CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203255Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	203255
Applicant Name	Novartis
Date of Submission	November 15, 2013
PDUFA Goal Date	December 15, 2014
Proprietary Name / **Established (USAN) Name**	Signifor LAR/Pasireotide
Dosage Forms / Strengths	Powder for injection / 20, 40, 60 mg IM every 28 days
Proposed Indication(s)	1. For the treatment of patients with acromegaly (b) (4)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Smita Abraham, MD
Statistical Review	Jennifer Clark, PhD
Pharmacology Toxicology Review	Miyun Tsai-Turton, PhD
CMC Review/OBP Review	Ravindra Kasliwal PhD, Milagros Salazar PhD, and John Duan PhD,
Clinical Pharmacology Review	Sang Chung PhD and Lian Ma PhD
DSI	Cynthia Kleppinger, MD
CDTL Review	Dragos Roman, PhD

OND=Office of New Drugs
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

On November 15, 2014 Novartis submitted a New Drug Application (NDA) for Signifor LAR under section 505(b)(1) of the Food, Drug and Cosmetic Act. The applicant is seeking to indicate Signifor LAR for the treatment of patients with acromegaly (b) (4) Signifor LAR is a somatostatin receptor agonist and binds to four of the five known somatostatin receptor subtypes (SSTR1, 2, 3 and 5). The dosage form is a powder for suspension, for injection, and the proposed dosage is 20 or 40 or 60 mg delivered by intramuscular injection every 28 days.

2. Background

Acromegaly is a clinical syndrome most commonly caused by a growth hormone (GH) secreting pituitary adenoma and characterized by disordered somatic growth and metabolic abnormalities. The syndrome arises due to chronic hypersecretion of growth hormone (GH) which in turn stimulates hepatic production of insulin-like growth factor-1 (IGF-1). Acromegaly has historically been considered a rare disease, with a reported estimated prevalence ranging from 38 to 69 cases per million and an annual incidence rate of 3 to 4 cases per million. However, recent cross-sectional studies using screening techniques relying on IGF-1 have reported a much higher disease prevalence (i.e., 480-1000 per million individuals)[1],[2].

The clinical manifestations of acromegaly include signs and symptoms attributed to tumor mass effects (i.e., headaches, vision loss, pituitary dysfunction), effects related to disordered somatic growth (i.e., enlargement/overgrowth of soft tissue, skin, bone, joints and other visceral organs) and effects related to disordered metabolism (e.g., insulin resistance/diabetes). The effects on somatic growth and on metabolism are the direct results of excess GH/IGF-1 levels and are believed to be major contributors to the increased mortality[3] in patients with acromegaly.

The goal of therapy in acromegaly is to correct the excess GH secretion, to lower circulating IGF-1 to sex and age appropriate reference levels (i.e., biochemical normalization) and to address tumor-related mass effects. Biochemical normalization has been reported to improve soft tissue swelling (e.g., carpal tunnel syndrome), hyperglycemia, sleep apnea visceral enlargement (e.g., left ventricular mass) and cartilaginous overgrowth in case series.

Transsphenoidal surgery (TSS) is the treatment of choice for microadenomas, noninvasise macroadenoma or for large tumors causing mass effects (e.g., visual impairment due to optic nerve compression). The success of transphenoidal surgery is dependent on both the

[1] Clin Endocrinol (Oxf). 2008 Sep;69(3):432-5.
[2] Pituitary. 2011 Sep;14(3):217-21.
[3] Patients with acromegaly die predominantly from cardiovascular complications which has been attributed hypertension, left ventricular hypertrophy, cardiomyopathy, and sleep apnea that arises due to excess GH/IGF-1

technical expertise of the neurosurgeon and the size of the tumor. Biochemical normalization rates have been reported to range between 75-95% and 40-70% at one year post-TSS for micro and macroadenoma respectively. Complications of surgery include mortality (1% for large invasive adenomas), pituitary hormone insufficiency, central diabetes insipidus, meningitis and cerebrospinal fluid rhinorrhea.

Drug therapy is reserved for patients who; have persistent or recurrent disease, refuse surgery, have unressectable tumors[4] or have unacceptable surgical risks (e.g., severe cardiomyopathy or cardiopulmonary disease). Approved therapies with an indication for the treatment of acromegaly include somatostatin analogs[5] and GH receptor antagonists[6]. These products were approved on the basis of demonstrating reductions in IGF-1-levels at the end in short term (i.e., 4-12 weeks) randomized, double-blind, placebo-controlled trials. In the majority of patients drug therapy does not fully normalize biochemical abnormalities but reduces levels of IGF-1 and in the case of the GH receptor antagonist improved symptoms and signs associated with acromegaly (ring size, soft tissue swelling, arthralgia, headache, perspiration). Adverse reactions associated with somatostatin analogs include gastrointestinal tolerability issues (nausea, abdominal pain, and diarrhea), glucose intolerance, reductions in gallbladder contractility and delay in gallbladder emptying and an increased risk for gallstone as well as bradycardia. Adverse reactions associated with the GH receptor antagonist include liver injury and hypoglycemia. The dopamine agonist cabergoline is used off-label for the treatment of acromegaly, it is reported to be less effective than somatostatin analogue or GH receptor agonist for biochemical normalization but has the advantage of being orally administered.

Radiation therapy is a third treatment option however this therapeutic modality takes years to become effective and is usually reserved for patients whose disease is not controlled by surgery or medications.

3. CMC/Device

I concur with the conclusions reached by the CMC/Device reviewers that there are no outstanding CMC/Device issues that preclude approval. Pasireotide is presented as a kit containing a 6 mL glass vial with powder, a 3mL pre-filled syringe with diluent for suspension, a (b) (4) plunger rod, a vial adapter, and a 20 gauge 40 millimeter stainless steel injection needle. The stability studies support an expiration date of 36 months at 5 degrees Celsius for the vials containing pasireotide powder and 60 months at 5 degrees Celsius for the pre-filled syringe containing diluent. Once reconstituted the suspension must be used immediately and administered intramuscularly by a trained healthcare professional.

[4] e.g., Large tumors invading the cavernous sinus in close proximity to the internal carotid
[5] octreotide (sandostatin and sandostatin LAR), lanreotide (somatuline depot)
[6] Pegvisomant

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Tsai-Turton, the nonclinical pharmacology/ toxicology reviewer, that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

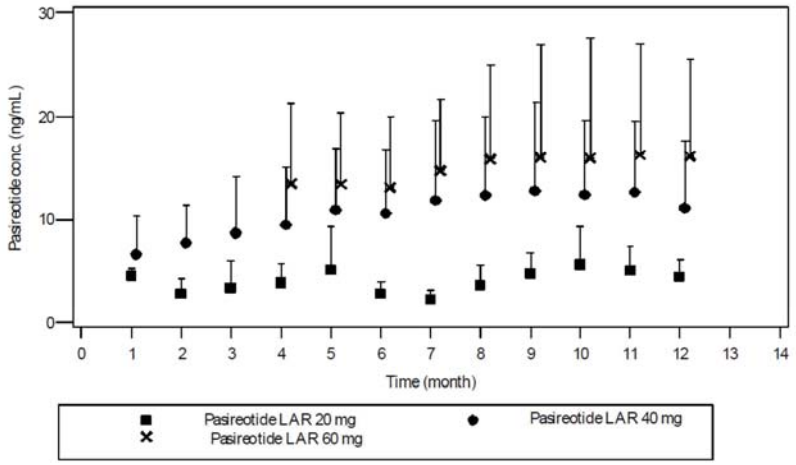
5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by Drs. Chung and Ma, the clinical pharmacology/ biopharmaceutics reviewers, that there are no outstanding clinical pharmacology issues that preclude approval. Key aspects of their review are summarized below.

Single dose administration studies in healthy volunteers revealed dose-proportionality within the proposed dosing range, a prolonged terminal apparent half-life (16 days), a maximal serum concentration achieved on ~ Day 20, and a mean maximum serum concentration (C_{max}) at the 60 mg dose of ~20 ng/mL.

Multiple dose PK studies in patients with acromegaly revealed, approximate proportionality within the proposed dosing range, achievement of steady state concentration after three injections and minimal drug accumulation with repeated injections. Mean trough drug concentrations achieved by dose for each of the twelve months in pivotal study C-2305 are shown in figure 9 of the clinical pharmacology review and re-copied below (note that the 60 mg was used only in patients who needed additional control at 12 weeks).

Figure 9.



PK/PD modeling from early studies had suggested that the effective concentration needed to achieve GH normalization ($C_{effective}$) was ~ 5 ng/mL and doses were select to achieve trough levels at or above this concentration. Figure 1 in the clinical pharmacology review shows that in pivotal trial C-2402 mean steady state drug concentrations were above 5 ng/mL for more than two third of all subjects treated with both 40 and 60 mg of pasireotide LAR. The clinical

pharmacology reviewers agree that data from dose response exploration in pivotal trial C-2402 appear to support incremental benefit in term of GH suppression of the 60 mg dose over the 40 mg dose.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Drs. Abraham and Clark have reviewed the efficacy findings in details and Dr. Roman has summarized key findings in his CDTL memorandum. Refer to these reviews for full discussions. The efficacy of Signifor LAR for the treatment of patients with acromegaly was demonstrated in two randomized controlled trials evaluating patients who were naïve to drug therapy (C-2305) and patients who were inadequately controlled on available drugs (C-2402). Although these trials demonstrated efficacy, they did not provide substantial evidence to conclude that Signifor LAR is clinically superior to octreotide LAR for the treatment of acromegaly. The reasons for this will be discussed below.

Trial C-2305: Efficacy in patients with Acromegaly Naïve to Drug Therapy

This trial was a randomized, blinded[7], active controlled trial comparing the efficacy of pasireotide LAR to that of octreotide LAR. The primary objective of the trial was to compare the biochemical response rate at the end of 12 months between the two treatment arms. Biochemical response was defined as having a GH level of less than 2.5 mcg/L and an IGF-1 within the normal range (appropriate for age and sex).

Patients were eligible to participate in the study if they had acromegaly[8] and had not previously received medical therapy. Patients in this study could but were not required[9] to have had at least one past pituitary surgery. The study excluded patients with diabetes who had an HbA1c above 8% and patients with: class III and IV heart failure, liver disease, risk factors for torsades de pointes, a history of gallstone disease, a creatinine two times above the ULN and who had radiation therapy within 10 years preceding the screening visit.

[7] True double-blind treatment was not feasible due to differences in appearance between the two-treatments. An unblinded nurse administered treatment and completed an Unblinded Dosage Administration Record case report form. Blinding of patients, investigator and sponsor was to remain intact throughout the study.
[8] Defined as a past GH-secreting adenoma surgery or the presence of a pituitary adenoma on MRI and by a documented inability to suppress GH levels below 1 mcg/L after a 75 gram oral glucose tolerance test, or by GH levels greater than 5 mcg/L on a 5-point profile over 2 hours, or by IGF-1 levels above the upper limit of normal for age and sex.
[9] Deemed ineligible for medical reasons or who had refused surgery.

Subjects were randomized 1:1 to monthly injections of Signifor LAR 40 mg (N=176) or octreotide LAR 20 mg (N=182) and randomization was stratified according to surgical status. The doses of Signifor LAR and octreotide LAR could be increased to 60 mg and 30 mg respectively at three months in patients who tolerated the drugs and had not achieved biochemical control.

An important shortcoming of the trial design was that the maximally effective dose of octreotide LAR approved for use in the United States was not used (i.e., 40 mg). Interpreting findings of superiority in a trial where the comparator is not used at maximally effective dose is problematic because it raises questions with regards to the fairness of the comparison[10]. In this type of design, the comparator is placed at an unfair disadvantage and the overall results are biased in favor of the new drug.

Demographics and disease characteristics were mostly balanced at baseline (refer to Tables 5 and 12 in Drs. Clark and Abraham's reviews respectively for details). Overall the study population was comprised of subjects younger than 65 years (94%), female (52%), Caucasian (60%) and Asian (23%). The mean age at baseline was 45 years and on average patients had been diagnosed for 2 years prior to randomization. Slightly more patients randomized to octreotide had had surgery (40% versus 44% see Table 10 in Dr. Abraham's review). This could be important in interpreting efficacy if there are differences in refractoriness of treatment predicted by surgical failure. The median baseline GH levels were 9 and 10 mcg/L respectively in the Signifor LAR and octreotide LAR arm, the median baseline IGF-1 levels were 2.9 fold above the upper limit of normal for age and sex in both groups.

During the trial, more patients on Signifor LAR discontinued before month 12 (i.e., 80% versus 86%) and cited product related reasons[11] for discontinuations (i.e., adverse events 8% versus 3%).

The primary analysis was performed on all randomized patients, used an LOCF strategy to handle data missing at month 12[12] and compared the proportion of patients who had a GH level of less than 2.5 mcg/L and normalization of IGF-1 levels (age and sex appropriate) at end of treatment between the two treatment arms.

The proportion of subjects who had biochemical normalization on the sponsor's analysis and on Dr. Clark's sensitivity analysis are shown in the table below. Subjects who met the GH criterion but who had an IGF-1 level below the normal range were considered non-responders for the purpose of the main analysis. Considering these patients as responders would not alter conclusions (refer to Table 19 in Dr. Abraham's review).

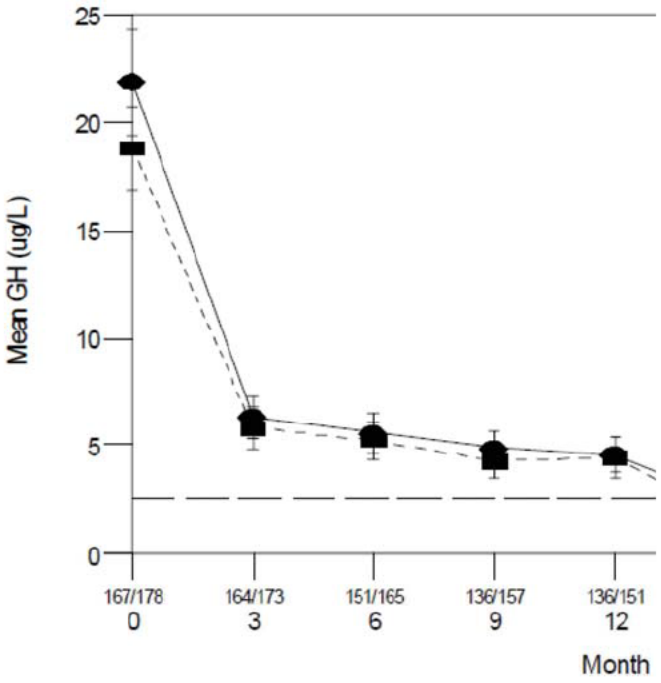
[10] Refer to International Conference on Harmonization (ICH) guidance E10 (Choice of Control Group and Related Issues in Clinical Trials): Section on Fairness of Comparisons.
[11] Hyperglycemia
[12] See Dr. Clark's review for full discussion.

Table 1: Proportion of Patients Achieving Normalization at Month 12 in Main Analysis and One Sensitivity Analysis (Source: Adapted from Table 9 in Dr. Clark's review)

	Signifor LAR (N=176)		*Octreotide LAR (N=182)*			
	%	*(Exact 95% CI)*	*%*	*(Exact 95 % CI)*	*OR (95% CI)*	*p-value*
LOCF	*31.3*	*(24.5, 38.7)*	*19.2*	*(13.8, 25.7)*	*1.9 (1.2, 3.2)*	*0.0075*
Missing Considered Non-Responders	*29.0*	*(22.4, 36.3)*	*18.1*	*(13.8, 25.7)*	*1.9 (1.1, 3.1)*	*0.0138*

The primary endpoint was a two-component composite of GH and IGF-1 requiring that patients satisfy both criteria to be declared a "responder". Dr. Clark examined each of the two components individually and found that GH suppression to less than 2.5 mcg/L (i.e., the first key secondary endpoint) and to less than 1 mcg/L was similar between Signifor LAR and octreotide LAR groups (refer to Tables 10 and 11 of her review). In addition, no significant difference in mean percent GH reduction from baseline was observed between groups [Mean (SD) % decrease from baseline: 70 (26) % and 65 (32) % for Signifor LAR versus octreotide LAR respectively]. This concept is illustrated in figure 5 (copied below) of Dr. Abraham's review which plots mean GH levels in mcg/L across each of the monthly visits over 12 months.

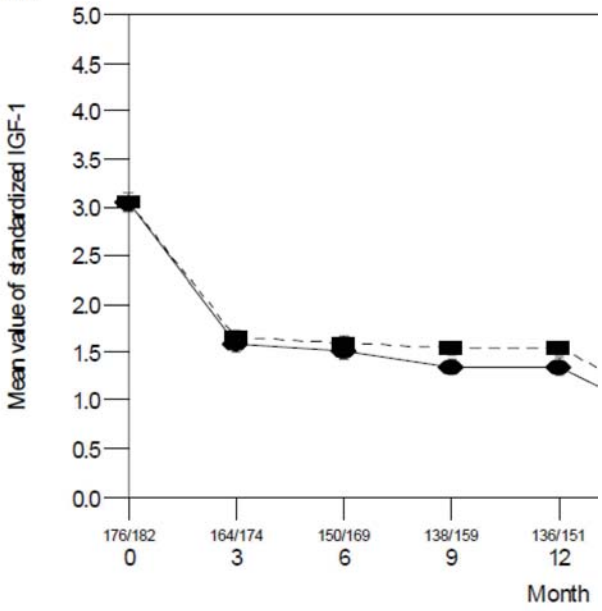
Figure 5. Mean (+/-) of GH level by visit and treatment, da



Dr. Clark also examined the IGF-1 response between the two groups and found that more subjects on Signifor LAR met the IGF-1 criterion than subjects on octreotide LAR (refer to Table 13 of her review). Non-significant differences in mean IGF-1 change from baseline (p-value = 0.09) and significant differences in mean percent IGF-1 decrease from baseline (p-value= 0.01) were seen between groups. The magnitude of the between group difference in

mean IGF-1 reduction from baseline was small and unlikely to be clinically meaningful [Mean change from baseline (SD) expressed as the number of standard deviation above the upper limit of the normal range: -1.7 (1.2) versus -1.5 (1.3) for Signifor LAR versus octreotide LAR]. The percent decrease (SD) from baseline was 54 (29) % versus 44% (40) for Signifor LAR and octreotide LAR respectively. This is illustrated in figure 6 of Dr. Abraham's review copied below.

Figure 6. Mean of standardized IGF-1 level by visit and tr
C2305



There were a number of other important secondary endpoints which did not support a conclusion that Signifor LAR offered clinically superior control over a sub-maximal dose of octreotide LAR. First, no between group differences in tumor volume reduction from baseline were noted (refer to Table 15 in Dr. Clark's review). Second, symptoms score (headache, arthralgia, ring size, fatigue) improved to a similar extent in both groups.

The applicant used 22 questions from the AcroQoL 38 item questionnaire to measure changes in health-related quality of life in C-2305. This instrument and its ability to measure health-related quality of life was reviewed by Dr. Choudry from the SEALD team. The instrument was found to lack construct (snoring and articulating words are not psychological related impacts) and content validity because it omits important patient experience with acromegaly (e.g., paresthesias, loss of memory, severe headaches, vision problems, tremors, excessive sweating) susceptible to influence health-related quality of life.

Trial C-2305 demonstrates that Signifor LAR is effective in reducing both GH and IGF-1 levels in subjects with acromegaly who had not received previous medical therapy. Reduction in both GH and IGF-1 levels was associated with improvement in symptoms associated with acromegaly (i.e., ring size, headache, fatigue, perspiration, paresthesia, arthralgia). Signifor

LAR was at least as effective as a high, though submaximal dose, of octreotide LAR a known effective drug in this disorder. Even in the absence of control it is unlikely that reduction in GH and IGF-1 to the extent seen in this trial could occur spontaneously. Although only 30% achieved targeted biochemical control, 49% of participants randomized to Signifor LAR partially responded to therapy (refer to Table 19 in Dr. Abraham's review).

Trial C-2402: Efficacy in patients with Acromegaly Inadequately Controlled on Somatostatin Analogues

This trial was a randomized, open-label[13], three-arm, parallel group trial comparing initiation of Signifor LAR 40 mg and Signifor LAR 60 mg to continued somatostatin analogue therapy. The primary objective of the trial was to demonstrate that the biochemical response rate at the end of 6 months on Signifor LAR 40 mg and Signifor LAR 60 mg was no worse than continuing failed somatostatin analogue therapy. Biochemical response was defined as having a GH level of less than 2.5 mcg/L and an IGF-1 within the normal range (appropriate for age and sex) at end of treatment.

Patients were eligible to participate in the study if they had acromegaly and had not achieved biochemical normalization on octreotide LAR 30 mg or lanreotide LAR 120 mg for the six months which preceded study entry. Patients on GH receptor antagonist or dopamine agonists at screening were to undergo an 8 week washout prior to randomization.

The study excluded patients with diabetes who had an HbA1c above 8% and patients with: class III and IV heart failure, liver disease, risk factors for torsades de pointes and arrhythmia, a history of gallstone disease, pancreatitis, bile duct dilatation, a creatinine two times above the ULN and who had radiation therapy within 10 years preceding the screening visit.

Subjects were randomized 1:1:1 to monthly injections of Signifor LAR 40 mg (N=65), Signifor LAR 60 mg (N=65) or continued failed somatostatin analogues (N=68: octreotide LAR 30 mg accounting for 75% and lanreotide LAR 120 accounting for 25%).

In addition to the fact that this trial was open-labeled, an important shortcoming of the trial design was that the maximally effective dose of octreotide LAR approved for use in the United States was not used (i.e., 40 mg) and that subjects were selected specifically on the basis of having failed the comparator group. Interpreting findings of superiority in a trial where one of the comparator is not used at maximally effective dose and where patients are selected on the basis of having failed the comparator is problematic because it raises questions with regards to the fairness of the comparison. In this type of design, the comparator is placed at an unfair disadvantage and the overall results are biased in favor of the new drug. Had patients been selected on the basis of having failed Signifor LAR therapy it is likely that the results would have favored the two other somatostatin analogues.

[13] Signifor LAR dose was blinded.

Demographics and disease characteristics were mostly balanced at baseline (refer to Tables 9 and 11 in Dr. Abraham's review for details). Overall the study population was comprised of subjects younger than 65 years (>90%), female (~54%), Caucasian (~80%) and Black (8%). The mean age at baseline was ~45 years and on average patients had been diagnosed for ~3 years prior to randomization. Sixty to 80% of patients had had pituitary surgery. The median baseline GH levels were 7, 5, and 6 mcg/L in the, Signifor LAR 40 mg, Signifor LAR 60 mg and continued somatostatin analogue arms respectively. The median baseline IGF-1 levels were 2.3, 2.6 and 2.9 fold above the upper limit of normal for age and sex across those three groups.

At the end of 24 weeks 10 (15%), 13 (20%), and 0 (0%) of patients achieved biochemical normalization on Signifor LAR 40 mg, Signifor LAR 60 mg and previous somatostatin analogue therapy respectively. The results of this trial suggest a dose response between the low and high dose Signifor LAR. It also suggests that a small percentage of patients who do not benefit from currently available therapy could benefit from Signifor LAR. The results of this trial do not support a superiority claim against available therapies because of trial design issues reviewed above.

8. Safety

The main safety issues identified in the review included issues related to glucose abnormalities, gastro-intestinal tolerability issues and issues related to gall-bladder disorders (i.e., motility and gall stone disease).

Dr. Abraham has reviewed the safety of Signifor LAR in details. Dr. Roman has summarized the main findings in his CDTL memorandum. 176 and 130 subjects were exposed to Pasireotide LAR in C-2305 and C-2402 phase 3 trials. The mean duration of exposure to Signifor LAR in the core-phase of C-2305 was 301 days. The mean duration of exposure to Signifor LAR in the core-phase of C-2402 was ~ 164 days. Additional safety data for patients volunteering to participate in the extension phases of both of these trials were received at the time of the 120 day safety update.

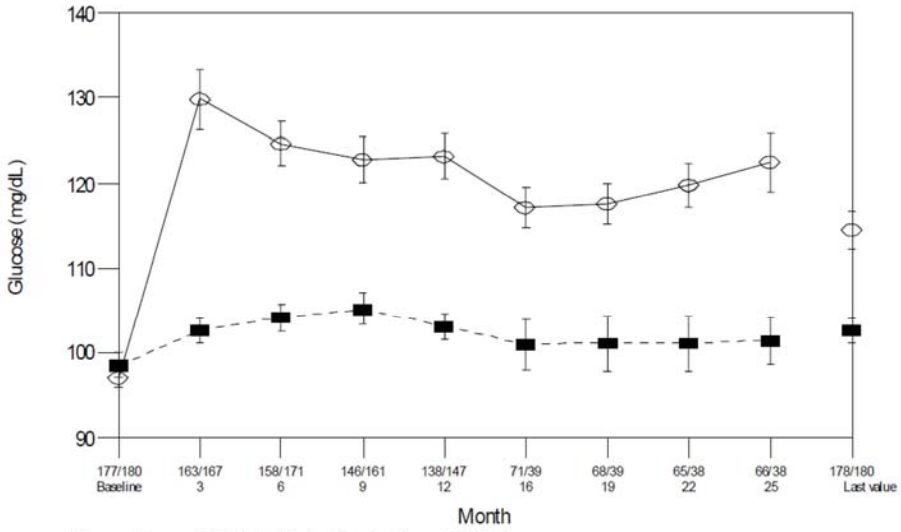
Two deaths occurred in patients receiving Signifor LAR (causes were myocardial infarction and suicide) and two in patients receiving octreotide (causes were sepsis and aortic aneurysm). Review of death narratives did not suggest drug-relatedness. Serious adverse events were balanced or minimally imbalanced across all system organ classes considered except for glucose abnormality (refer to Table 29 in Dr. Abraham's review). In trial C2305, cholelithiasis occurred in 2 patients receiving Signifor LAR and in two patients receiving octreotide LAR. One patient receiving Signifor LAR was diagnosed with acute pancreatitis. Octreotide is known to cause biliary contractility, motility and stone disorders. The risk of biliary disorders appears to be similar with Signifor LAR. Common adverse reactions included hyperglycemia (60%), diarrhea (40%), gallbladder and biliary disease (40%), nausea (17%),

pancreas-related adverse events (16% and mostly asymptomatic elevation in amylase and lipase), bradycardia (15%).

Dr. Abraham reviewed liver safety issues starting on page 96 of her review. Preferred terms of ALT increase (4.4% versus 7.8%) and bilirubin increased were reported more frequently in patients receiving Signifor LAR than octreotide LAR in C-2305 (Refer to Table 39 in Dr. Abraham's review). A single patient in both the Signifor LAR and in the octreotide arm had a laboratory ALT value 5 times above the upper limit of normal. There were no cases of Hy's Law in patients receiving Signifor LAR. Case narratives for patients with significant liver enzyme abnormalities and bilirubin abnormalities were summarized starting on page 99 of Dr. Abraham's review and revealed confounding (e.g., presence of gallstone, hepatic steatosis, other medications) and did not suggest direct pasireotide-induced hepatoxicity. There was one case (C2305-0802-00001), of obstructive (increased alkaline phosphatase and GGT) acute liver injury identified in the review (ALT 17X the upper limit of normal > 6months after therapy initiated) without bilirubin increase. The injury corrected in spite of continued Signifor LAR treatment. Overall, the assessment of liver safety did not suggest a propensity for direct, drug-related, liver injury. Signifor LAR does impact biliary motility and function and may have an indirect impact on the liver.

Abnormalities in glucose control were more common with Signifor LAR than octreotide LAR. Dr. Abraham reviewed the case narrative for five patients who had normal glucose control or slightly abnormal glucose metabolism at baseline and developed severe hyperglycemia with glucose levels in the 300 to 400 mg/dL range within the first month of starting Signifor LAR. Several patients had to be hospitalized as a result of this complication. Events usually resolved within 1 day of admission, in some hyperglycemia abnormalities recurred and in some the recurrent severe hyperglycemia lead to discontinuation of the product. In the core phase of trial C-2305 (Month 1-2) mean glucose values throughout treatment were >20 mg/dL higher in the Signifor LAR group compared to the octreotide LAR group. The apparent reduction after month twelve in the figure is due to the large dropout of patients between the CORE and voluntary extension phase.

Figure 11. 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

Disordered glucose metabolism is a known side effect of Signifor and was seen for the short acting Signifor formulation developed for Cushing's disease (i.e., a disease population at greater risk for glycemic abnormalities). This was discussed at advisory committee in the Cushing's setting. Advisors did not feel that this adverse reaction would preclude approval in this setting. The exact mechanism of action for the cause of pasireotide-induced hyperglycemia is unknown though it is recognized that somatostatin is produced in islets of Langerhan's and has a role in suppressing endogenous insulin secretion (it is used in clamp studies for this purpose). Hyperglycemia will be mitigated through labeling. Prescribers will be asked to screen patients for baseline glucose abnormalities, correct these prior to prescribing the drug, monitor glucose levels during therapy, adjust glucose lowering therapies or discontinue patients from this therapy if this is appropriate. There are a paucity of treatment options for this rare disorder and results from study Trial C-2402 suggest Signifor LAR may offer a benefit in patients who do not respond to available somatostatin analogue therapies.

The impact of Signifor LAR on ventricular repolarization and cardiac conduction was examined in the safety review. Signifor is known to be associated with QT prolongation and bradycardia. These adverse reactions are currently in the Warnings and Precautions section of the immediate release formulation product label. Review of serious, common, and discontinuation adverse events did not reveal an imbalance in bradyarrhytmia-related events between Signifor LAR and comparator (refer to Tables 29 and 45 in Dr. Abraham's review).

9. Advisory Committee Meeting

Efficacy and safety issues identified in the application did not rise to the level of requiring the input from an advisory panel. Therefore no advisory committee was convened.

10. Pediatrics

Refer to Dr. Roman's and Abraham's reviews for details.

11. Other Relevant Regulatory Issues

There were several issues related to good clinical practice at sites in Mexico and Brazil which are discussed in Drs. Kleppinger, Abraham and Clark's reviews. These issues did not materially affect overall conclusions. For full discussions refer to these reviews.

12. Labeling

Refer to Dr. Roman's review for details.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

I agree with recommendations made by Drs. Abraham and Roman and recommend approving Signifor LAR for: *the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.*

Trial C-2305 demonstrated that Signifor LAR was effective in reducing both GH and IGF-1 levels in subjects with acromegaly who had not received previous medical therapy. A reduction in GH and IGF-1 levels was associated with reported improvements in symptoms of acromegaly (i.e., ring size, headache, fatigue, perspiration, paresthesia, arthralgia). Signifor LAR was at least as effective as a known active comparator used at standard though submaximal dose. Even in the absence of control it is unlikely that reduction in GH and IGF-1 to the extent seen in this trial could occur spontaneously. Although only 30% achieved targeted biochemical control, up to 49% of participants randomized to Signifor LAR partially responded to therapy. Trial C-2402 suggested that Signifor LAR could improve control in some patients failing available somatostatin receptor agonist therapies. Since patients were selected on the basis of having failed active comparator therapy, randomization to the failed therapy biases the results in favor of pasireotide LAR and these data do not support a claim of superiority against ocreotide LAR.

Although the sponsor demonstrated statistical superiority for the primary endpoint against the comparator in trial C-2305, the comparison was not a truly fair comparison either because the maximal dose approved for use in the US was not used. Octreotide LAR is approved at the 40 mg dose in the United States and Japan only (this dose was not available

in all countries participating in this multinational trial). In addition, between-group differences in biochemical control were limited to IGF-1 levels and the absolute between group differences in mean IGF-1 levels achieved at trial end were small and not perceived as clinically meaningful per symptom scores (i.e., a difference of 0.2 standardized unit above the upper limit of normal). In a document submitted to the application on 12/5/2014, the sponsor provided the results of queries from the Optum claims database from United Health Care ((b) (4) US insurer insuring (b) (4) % of the population) and the SDI database (representing ~ (b) (4) % of all insurance claims in the US) to determine the most commonly used doses of octreotide LAR in the United States. The results of these queries reveals that only a minority of patients with acromegaly in the US are treated with 40 mg of octreotide LAR (i.e., (b) (4) %). The doses used in the trial were therefore reasonably representative of the US standard of care.

The major risks identified included hyperglycemia, gastro-intestinal tolerability issues and choledochal related adverse reactions. These risks were similar to the risks identified for the short acting version of Signifor currently approved for the treatment of Cushing's disease. These risks do not preclude product approval and can be mitigated through product labeling, appropriate patient selection and monitoring.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No new safety findings from this clinical development program prompt the need for a postmarketing risk evaluation and management strategies.

- Recommendation for other Postmarketing Requirements and Commitments

No new safety findings from this clinical development program prompt the need for a postmarketing requirements and commitments.

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/s/

JEAN-MARC P GUETTIER
12/15/2014