%)	166 (92.22%)	
Previous Treatment (Stratification)	Post-surgery	76 (42.70%)	73 (40.56%)	0.6811
	De novo	102 (57.30%)	107 (59.44%)	
Age at baseline	N	178	180	0.0539
	Mean	46.7	44.1	
	SD	12.9	12.3	
	Median	46.5	44.0	
	Min	24.0	18.0	
	Max	80.0	85.0	
BMI	N	177	179	0.0499
	Mean	29.2	28.2	
	SD	5.1	4.7	
	Median	28.7	27.3	
	Min	19.3	19.0	
	Max	55.8	44.4	

Characteristic	Category	GH < 2.5 mg/L (N=178)	GH ≥ 2.5 mg/L (N=180)	P Value
Height (cm)	N	177	179	0.4053
	Mean	168.8	169.8	
	SD	10.8	11.2	
	Median	168.0	169.0	
	Min	146.0	146.0	
	Max	198.0	202.0	
	Weight (Kg)	N	178	
Mean		83.9	82.0	
SD		19.3	18.4	
Median		80.2	79.0	
Min		51.3	50.0	
Max		169.0	138.0	

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/s/

JENNIFER J CLARK
08/11/2014

MARK D ROTHMANN
08/11/2014
I concur

THOMAS J PERMUTT
08/12/2014
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203255

Applicant: Novartis

Stamp Date: 12/15/2013

**Drug Name: Signifor LAR
(pasireotide) injection**

NDA/BLA Type: NDA

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 (if applicable).	X			
4	Data sets in EDR are accessible and do they 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.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Clarification needed for what was done when 'treatment assignments were balanced by country'.
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			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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/s/

JENNIFER J CLARK
01/08/2014

MARK D ROTHMANN
01/08/2014
concur