CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 15, 2014
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	203255/000
Applicant	Novartis Pharmaceuticals
Date of Submission	November 15, 2013
PDUFA Goal Date	September 15, 2014 (initial date); changed to 12/15/2015 following major amendment
Proprietary Name / Established (USAN) names	Signifor LAR (pasireotide pamoate) injection
Dosage forms / Strength	Powder for reconstitution as an injectable suspension of 20 mg, 40 mg, and 60 mg to be administrated once every 4 weeks
Proposed Indication(s)	Treatment of patients with acromegaly (b) (4)
Recommended:	Approval

1. Introduction

Signifor LAR is a long acting formulation of pasireotide, a somatostatin analog which was approved on 12/14/2012 under the commercial name Signifor as an immediate release formulation for the treatment of adults with Cushing's disease. While Signifor is administered twice daily subcutaneously, Signifor LAR is injected intramuscularly once monthly. Signifor LAR is synthesized as a pamoate salt of pasireotide, which has a lower water solubility than the pasireotide diaspartate salt contained in Signifor. This, in addition to the changes in formulation (b) (4) Chemically, pasireotide is a cyclohexapeptide analog of human somatostatin.

Novartis is proposing the following indication for Signifor LAR:

> *SIGNIFOR LAR is indicated for the treatment of patients with acromegaly* (b) (4)

Acromegaly is a rare disease with a prevalence of 40-125 cases per million, and an incidence of 13 cases per 100,000.[1] In the majority of cases acromegaly is due in to a GH-secreting

[1] Katznelson, Laurence: Diagnosis and Management of Acromegaly in 2012, European Endocrinology, 2012;8(1):48-52

pituitary adenoma (pituitary acromegaly) and only very rarely to an ectopic source of GH. Therefore for practical purposes, acromegaly is a pituitary disease. Although the treatment of choice of pituitary acromegaly is surgical removal of the pituitary mass via transsfenoidal route, the success rate is variable (90% in patients with microadenoma and below 50% in patients with macroadenomas).

Patients who fail surgery (or cannot undergo surgery for a variety of reasons) benefit from radiation or pharmacological therapy. Because the effects of radiation may take years to reach effectiveness, medical therapy is almost invariably used in patients who respond poorly or incompletely to surgical management. Tight GH control and a normalization of serum IGF-1 are the goals of medical treatment. GH reductions to ≤1 μg/L using a modern sensitive immunoassay (approximately equivalent to 2.5 μg/L measured by RAI)[2] following an oral glucose load are desirable.

There are three drug products that have been approved by the FDA for the medical treatment of acromegaly. From a mechanism of action perspective they belong to two distinct classes: somatostatin analogs (octreotide and lanreotide) and GH receptor antagonists (pegvisomant).

Pegvisomant (SOMAVERT) is a pegylated GH analog and acts as a GH receptor antagonist. It competes with endogenous GH for GH receptor binding. Once bound to the GH receptor it prevents receptor dimerization and subsequent intracellular signaling, thus blocking generation of IGF-1. The major safety signal identified with pegvisomant is transient liver enzyme elevation; however, no drug-induced liver failure has been documented to date.

Two somatostatin analogs have been approved by the Agency for the acromegaly indication: octreotide (Sandostatin and Sandostatin LAR) and lanreotide (Somatuline Depot). They have similar safety profiles that are reflected in overlapping albeit not identical WARNINS AND PRECAUTIONS sections of the respective labels, which include: cholelithiasis, alterations in glucose metabolism (hypoglycemia but mostly hyperglycemia), hypothyroidism, and cardiac function abnormalities (bradycardia, arrhythmia, or conduction abnormalities). The pasireotide label for the Cushing's indication includes a similar set of warnings. The only notable exception is the occurrence of hyperglycemia, which is in excess to that seen with other somatostatin analogs.

Despite sharing many similarities to the already approved somatostatin analogs, pasireotide differs in its somatostatin receptor (SSTR) binding characteristics. Whereas octreotide and lanreotide bind primarily to SSTR2, pasireotide binds to a broader range of receptors: SSTR 1, STTR2, STTR3 and SSTR5, and has particular affinity for SSTR5. The binding affinities of native somatostatin (SRIF-14), pasireotide, octreotide, and lanreotide to the five human SSTR subtypes (SSTR 1-5) (expressed as mean ± SEM of IC_{50} values expressed as mmol/L) are displayed below:

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[2] Holdaway IM, et al. A meta-analysis of the effect of lowering serum levels of GH and IGF-1 on mortality of acromegaly. European Journal of Endocrinology, 159, 89-95, 2008.

Melmed S. et al., Guidelines for acromegaly management: An update. J Clin Endocrinol Metab 94: 1509-1517, 2009.

Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin (SRIF-14)	0.93±0.12	0.15±0.02	0.56±0.17	1.5±0.4	0.29±0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	> 100	0.16±0.01
Octreotide	280±80	0.38+0.08	7.1±1.4	> 1000	6.3±1.0
Lanreotide	180±20	0.54±0.08	14±9	230±40	17±5

2. Regulatory Background

The major regulatory interactions between the FDA and Novartis during the development of the Signifor LAR are as follows:

- An IND (74,642) was opened in March 2006 to study pasireotide (early drug development name: SOM230).
- An End-of-Phase-2 meeting was held on October 15, 2007 during which the Phase 3 program was discussed. FDA provided comments regarding patient population selection (surgical failures or de novo diagnosed patients were deemed acceptable), trial design (use of octreotide as active comparator was accepted), inclusion/exclusion criteria, duration of the trial (12 months requested by FDA), requirement for a thorough QTc study), and endpoint selection.
- Pasireotide was granted Orphan Drug designation for the "treatment of acromegaly" on August 25, 2009 by the Office of Orphan Products Development.
- A pre-NDA meeting was held on November 29, 2011 for Signifor LAR. The NDA format and structure were discussed. There were no areas of disagreement. FDA agreed with the statistical analysis plan, and requested that the application contain a comprehensive report on liver safety. Advice was given about how the hyperglycemia information should be presented in the NDA.
- NDA 200677 for Signifor (immediate-release pasireotide) for the Cushing's Disease indication was approved on 12/14/2012. The application was discussed at an Endocrinologic and Metabolic Advisory Committee meeting held in November 2012. From a safety perspective, major topics of discussion were the high incidence of hyperglycemia and several cases of liver enzyme elevation for which, there was no obvious explanation.
- A second pre-NDA meeting was held on September 9, 2013 for Signifor LAR. Novartis had decided to delay the NDA submission until the results of a second Phase 3 clinical trial became available. During the meeting, FDA confirmed that the content of the NDA was acceptable, agreed with the statistical analysis plan, and addressed several standard regulatory questions.
- The current NDA was submitted on November 15, 2013, under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.
- A Major Amendment was issued on September, 2, 2014. The amendment was triggered by the submission of additional data during the current review cycle.

3. CMC/Device

The CMC review (DARRTS 8/11/2014) recommends approval pending completion and positive recommendations from CDRH, microbiology, biopharmaceutics, and Office of Compliance. The reviewer does not recommend any Phase 4 studies.

The Signifor LAR presentation is a vial that comes in 3 strengths (20 mg, 40 mg, and 60 mg). The drug product consists of microparticles containing a biodegradable polymeric matrix made of poly(D,L-lactide-coglycolide) (b) (4) . The microparticles are to be suspended in an aqueous diluent prior to injection. The diluent (2mL volume) comes in a 3mL glass syringe as part of a kit that contains all the necessary elements for reconstitution and injection, and includes the following:

Ingredient	Composition in mg/ml	Composition in mg/syringe	Function
Mannitol	45.0	90.0	(b) (4)
(b) (4)	7.0	14.0	
Carboxymethylcellulose sodium			
(b) (4)			
Poloxamer 188	2.0	4.0	
Water for injections / (b) (4)	ad 1.0ml	ad 2.0ml	

Once the resuspended drug product is injected, pasireotide pamoate, which is uniformly distributed within the microparticles, (b) (4) . All three dosage strengths (20mg, 40mg and 60mg) are derived (b) (4) and differ only in the amount of powder filled in the vials. All excipients were found to be acceptable as they met the compendial criteria.

The CMC reviewer states that the data presented in this submission establishes the identity, purity, strength and quality of the drug product, and there are no pending CMC issues. He goes on to comment that (b) (4)), that all related impurities are below the qualification limit as per ICH Q3B, and that residual solvent specifications comply with ICH Q3C.

The container closure system was found to be adequate, and the in-use leachable studies, syringe stopper studies and the long-term stability studies of the diluent product in prefilled syringes were adequate to support the use of the kit components.

The CMC reviewer recommends that the expiration times proposed for the drug products are supported by real time stability and should be granted (and labeled). The shelf-life for the drug product kit stored at 2°C–8°C (36°F–46°F) is 36 months. Once reconstituted the product is to be used immediately.

A CDRH review of the device (DARRTS 12/08/14) concludes that this application is "approvable" given that 1) no deficiencies were identified with respect to "compliance with the Quality System Requirements" and 2) "there were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination".

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review (DARRTS; 8/1/2014) recommends approval without any additional nonclinical studies.

The reviewer points out that most nonclinical studies had already been submitted and reviewed as part of the Signifor NDA (NDA 200677), and there are few new nonclinical studies conducted with the current pasireotide LAR formulation. They include:

- a pharmacodynamic (PD) study in male rats showing that at equal doses (10 mcg/kg/h), pasireotide LAR caused a stronger inhibition of GH and IGF-1 and showed less tachyphylaxis relative to octreotide
- two safety pharmacology studies in vitro; one study evaluated the effect of pasireotide on a hERG current in HEK293 cells transfected with HERG cDNA and showed hERG inhibition at high concentration (≥ 100 μM) - this is consistent with the known effect of pasireotide on QT interval; the second study looked at the effect of ten cloned ion channels expressed in mammalian cells, and showed inhibition of NCX1 ion channel with an IC50 = 21.7 μM; however, no toxicity is expected on the basis of NCX1 ion channel data alone since many other ion channels which were tested showed no inhibition at the highest concentration tested
- three in vitro PK drug interaction studies were performed with: 1) human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP); 2) human organic cation transporters 1 and 2; and human organic anion transporters 1 and 3. Pasireotide inhibited P-gp/BCRP and OAT1/OAT3 but was not an inhibitor of OCT1/OCT2, indicating that there was potential of P-pg mediated and/or transporter mediated drug-drug interaction in vivo. These effects are already labeled for Signifor and will be labeled for Signifor LAR.

The maximum pasireotide LAR dose of 60 mg once monthly has 2.7X safety multiples for C_{max} and 1.3X for AUC relative to the rat NOAEL.

Several local toxicity studies and repeated dose studies were conducted with the pasireotide LAR formulation under the previous NDA, and did not raise any formulation-specific safety concerns. The review also points out that impurities were qualified and that there here were no novel excipients in Signifor LAR.

Specific labeling recommendations are made seeking consistency between the Signifor LAR and the Signifor label.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review (DARRTS, 8/15/2014) recommends approval without any additional Phase 4 studies.

The review recommends that the starting dose of Signifor LAR should be 40 mg with up-titration to 60 mg if the GH and IGF-1 decline is not sufficient after Signifor LAR steady state has been achieved (generally, a little before 3 months of treatment); down-titration to 20 mg, temporarily or permanently, is recommended in case of poor tolerability or adverse events. The review also recommends a lower starting dose of 20 mg for patients with moderately impaired hepatic function (Child-Pugh B), not to exceed a maximum dose 40 mg; use in patients with severe hepatic impairment (Child Pugh C) is to be avoided. The recommendation for dose reductions in patients with hepatic impairment is consistent with the current Signifor label which describes the results of a clinical pharmacology study indicating that higher exposures are to be expected in patients with moderate or severe hepatic impairment (pasireotide is eliminated primarily via the hepatic route and it is excreted in the feces mainly in unchanged form). Because renal elimination is not significant for pasireotide, dose adjustments in patients with renal impairment are not necessary.

The review points out that Signifor and Signifor LAR share the same active ingredient and, consequently the human absorption, distribution, metabolism and excretion information, QT data, renal impairment, hepatic impairment, and drug-drug interactions study results submitted with the subcutaneous formulation are relevant to the LAR formulation as well. Consequently, there were no expectations that such studies be repeated for this NDA, and this was communicated by the FDA to the applicant in the pre-NDA stage. Therefore, the Clinical Pharmacology section in the proposed Signifor LAR label includes largely the same information submitted with the immediate-release pasireotide NDA, to which pharmacokinetics information obtained with the long –acting form of pasireotide was added.

Dose selection for the Signifor LAR Phrase 3 program

Novartis did not conduct a traditional dose-response trial in patients with acromegaly for the selection of a pasireotide LAR dose(s) for the Phase 3 program. Instead, Novartis estimated the dosing frequency and dose range for the Phase 3 studies via PK/PD modeling, with a goal of reaching pasireotide trough concentrations above a serum concentration required for complete GH normalization ($C_{effective}$ = 5.09 ± 4.19 ng/mL). The results of the PK/PD modeling were confirmed in one study conducted with pasireotide LAR, which showed that the 40 mg and 60 mg doses reached steady-state trough concentrations above $C_{effective}$ for GH normalization (this was not the case for the 20 mg dose). Specifically, the steady-state trough concentrations were 5.92 ± 2.85 ng/mL with the 40 mg dose and 8.87 ± 4.53 ng/mL with the 60 mg dose (both above the mean $C_{effective}$ concentration of 5.09 mL). In contrast, the trough concentration reached with the 20 mg dose was only 2.74 ± 1.33 ng/mL.

These clinical pharmacology reviewer notes that the 40 mg LAR dose was the closest to the labeled 0.6 mg bid Signifor dose in terms cumulative monthly dose (1.2 mg/day × 28 days = 33.6 mg). Therefore the 40 mg was the monthly starting dose in Study C2305, and was one of two doses tested in Study C2402 (Studies C2305 and C2402 are the Phase 3 Signifor LAR clinical trials and are described in the clinical section of this memorandum). The proposed initial dose of 40 mg once a month appears reasonable as a starting dose for labeling given the modest trend of higher response rate (GH and IGF-1 normalization) and potential risk of elevated plasma glucose levels seen with the 60 mg Signifor LAR dose in the clinical program (to be discussed further).

PK characteristics for LAR formulation

The PK profile for pasireotide LAR in healthy volunteers is reproduced below (Figure 8 of the Clinical Pharmacology Review). It indicates an uneven exposure during the 28 days following administration, with a greater exposure during the second half of the dosing interval. The apparent half-life of pasireotide LAR is approximately 16 days.

Mean (SD) plasma concentration versus time for pasireotide LAR 60 mg in healthy volunteers (Study C2111).

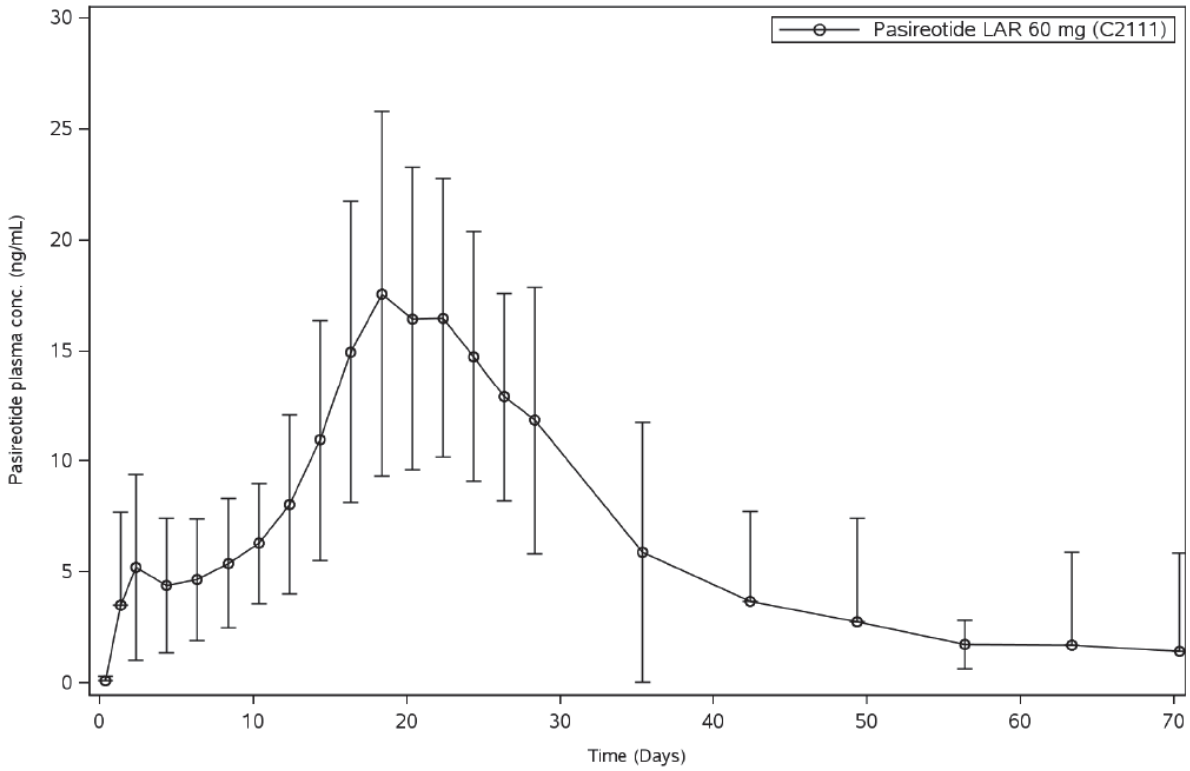
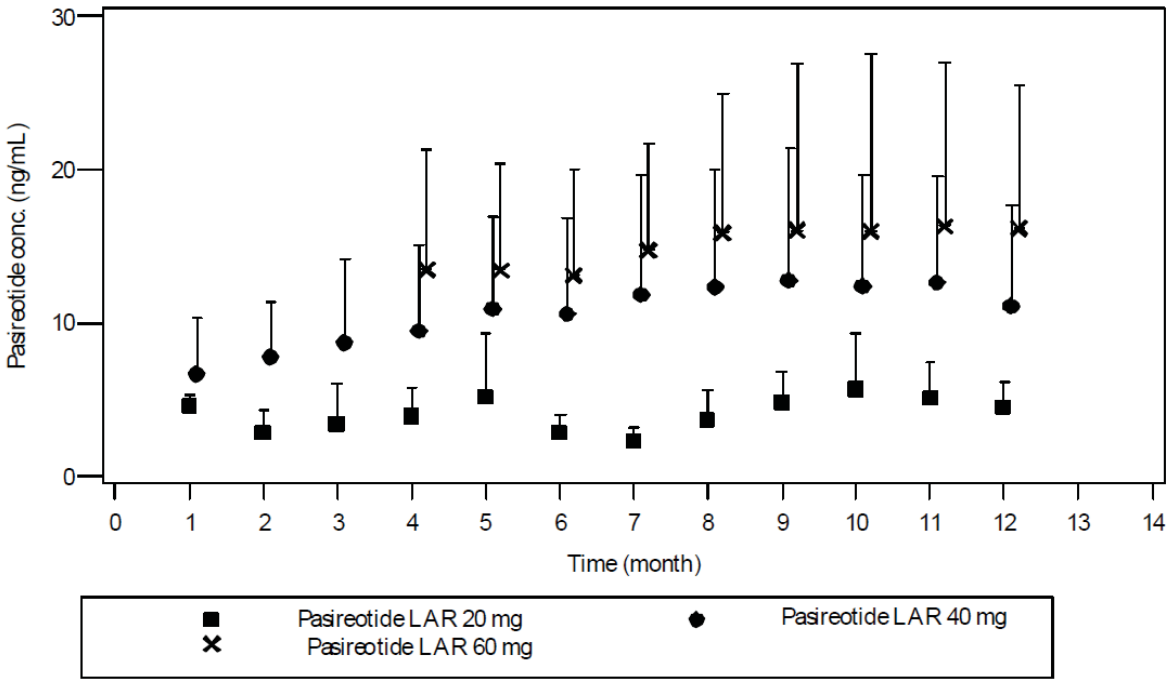


Figure 9 of the Clinical Pharmacology review (reproduced below), displays the mean (SD) plasma concentration versus time profiles by dose following pasireotide LAR doses of 20, 40

and 60 mg administered to acromegaly patients in the Phase 3 study C2305 (core phase). The reviewer indicates that in patients with acromegaly, PK exposures of pasireotide are approximately dose proportional within the dose range evaluated in the Phase 3 program (20 to 60 mg). Steady state concentrations are reached after 3 injections, and PK characteristics were found to be comparable between patients with acromegaly and healthy volunteers.



Exposure-response analyses

The FDA Clinical Pharmacology and Biometrics teams conducted exposure-response analyses for both efficacy and safety. With respect to efficacy, the evidence for exposure-response was weak. The review indicates that there was only a modest probability of becoming a responder with increasing exposure (a responder was defined as a patient reaching GH levels < 2.5 µg/L and having a normal IGF-1). This is consistent with observations made in the phase 3 clinical trial C2305 in which, of the patients who failed to respond at the end of 3 months of treatment and had a dose increase from 40 mg to 60 mg, only 12.4% responded at month 12. Overall, these analyses suggest that there may be some but relatively modest benefit that the 60 mg dose may provide over the 40 mg monthly dose.

In analyzing the exposure-response from a safety perspective, the clinical pharmacology review focused on the occurrence of hyperglycemia, the most common of the clinically relevant adverse events associated with pasireotide. The analysis used similar measures of hyperglycemia that were utilized in the Signifor NDA: a change in free plasma glucose (FPG) from baseline >36 mg/dL (as proposed by the applicant), and a change in HbA1c from baseline >1% .

Because pasireotide-induced hyperglycemia reached a plateau at month 3, the exposure-response analysis was conducted at this timepoint. A trend toward an increased risk of hyperglycemia is observed for both glycemic measures evaluated (FPG and HbA1c) in both Phase 3 clinical trials. Figure 6 (derived from data obtained in Phase 3 trial C2402) and Figure 7 (including data from Phase 3 trial C2305) of the clinical pharmacology review are reproduced below. Hyperglycemia is further discussed in the Safety section (Section 8) of this review.

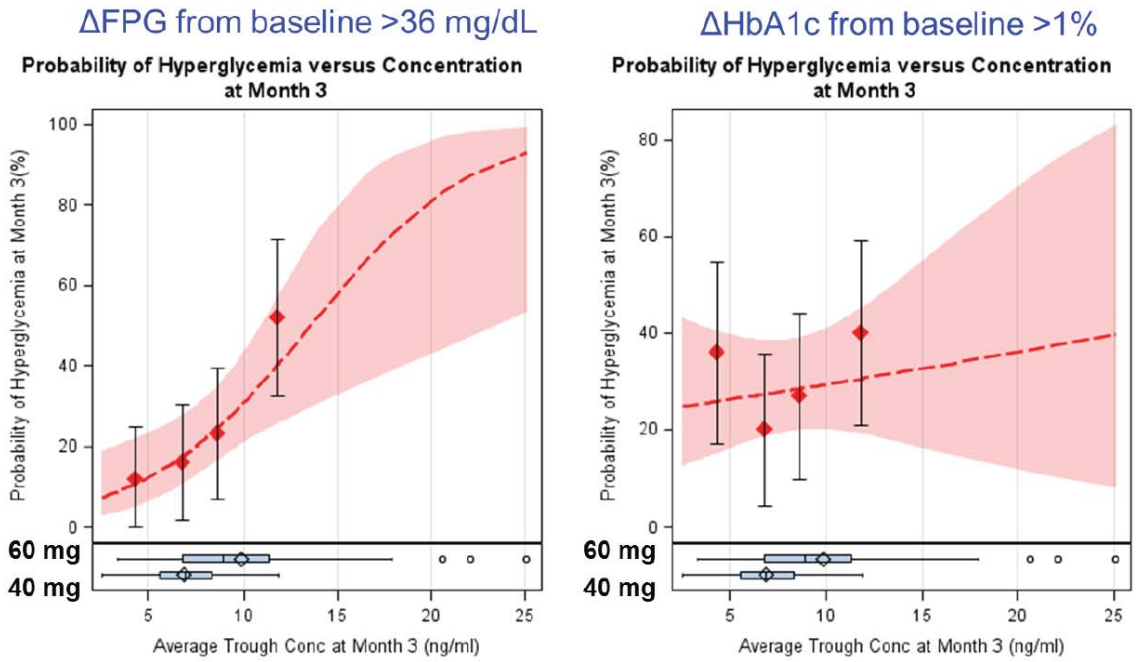


Figure 6. Increase in probability of developing post-baseline hyperglycemia at month 3 with the increase of pasireotide exposure after adjusting for baseline HbA1c (Study C2402). Logistic regression model includes the probability of post-baseline hyperglycemia at month 3 as a function of average pasireotide concentration at month 3 after controlling for baseline HbA1c. For definition by glucose (ΔFPG from baseline >36 mg/dL): Ctrough p value= 0.003; Baseline HbA1c p-value=0.067). For definition by HbA1c (ΔHbA1c from baseline >1%): Ctrough p-value=0.66; Baseline HbA1c p-value=0.0002).

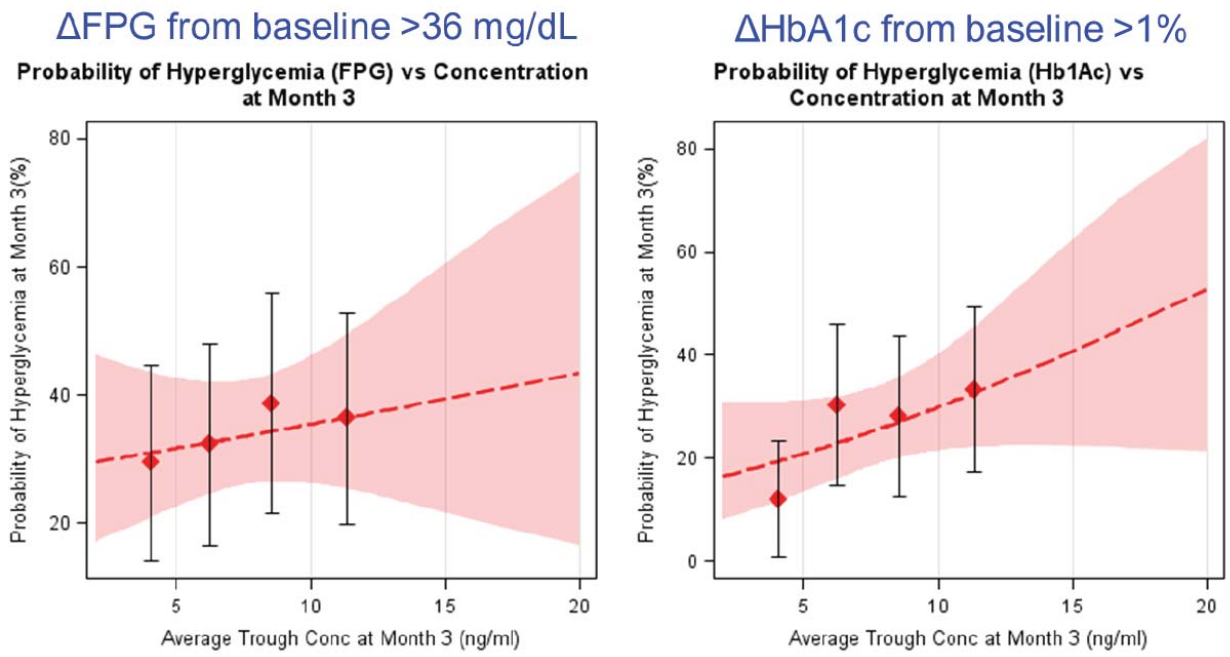


Figure 7. Increase in probability of developing post-baseline hyperglycemia at month 3 with the increase of pasireotide exposure after adjusting for baseline HbA1c (Study C2305). Logistic regression model includes the probability of post-baseline hyperglycemia at month 3 as a function of average pasireotide concentration at month 3 after controlling for baseline HbA1c. For definition by glucose (ΔFPG from baseline >36 mg/dL): Ctrough p-value=0.53; Baseline HbA1c p-value=0.04). For definition by HbA1c (ΔHbA1c from baseline >1%): Ctrough p-value=0.10; Baseline HbA1c p-value=0.24).

6. Clinical Microbiology

The Quality Microbiology Review (DARRTS 8/21/2014) recommends approval. There are no deficiencies and no unresolved issues.

7. Clinical/Statistical- Efficacy

The phase 3 clinical program for Signifor LAR included two clinical trials that compared the efficacy and safety of Signifor LAR to that of two somatostatin analogs currently approved for medical therapy in acromegaly. The first trial (Study CSOM230C2305 or C2305) was conducted in patients with acromegaly who were naïve to medical treatment, and compared Signifor LAR to Sandostatin LAR. The second trial (Study CSOM230C2402 or C2402) studied patients who had been previously treated with the currently approved somatostatin analogs octreotide and lanreotide, but had not achieved biochemical control; this study compared two Signifor LAR doses to continuation of the pre-trial octreotide and lanreotide regimens. The two trials asked different questions: how does Signifor LAR compare to Sandostatin LAR in patients naïve to medical treatment (Study C2305), and does Signifor LAR provide any benefit in patients who failed to achieve biochemical control with other somatostatin analogs (Study C2402), The efficacy of each of these studies is presented and discussed separately.

Study C2305

This was Phase 3, multicenter, randomized (84 sites in 27 countries), blinded[3] study that compared a pasireotide titration regimen of 40-60 mg given once a month to a monthly octreotide LAR regimen of 20-30 mg, both administered intramuscularly. Prior to treatment initiation patients were stratified based on whether they had received surgical treatment or not (40% in the pasireotide arm and 44% in the octreotide arm received such treatment). The first group included patients who had undergone one or more pituitary surgeries but had not been treated medically, while the second was made of acromegaly patients who either refused pituitary surgery or for whom pituitary surgery was contraindicated. The stratification takes into account the possibility that these two different categories of patients may have different characteristics and may respond differently to medical treatment (which indeed turned out to be the case to some extent, as further discussed in the presentation of efficacy results).

A total of 358 patients were enrolled and randomized 1:1 to pasireotide LAR (n=176) and octreotide LAR (n=182). Inclusion criteria ensured that patients had active acromegaly. Specifically, patients had to have a mean 5-point GH concentration profile over 2 hours that was greater than 5 μg/L, or had to demonstrate a lack of suppression of GH to <1 μg/L following an oral glucose tolerance test (this criterion was not applicable for diabetic patients)[4]. In addition, patients had to have an above-normal serum IGF-1 concentration adjusted for age and sex. Given that pituitary radiotherapy can confound the efficacy results, patients who underwent this treatment modality in the previous 10 years were appropriately excluded (patients were allowed however to have had radiation therapy within 4 weeks of study initiation on the basis of the fact that the effects of radiation therapy take time before becoming evident).

Because pasireotide is known to have a diabetogenic effect, patients with diabetes were allowed enrollment only if they had a HbA1C ≤ 8%; they could be on anti-hyperglycemic medication, and they had to be monitored closely and have their anti-diabetic treatment adjusted if necessary. This enrollment criterion allowed an assessment of the effect of pasireotide across a diverse group of acromegalic patients: patients with normal glucose metabolism at baseline, patients with impaired fasting glucose and patients with mild diabetes.

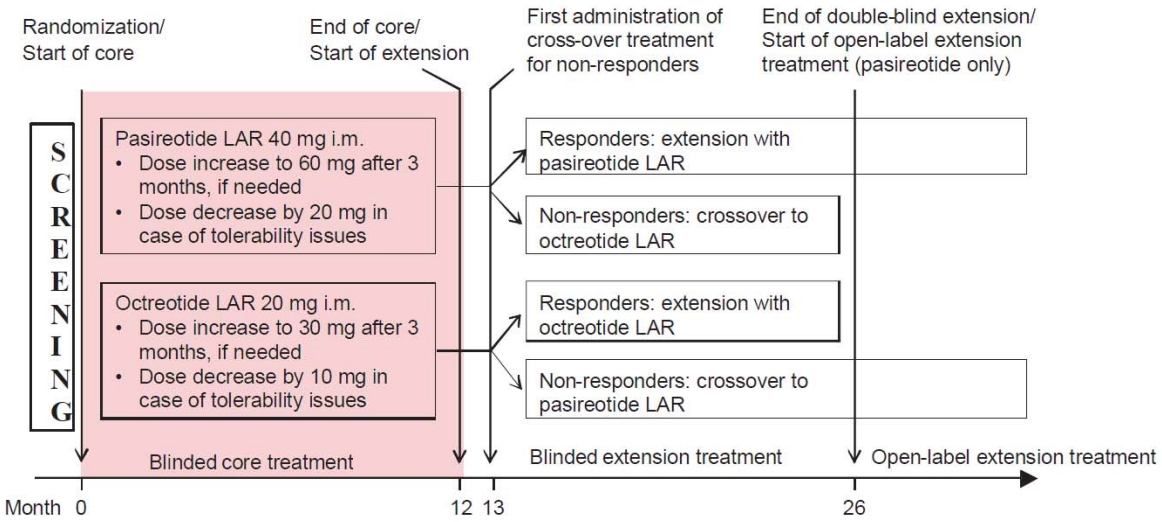
The study included a blinded, "core" period (from randomization to Month 12), a "crossover" period during which patients who responded to treatment were continued on the same regimen while non-responders were switched without randomization to the other treatment arm (Months 13-26) , and an open-label extension (beyond Month 26). This review focuses on the "core" period (highlighted in the study schematic illustrated below) because it represents the

[3] The patient, investigator, and sponsor were reportedly blinded to the treatment assignment. A dedicated independent nurse/coordinator prepared and administered the LAR treatment. This individual was not blinded to the treatment assignment because the study used commercially purchased octreotide, and pasireotide and octreotide LAR formulations had different appearance. The nurse/study coordinator was not to discuss treatment assignment with the patient or the investigator or the sponsor's clinical monitor.

[4] Baseline oral glucose tolerance test (OGTT) was required only in the U.S. but it was only optional outside of the U.S. As such, 90% of US patients had an OGTT compared to 43% outside the US. Because of this, the efficacy analyses are based on 5-point GH levels. The vast majority of patients had a mean 5-point GH level measured as at baseline (13 out of 358 patients did not have this measurement, but had a confirmatory OGTT).

most meaningful direct comparison between the two treatments in the setting of a randomized trial (the crossover did not involve randomization). Of note, the comparator arm was not titrated to at the maximum US approved dose of octreotide LAR of 40 mg, but only to 30 mg instead, which was the maximum approved dose of octreotide LAR in all non-US countries participating in the study. The implication of this trial feature for the efficacy results and labeling will be addressed later in this memorandum.

C2305 Study design



In general, patients' characteristics were balanced at baseline with respect to age (mean of 45.4 years), gender (equal gender distribution), race, and BMI (refer to the statistical review and Table 6 of the Clinical Review). They were also balanced with respect to the duration of disease from time of diagnosis to first dose. There were only minor differences in 5-point mean GH (21.9 µg/L for pasireotide and 18.8 µg/L for octreotide), while baseline mean standardized IGF-1 was the same in both arms (3.1). There were no major differences at baseline with respect to medication use and concomitant medical conditions. Completion of the "core" phase was high in both groups (80.1 % pasireotide, 85.7 octreotide), and there were no striking differences in the frequency of protocol violations and deviations. Compliance was assured by having the medication administered by study personnel.

The primary efficacy analysis was a between-group responder analysis comparing the proportion of patients who had a reduction of GH to <2.5 µg/L and normalization of IGF-1 at 12 months.[5] IGF-1 normalization was not based on absolute numbers or standard deviation score (SDS), which is a frequently used way of reporting IGF-1 in clinical trials. It was based instead on "standardized IGF-1," which is defined as the actual measurement divided by the upper limit of normal for age and gender. Of note, according to this measure, a responder had to have a standardized IGF-1value <1 (any standardized IGF-1value greater than 1 represents

[5] Patients with IGF-1 below lower limit of normal (LLN) were not considered responders in the primary efficacy analysis.

an elevated IGF-1). Discussion with the statistical reviewer did not identify any objections to this measurement.

Key secondary analyses were pasireotide to octreotide comparisons of responders for GH or IGF-1 alone, and tumor volume (all at month 12).

The results of the primary efficacy analysis are reproduced below, from the FDA statistical review. It indicates that 31% of Signifor LAR-treated patients and 19% of octreotide LAR-treated patients were biochemically controlled after 12 months of treatment, and this finding reached statistical significance. The FDA analysis was able to reproduce the applicant's primary analysis. Table 9 of the statistical review presents a variety of sensitivity analyses: excluding data from sites with significant protocol violations, using various methods of imputations for missing data, or using only observed data. They were all consistent with the primary efficacy analysis and all remained statistically significant.

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

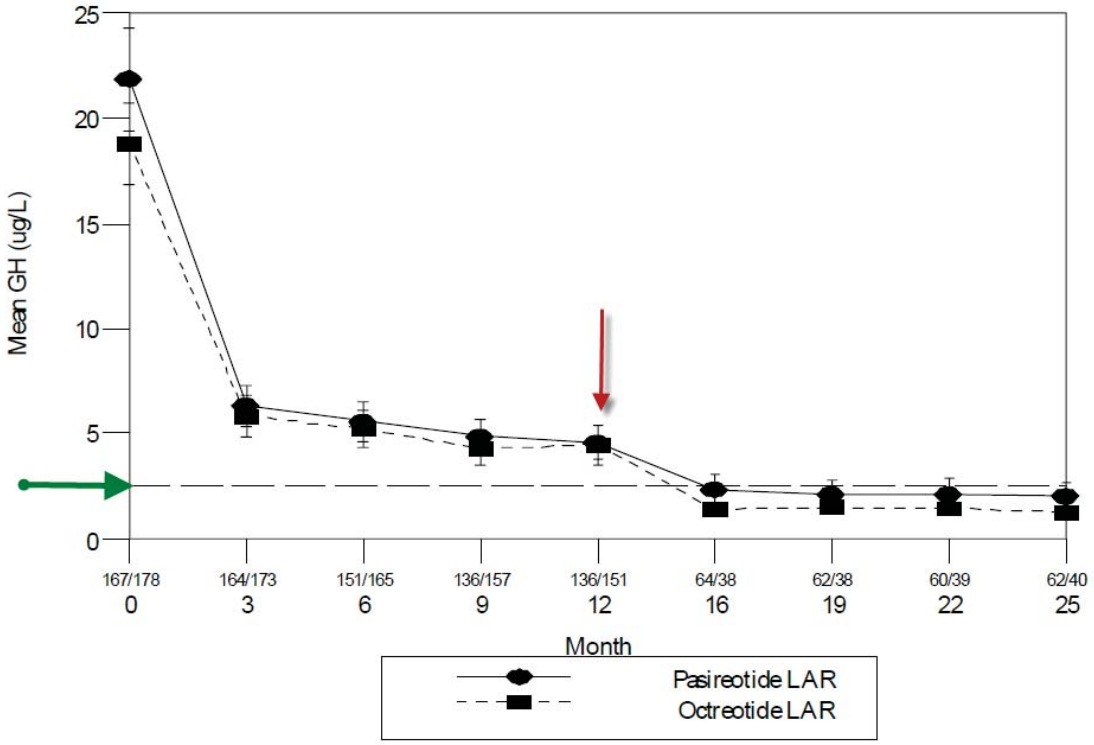
Analyses by stratification arm indicate that the response rates were lower for *de novo* patients than for previously treated ones. It should be noted that, when compared to previously treated patients, *de novo* patients started with higher GH and standardized IGF-1 values. This observed difference is consistent with the exposure-response analyses made by the clinical pharmacology reviewer who commented that patients with higher baseline GH and IGF-1 levels tend to have lower probability of response.

Even if the criterion of GH response was changed from the pre-specified criterion (<2.5 μg/L) to <1 μg/L (a recommended target of treatment by many experts), the between-treatment difference remained statistically significant (p=0.06). However, under this stringent definition the responder rate dropped by half (from 31% to 16.5% in the Signifor LAR arm and from 19% to 9.9% in the octreotide LAR arm).

An intriguing observation made in this trial was that a comparison of responders using the GH criterion alone (GH <2.5 μg/L) was not statistically significant at Month 12, while the opposite observation was true for IGF-1 responders, suggesting that the responder analysis seems to be driven by the IGF-1 response.

A timecourse of mean GH values is illustrated below; it indicates that GH values were above the 2.5 μg/L threshold during the core phase of the trial.

Figure 3-1 **Mean (+/- SE) of GH level by visit and treatment – FAS with data up to crossover - Study C2305**



The IGF-1 changes are shown in Table 14 of the statistical review, reproduced below. The absolute reduction in standardized IGF-1 at Month 12 was 1.7 in the pasireotide group and 1.5 in the octreotide group; the change from baseline to Month 12 was 53.6% in the pasireotide group and 44.3% in the octreotide group.

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

		Pasireotide LAR			Octreotide LAR			
			Mean (SD)	(Min, Max)		Mean (SD)	(Min, Max)	P
Standardized IGF-1	at Baseline	176	3.1 (1.3)	(0.9, 6.9)	182	3.1 (1.2)	(0.8, 7.3)	
Standardized IGF-1	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

A timecourse for mean standardized IGF-1 is reproduced below. At Moth 12 the mean standardized IGF-1 is above 1 in both treatment arms, i.e. above the upper limit of normal for age and gender.

Figure 3-2 **Mean (+/- SE) of standardized IGF-1 level by visit and treatment – FAS with data up to crossover - Study C2305 (FAS)**

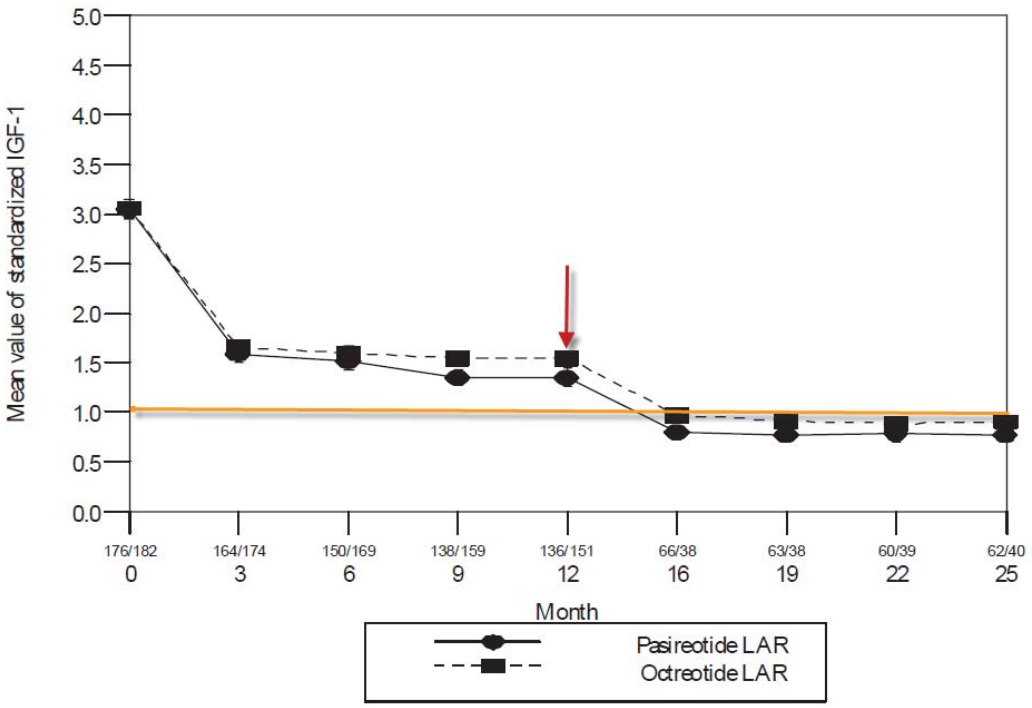


Figure 3.1 and 3.2 also illustrate the persistence of response beyond Month 12, albeit in a selected group of patients who continued in the extension study. It is not surprising that mean GH and IGF-1 were lower in the extension phase because the extension phase tends to enroll preferentially responders.

Finally, there were no differences in tumor reduction between the two treatment groups. The statistical reviewer points out that the change in tumor volume at Month 12 (a prespecified analysis), was -39.9 % for pasireotide LAR and -38.3 % for octreotide LAR and the difference was not statistically significant (p=0.86; from Table 15 of the statistical review). There were also no statistically significant differences in the use of health-related quality of life questionnaire (AcroQol).

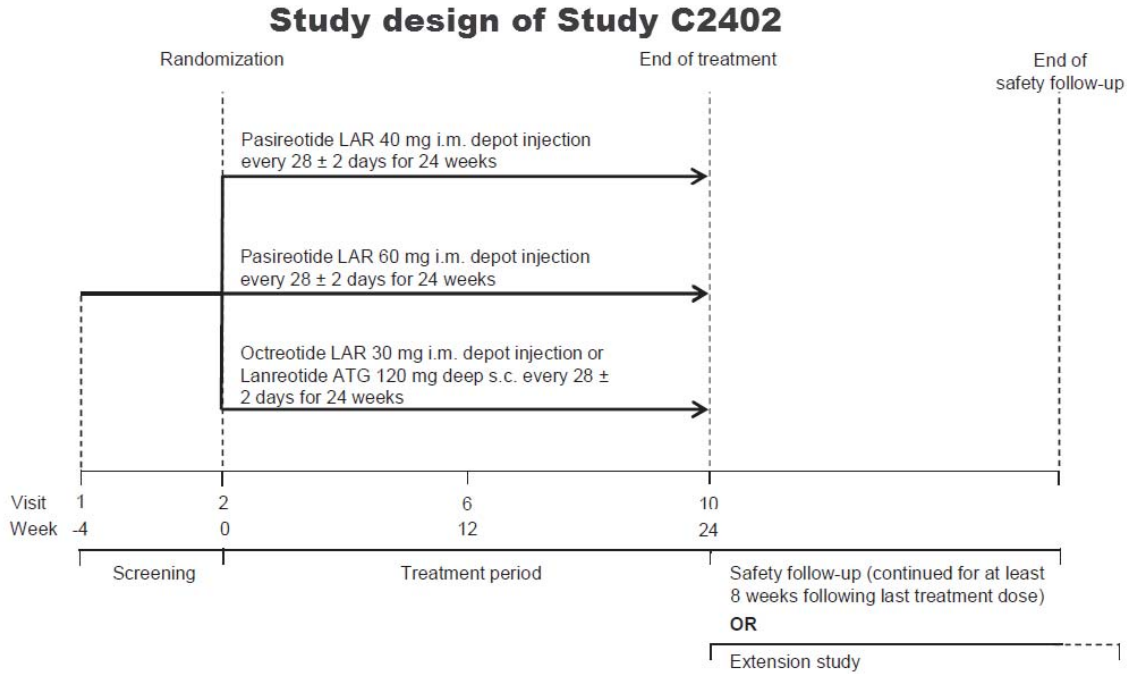
Study C2402

Study C2402 was a Phase 3, multicenter, international, randomized, parallel-group, three-arm study that compared two doses of pasireotide LAR (40 mg and 60 mg) in a double-blind fashion to open-label octreotide. All treatments were given monthly intramuscularly for 24 weeks. The trial enrolled patients with acromegaly who were inadequately controlled despite

being treated with the "maximum" dose of octreotide LAR or lanreotide autogel (ATG) for at least 6 months. Inadequate control was defined as a mean GH concentration of a mean 5-point profile over a 2-hour period >2.5 µg/L and IGF-1 >1.3 × ULN[6] prior to randomization. Octreotide LAR was given at a dose of 30 mg and lanreotide ATG at 120 mg. These doses were the maximum approved dose of octreotide LAR in most countries participating in the study except for the US, where the approved maximum dose of octreotide (Sandostatin LAR) is 40 mg. Exclusion criteria were similar to those in Study C2305 (patients with pituitary irradiation < 10 years were excluded, as were patients with diabetes and HbA1C >8%).

Patients were stratified according to previous treatment (octreotide LAR, lanreotide ATG) and GH level (>2.5 µg/L and ≤ 10 µg/L; and >10 µg/L). The criteria for stratification were different from those in study C2305 which took into consideration whether patients had prior surgery or not, rather than specific GH levels. Using prior treatment as a stratification criterion has sought avoidance of an imbalance by prior medical therapy.

A total of 198 patients were randomized to receive pasireotide LAR 40 mg (n=65), pasireotide LAR 60 mg (n=65) or active control (n=68). Patients were randomized 1:1:1 and were blinded to the specific pasireotide dose but not to octreotide/lanreotide which were administered open-label. In the active-control arm they continued on the same dose of octreotide LAR or lanreotide ATG as before randomization . The study included a six-month "core phase" and an open-ended extension. The trial design for the study is reproduced below.



[6] This inclusion criterion was slightly higher than the IGF-1 criterion used in study C2305, and was meant to account for some variability expected in the IGF-1 assay. In essence it remained a threshold closed to the upper limit of normal.

Patients enrolled in this study displayed small differences in some of the baseline characteristics such as time of diagnosis and/or surgery to first dose. Demographics were well balanced (mean age was 45 years and approximately equal proportions of men and women were enrolled). Mean baseline GH levels were quite different and ranged from 9.6 µg/L in the octreotide group to 12.1 µg/L (pasireotide LAR 60 mg) and 17.6 µg/L (pasireotide LAR 40mg). The mean baseline standardized IGF-1 levels ranged between 2.6 and 2.9. Three quarters of patients had previously received octreotide LAR and a quarter lanreotide ATG. More than half of all patients had received previous medical therapy with agents other than somatostatin analogs (e.g. cabergoline and/or pegvisomant). Two-thirds of all patients had undergone prior surgery.

Completion rates were high (close to or over 90%) and the rates of protocol violations/deviations and concomitant conditions were generally comparable between treatment arms. As in study C2305, treatment compliance was not an issue because study treatment was administered as a monthly intramuscular injection by designated staff at each investigational site.

The primary efficacy analysis compared rates of responders who received pasireotide LAR 40 mg or pasireotide LAR 60 mg separately versus continued treatment with octreotide LAR 30 mg/lanreotide autogel (ATG) 120 mg. Therapeutic response was defined as a GH level <2.5 µg/L and a normalized IGF-1 for sex- and age. The analysis was conducted for the 24 week timepoint. The applicant used a gatekeeping procedure to control the type I error.

None of the patients in the octreotide/lanreotide arm achieved the predefined thresholds of control, while 15% of patients treated with 40 mg of pasireotide LAR and 20% of patients treated with 60 mg of pasireotide LAR did so at Week 24. Both differences were statistically significant and were confirmed by the FDA statistician (40 mg pasireotide LAR versus active control yielded a p-value of 0.001, and 60 mg pasireotide LAR versus active control showed a p value of <0.0001) . A sensitivity analyses which imputed missing patients at week 24 to be responders in the active control arm and non-responders in the two experimental treatment arms (a worst case scenario) was also statistically significant. Table 16, of the statistical review, reproduced below, presents the results of the primary efficacy analysis as well as those for the secondary endpoint of normalized IGF-1 (also statistically significant).

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%)

The reduction of GH to <1 µg/L at Week 24 (a recommended target of treatment by many experts) was 18.5% in the pasireotide LAR 60 mg arm, 12.3%, in the pasireotide LAR 40 mg arm and only 2.9% in the active control arm.

Efficacy conclusions

Trial C2305 provides evidence that a pasireotide LAR titration regimen of 40-60 mg given as a monthly intramuscular injection compares favorably from a statistical standpoint to an octreotide LAR regimen of 20-30 mg once a month . Thirty-one percent of patients treated with pasireotide LAR achieved the prespecified response target, compared to 19% of the octreotide-treated patients. Reduction of GH to < 2.5 µg/L and normalization of IGF-1 represent the traditionally recommended goals for biochemical control in acromegaly. The basis for this goal is the observation that treated patients who achieve this goal have a reduction in mortality. With the use of more sensitive GH assays, the GH target has been changed recently to < 1 µg/L[7]. A pasireotide-to-octreotide difference in responder rate was observed when this criterion was applied.

There is some degree of uncertainty regarding the clinical significance of the primary efficacy analysis because the octreotide regimen was not used at the maximally US approved dose of 40 mg (in this international study several non-US countries capped octreotide doses at 30 mg). It is not known if the between-treatment difference would be the same if the octreotide dose could be further increased. (b) (4)

Trial C2402 indicates that pasireotide LAR regimens of 40 mg and 60 mg , when administered to a group of patients who failed to achieve biochemical control on other acromegaly medical treatments, can each induce control in approximately 15-20% of patients. This suggests that some acromegaly patients who cannot be treated successfully on standard medical therapy may respond to pasireotide. As it is the case with the previous study (C2305) (b) (4) should be moderated by the fact that the control arm could not use the maximally US approved dose of octreotide LAR (40 mg) and about ¾ of patients in this arm were in fact on octreotide LAR.

8. Safety

Dr. Abraham has conducted an extensive review of the safety data focusing appropriately on the controlled periods (the "core" phases) of studies C2305 and C2402. These treatment periods are indeed the most informative because they allow side by side comparisons of pasireotide LAR against the currently approved somatostatin analogs (in particular octreotide). Data for such comparisons were obtained in a blinded fashion in groups of randomized

[7] Holdaway IM et al.: A meta-analysis of the effect of lowering serum levels of GH and IGF-1 on mortality in acromegaly. European Journal of Endocrinology 159, 89-95, 2008.

patients treated in parallel, and the trials ensured that the treatment groups were well balanced at baseline with respect to demographics, co-morbidities, disease-specific history and use of concomitant medications. Given the high morbidity associated with the disease itself, having two homogenous groups of patients is of paramount importance in order to allow for meaningful drug-to-control comparisons. In addition, given the extensive experience with somatostatin analogs, in general, and immediate-release pasireotide for the Cushing's indication, in particular, the Signifor LAR program has been able to also focus on several class-specific safety characteristics such as hyperglycemia, liver enzyme elevations, and QT prolongation.

The number of patients studied at clinically relevant doses of Signifor LAR was 176 for 12 months in Study C2305 and 125 for 6 months in Study C2402 (both studies had high completion rates). Thus, approximately 300 patients were treated for 6 months and over 100 for one year, approximating the ICH E1 recommendations for minimum requirements of patient exposure needed to characterize the safety of chronically administered drugs before approval, even though acromegaly is an orphan indication.

The safety observations made during the pasireotide clinical program in acromegaly are consistent with the known safety profile established for the whole class of somatostatin analogs. They are also very similar to that established for immediate-release pasireotide in the Cushing's syndrome indication. No new, population specific, safety signals were identified in the Signifor LAR acromegaly program.

There were 4 deaths that occurred during Study C2035, two with pasireotide (suicide secondary to psychotic depression, and aortic aneurism), and two with octreotide (sepsis and myocardial infarction). None of them appear to be drug-related. There were no deaths during Study C2402.

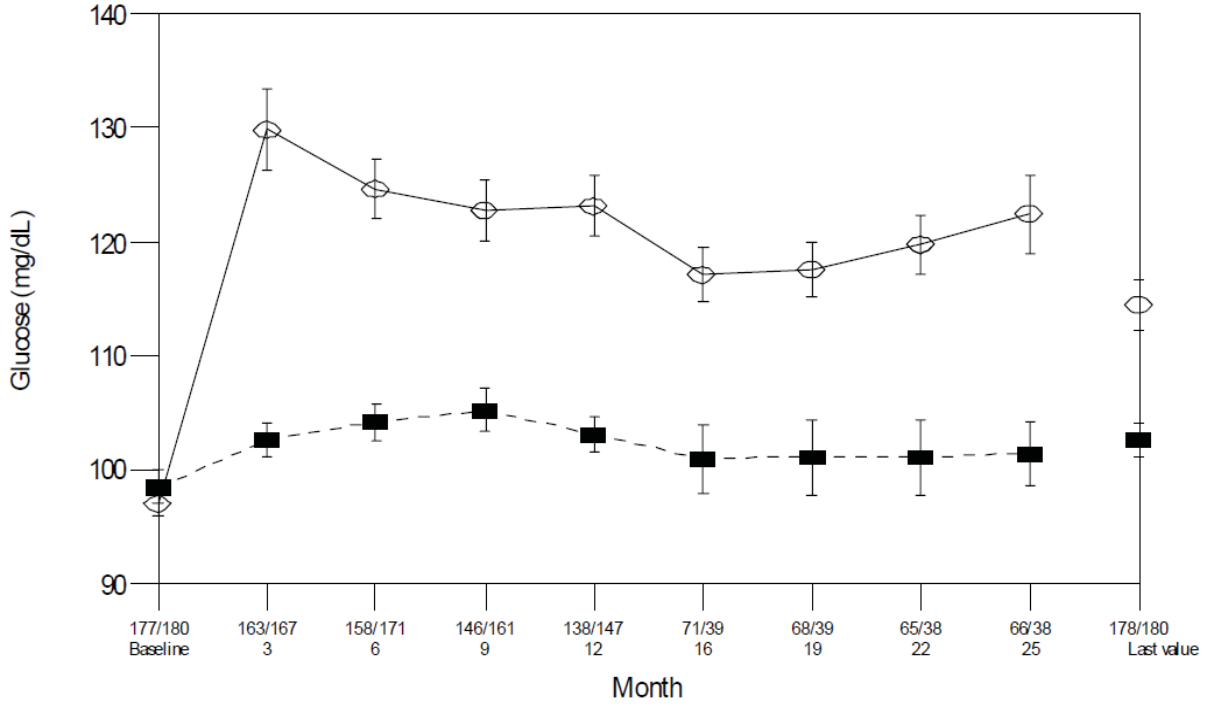
There were no marked imbalances between treatment arms in incidence rates of SAEs or discontinuation rates, although there was a discrete trend against pasireotide. For instance, in Study C2305 the incidence of SAEs was 12.9% for pasireotide and 10.6% for octreotide, and discontinuations due to adverse events occurred twice more frequently in patients in the pasireotide arm than in the octreotide group (7.9% vs.3.3%). A similar trend was observed in C2402 (no discontinuations with active control, and 4.8% and 6.5% discontinuations in the two pasireotide arms respectively, but no consistent between-treatment difference for SAEs). Dr. Abraham reviewed the narratives for these events and observed that in both Phase 3 clinical trials the metabolism and nutrition disorder SOC contributes a higher percent of SAEs and discontinuations (Tables 30, 31, and 32 of the Clinical Review). Importantly, there was no SAEs due to elevated liver enzymes.

Imbalances of several treatment-emergent adverse events were observed. The most striking one was related to adverse events related to glucose metabolism. Captured by preferred terms such as hyperglycemia, diabetes mellitus, blood glucose increase, type 2 diabetes, HbA1C increased, such events occurred invariably with higher frequencies in the pasireotide LAR group over the octreotide arm in Study C2305 (Table 43 of the Clinical Review). For most other adverse events the differences were relatively small. Of note, adverse events of

increased liver enzymes, ALT specifically, were seen more frequently with pasireotide: 7.9% vs. 4.4% with octreotide. Other gastrointestinal adverse events were more frequently observed with octreotide; they included headache, nausea and cholelithiasis, the latter being a well-known complication of somatostatin analog treatment.

All somatostatin analogs approved to date have in the WARNINGS/PRECAUTIONS sections of their labels a description of a hyperglycemic effect, for which the suspected mechanism is suppression of the insulin secretion. However, the hyperglycemic effect seen with pasireotide is much greater that that observed historically with other somatostatin analogs. Although pasireotide was not compared side by side with any other somatostatin analogs in the Cushing's disease program, a direct comparison is available in the acromegaly program and confirms the diabetogenic effect of pasireotide. As observed below in Figure 11 from the Clinical Review, the mean fasting serum glucose level increased from normal at baseline to values in the diabetic and prediabetic range.

Figure 1. Glucose by visit and treatment (SAS, C2305 (open circles, pasireotide LAR; black rectangles, octreotide LAR)

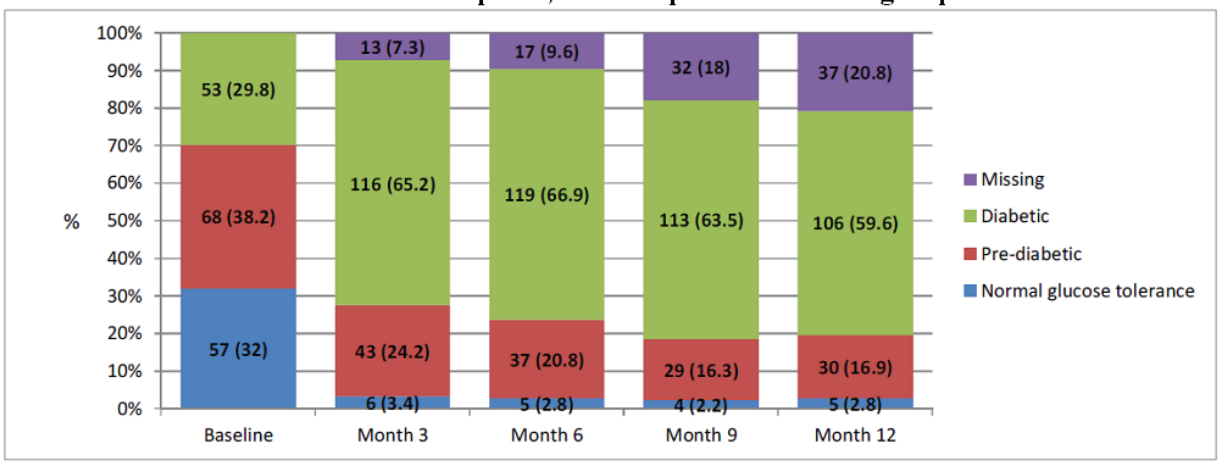


Source: Figure 14.3-1.1, Clinical Study Report C2305

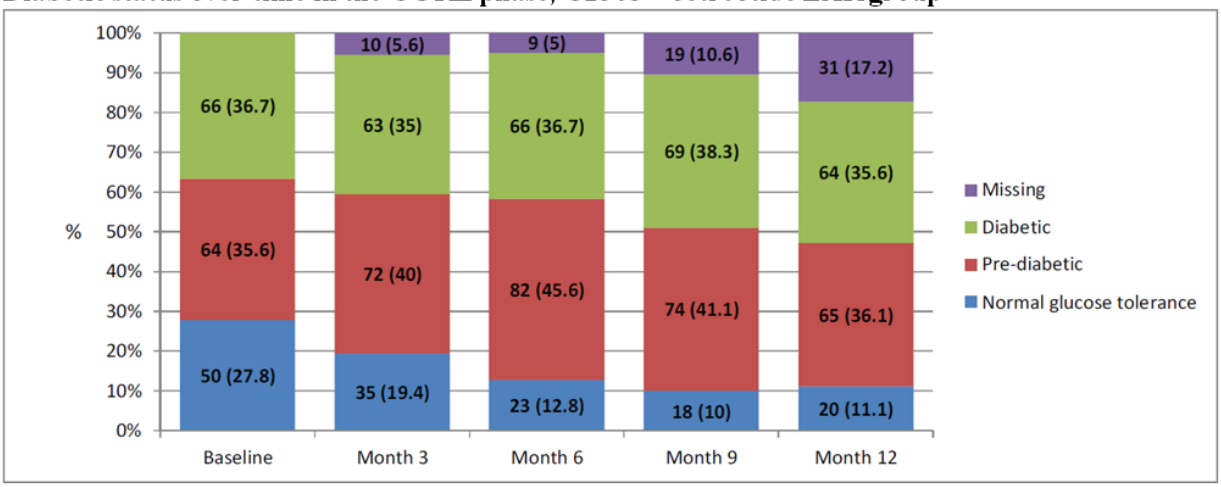
Another illustration describing the hyperglycemic effect of pasireotide in acromegaly patients is provided in the two figures, reproduced below. They describe the diabetes status over time in Study C2305 and were provided by Novartis in response to a clinical information request from the clinical team. At baseline, in both treatment groups the percentages of patients with diabetes, impaired or normal glucose metabolism were similar (about 1/3 of patients fell in each category). Within 3 months following pasireotide LAR treatment initiation, there is a clear reduction in the percentage of patients with normal glucose tolerance from 32% at

baseline down to 3%. Concomitantly, the percentage of patients who met the ADA definition of diabetes almost doubled and remained high throughout the trial. In contrast, in the octreotide arm, there is a steady but less striking reduction in the percentage of patients with normal glucose tolerance but the percentage of patients with diabetes does not change significantly. A similar general picture can be seen in Study C2402 (the glucose metabolic status at enrollment was different in this trial since patients had been previously treated with somatostatin analogs).

Diabetic status over time in the CORE phase, C2305 – pasireotide LAR group



Diabetic status over time in the CORE phase, C2305 – octreotide LAR group



The Clincal Review includes comprehensive analyses of other changes in glycemic parameters such as mean fasting plasma glucose over time by treatment arm, mean changes in HbA1c, graphic displays of individual HbA1c changes, and use of antidiabetic medication. Dr. Abraham points out that significant hyperglycemia occurred in approximately 60-70% of patients in all pasireotide LAR groups compared to approximately 30-35% in the active control groups; that glucose related abnormalities accounted for 21.7% of serious adverse events and 35.7 % of drug discontinuations in the controlled phase of Study C2305. In contrast, glucose related abnormalities resulted in no SAEs and only 1 out of 6 discontinuations in the octreotide LAR group. Similar observations were made in study

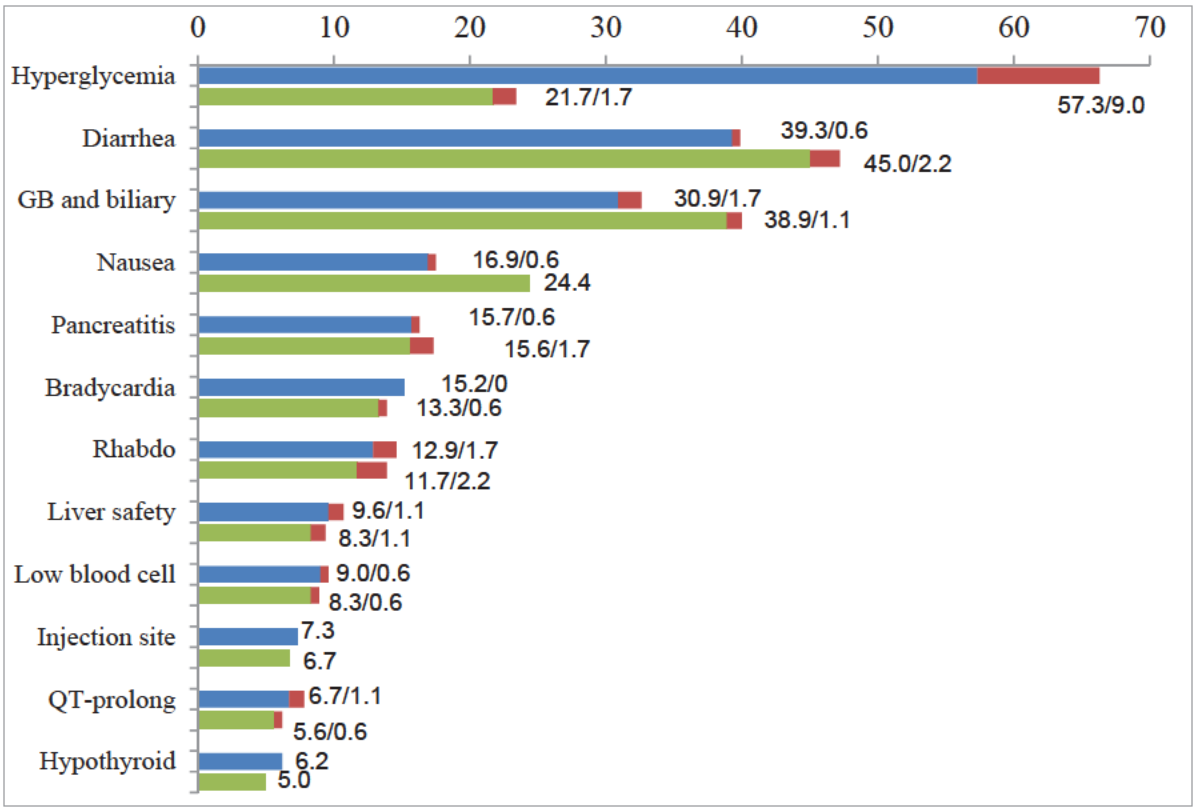
C2402, in which glucose related abnormalities were responsible for 25% of SAEs and 83.3% of drug discontinuations across the combined pasireotide LAR 40 and 60 mg groups in the core phase of the study, while no SAEs and no discontinuations occurred in the active control group.

Hepatic safety received special attention in the current submission because in NDA 200677 a few cases of concomitant liver enzyme and bilirubin elevation were observed. These cases received special attention during the NDA review and were discussed at an Endocrinological and Metabolic Advisory Committee meeting held prior to approval of Signifor. Part of the difficulty of interpreting the above-mentioned findings was the fact that the applicant did not conduct an extensive hepatological evaluation to formally rule out Hy's law, the definition of which includes the provision that no explanations can be found after an extensive work up. After an extensive evaluation, the Advisory Committee consensus was that none of the cases discussed was consistent with drug-induced liver injury.

In Study C2305 the frequency of adverse events of elevated ALT was slightly higher with pasireotide (7.8%) than in the octreotide group (4.4%). Laboratory only ALT elevations >3xULN were seen with similar frequencies (4.5% pasireotide and 3.3% octreotide). No patients with elevated liver enzymes met the criteria for Hy's law. One patient had ALT elevations as high as 7xULN on treatment without evidence of hyperbilirubinemia, and improved without treatment interruption and completed the core phase of the study. In study C2304 a pasireotide-treated patient developed an ALT> 5.7xULN, had the study drug discontinued until liver enzymes returned to normal and was restarted on pasireotide LAR without any recurrence of liver enzyme elevation and completed the study. The Clinical Review presents detailed descriptions of the liver safety findings and narratives.

The clinical review also provides detailed analyses of the frequency and severity of several treatment-emergent adverse events of interest, i.e. adverse events known to occur in association with somatostatin analogs, in general, and with pasireotide, in particular. Figure 76 presents both graphically and numerically a comparison between pasireotide and octreotide in Study C2305. Hyperglycemia was the only adverse event of interest that occurred with a difference > 5% with pasireotide LAR in comparison to octreotide (57.3% vs. 21.7%). AEs that occurred with higher frequency in the octreotide LAR group using the same criteria were diarrhea, gallbladder and biliary-related, and nausea. The rates of AE in the remaining categories were not different by more than 2% between pasireotide LAR and octreotide LAR. Similar overall observations, in particular with respect to hyperglycemia imbalances, were made in Study C2402.

Figure 76. Percentage of patients with AEs of special interest (>5% shown) by treatment group (pasireotide LAR (N=178), blue; octreotide LAR (N=180), green; red, grade 3/4) in CORE phase, C2305, SAS



Finally, I agree with Dr. Abraham's conclusion that with the exception of hyperglycemia, the overall safety profiles of pasireotide LAR and the active control groups are similar in patients with acromegaly.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application.

10. Pediatrics

Signifor LAR has received Orphan Drug designation for the acromegaly indication. herefore, PREA does not apply to this application.

11. Other Relevant Regulatory Issues

11.1 Good Clinical Practice compliance and OSI inspections

In final analysis, both phase 3 clinical studies were conducted in accordance with Good Clinical Practice standards. As described in the clinical review there were several violations however. Two sites in Mexico were closed by Novartis prior to submission of the NDA (they included 22 out of the 358 patients of Study C2305). Novartis provided the efficacy data with and without these two sites. The two analyses were consistent. At two other sites relatively minor GCP violations were identified during FDA inspections.

The Clinical Inspection Summary (DARRTS 7/21/2014) indicates that one domestic site and four foreign clinical sites as well as a contract research organization were audited. It resulted in two Voluntary Action Indicated letters, and four No Action Indicated decisions. The review concludes that "the inspectional findings support validity of the data as reported by the sponsor under this NDA."

11.2 Financial Disclosure

Three investigators had financial agreements with Novartis in the form of research grants. Because two of the sites enrolled only 1 patient each and the third enrolled 2 patients, no additional sensitivity analyses were conducted. Given the small number of patients enrolled at these sites and the objective assessments required for the primary efficacy analyses (laboratory measurements performed centrally) it is highly unlikely these three sites could bias the final study results in any significant way.

11.3 Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

At the request of DMEP the Interdisciplinary Review Team (IRT) provided a consult for this application (DARRTS 7/17/2014). Of note, two QT studies (B2113, B2125) have been performed with the subcutaneous formulation and have already been reviewed by IRT. A significant QTc prolongation effect of pasireotide was detected and subsequently labeled for Signifor. The current Signifor label contains a WARNING/PRECAUTION for QT prolongation and bradycardia. With respect to QT prolongation the label describes the risk for prolongation at therapeutic doses, advises that a baseline ECG and subsequent monitoring are advisable, as is monitoring of hypokalemia and hypomagnasemia, and recommends cautious use in patients at risk.

Within this submission, the sponsor performed drug concentration-QT analysis with data from the two registration trials (C2305, C2402) using the LAR formulation. No significant QT effect was observed. The IRT consult comments that the Cmax following the highest therapeutic LAR dose of 60 mg is similar to that of the 0.6-mg bid therapeutic dose in the QT study (the currently approved Signifor doses are 0.3, 0.6 and 0.9 mg bid), and that it is expected that the QT effect of the LAR formulation will be covered by the studies done with the immediate-release product.

The consult agrees with applicant's assertion that no new cardiac safety concerns have emerged in the Phase 3 studies conducted in the acromegaly population, acknowledges the

proposed labeling but does not recommend any specific changes, deferring the final labeling decisions to the DMEP.

11.4 Risk Evaluation and Mitigation Strategy (REMS) Review

A REMS consult was provided by the Division of Risk Management (DRISK) on 8/8/2014. After reviewing the regulatory history of Signifor and Signifor LAR, and the safety results of the current NDA, the consult concludes that the benefit-to- risk profile of the proposed pasireotide LAR doses for the medical treatment of patients with acromegaly is acceptable and, based on the reported data, a REMS is not necessary at this time.

11.5 CDRH Human Factors Consult

A CDRH Human Factors Consult is provided by the Center for Devices and Radiological Health's Human Factors Premarket Evaluation Team in response to a DMEP request (DARRTS 8/19/2014). The consult summarizes some of the relevant user failures observed during the human factor study and the proposed changes to the IFU that Novartis has implemented following review of the study results (primarily extending to 30 minutes the period of time necessary for temperature equilibration of the drug product to room temperature prior to reconstitution, and shaking the vial moderately after adding the diluent to ensure a uniform mixture). The consultant does not believe that these changes to the IFU need to be re-tested.

The consultant also notes that one participant experienced minor leakage of the vial content between the vial adapter and the vial while shaking. The volume of fluid that leaked is estimated to be less than 15% of the total volume.

12. Labeling

At the time of this memorandum, the label has already undergone significant revisions following input from all disciplines. Clams of superiority favoring pasireotide have been removed from the label because the comparator arms did not use the maximum US approved dose of Sandostatin LAR.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval.

- Risk Benefit Assessment

The Signifor LAR program has demonstrated that this long acting formulation of pasireotide can be an effective treatment capable of suppressing GH and IGF-1 levels in the normal range in approximately 31% of patients with acromegaly who are naïve to medical therapy. It also showed that some patients (20%) who could not be managed successfully on other somatostatin analog regimens may benefit from treatment with Signifor LAR. Any comparison to the current standard of care regimens should be interpreted with caution, however, because the active control arms in the Signifor LAR phase 3 clinical trials did not use the highest approved US dose, and there is the theoretical possibility that patients in the control arms could have responded differently if higher somatostatin doses had been used.

The safety profile of pasireotide is largely similar to that of other approved somatostatin analogs with the exception of hyperglycemia and the degree of diabetogenic potential. This issue has been discussed in detail at the Signifor EMDAC for the Cushing's disease indication in 2012 when the final recommendation was that this adverse reaction should not preclude approval of the drug for the Cushing's disease indication. I think that similar considerations can apply to the acromegaly indication as well. Normalization of GH and IGF-1 has been associated with reductions in mortality rates in acromegalic patients, and hyperglycemia can be managed by using antidiabetic medications or by discontinuing the drug if the hyperglycemic response is substantial. With these considerations in mind, I believe that the benefit-to-risk ratio is overall favorable, and Signifor LAR can provide another tool for endocrinologists to manage and further individualize the medical treatment of acromegaly.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

No comments in addition to those related to the approval decision and the final agreed label.

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

/s/

DRAGOS G ROMAN
12/15/2014

JEAN-MARC P GUETTIER
12/15/2014
I concur.