CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203255Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203,255
Priority or Standard	Standard
Submit Date(s)	November 15, 2013
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PDUFA Goal Date	September 15, 2014
Division / Office	Division of Metabolism and Endocrinology Products (DMEP)/Office of Drug Evaluation II
Reviewer Name(s)	Smita Baid Abraham
Review Completion Date	August 29, 2014
Established Name	Pasireotide
(Proposed) Trade Name	Signifor® LAR
Therapeutic Class	Somatostatin analogues
Applicant	Novartis
Formulation(s)	Powder for suspension for injection
Dosing Regimen	40 mg IM once every 28 days with up-titration to 60 mg or down-titration to 20 mg as appropriate
Indication(s)	Medical treatment of

Intended Population(s)	acromegaly Adults with acromegaly (b) (4) [redacted]

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of Signifor® LAR for medical treatment of acromegaly.

1.2 Risk Benefit Assessment

In the phase 3 clinical development program, Novartis conducted two pivotal trials to demonstrate the safety and effectiveness of Signifor® (pasireotide) LAR in the treatment of patients with acromegaly. In both trials, the primary objective and endpoint was to show superiority of Signifor® LAR over active control in achieving biochemical control of the disease. Biochemical control was appropriately defined as normalization of GH and IGF-1 (age and sex adjusted) levels.

In **C2305**, the main pivotal trial, Signifor® LAR was significantly more effective in normalizing GH and IGF-1 than octreotide LAR in **medically naïve** (prior transsphenoidal surgery [TSS] allowed) patients with acromegaly after 12 months of treatment.

Similarly, in **C2402**, the second pivotal trial, Signifor® LAR was significantly more effective in normalizing GH and IGF-1 than the 1st generation somatostatin analogues (1st gen SSAs) , octreotide LAR or lanreotide ATG in **inadequately controlled** (prior TSS and medical therapy with SSAs allowed) acromegaly patients after six months of treatment. The expectation that patients not responding to 1st gen SSAs would then achieve biochemical control with an additional six months of the same therapy in the C2402 trial was low. However, several acromegaly patients who were not responding to octreotide LAR or lanreotide ATG therapy did achieve biochemical control while taking Signifor® LAR. Therefore, the results of C2402 provide valuable knowledge that resistance to first generation somatostatin analogues (SSAs) does not imply resistance to second generation SSAs.

As with Signifor® (pasireotide s.c.), the major safety concern with Signifor® LAR is induction of dramatic hyperglycemia and exacerbation of diabetes mellitus. Additional safety concerns raised in the Signifor application were QT prolongation and hepatic injury. Review of the safety data in C2305 and C2402 did not show new or increased severity of treatment related adverse events in these areas. Overall, the safety data for C2305 and C2402 did not reveal new treatment-related adverse events that have not been observed with other SSAs.

Signifor LAR has a favorable risk benefit assessment. The safety issues should be manageable with appropriate labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Pasireotide is somatostatin analogue (SSA). Signifor® LAR is a long-acting formulation of pasireotide formulated as an intramuscular (IM) injection to be given every 28 days. Novartis seeks the following indication for pasireotide LAR: treatment of patients with acromegaly (b) (4) Pasireotide, the active ingredient in Signifor LAR, was approved in December 2012 as medical therapy for Cushing's disease under the brand name Signifor®. In contrast to Signifor LAR, which is given intramuscularly, Signifor® is to be used subcutaneously, and is given as a daily regimen.

Signifor LAR injection is supplied in a single-use kit containing a 6-mL vial of 20 mg, 40 mg or 60 mg dose strength of Signifor LAR powder, a pre-filled syringe containing 2 mL of diluent solution for reconstitution, one sterile 20G x 1.5" safety injection needle, and one vial adapter for drug product reconstitution. The Signifor LAR injection must be administered by a medically trained professional.

2.2 Tables of Currently Available Treatments for Proposed Indications

Acromegaly is a rare disease with a reported prevalence of 38-69 per million. Acromegaly is most commonly caused by excess growth hormone secretion from a pituitary adenoma (somatotropinoma). The signs and symptoms have an insidious onset causing diagnosis of the disease to be delayed over the course of years. The chronic elevation of GH and IGF-1 levels is responsible for the long term complications of acromegaly, and is associated with premature mortality, although the pituitary adenoma itself is generally benign[1]. The goal of therapy is to reduce GH and IGF-1(adjusted for age and sex) to normal levels. GH and IGF-1 normalization has been associated with a reduction in morbidity and mortality[2].

Transsphenoidal surgery (TSS) is the treatment of choice when chance of cure is high, i.e. size and location of tumor are amenable to complete resection. Medical therapy is an effective alternative option for those in whom adenoma resection either is contraindicated or has a low chance of cure. With the advent of effective medical therapies, the indications for radiation

[1] Sherlock M, et al. Medical therapy in acromegaly. Nat. Rev. Endocrinol, 2011
[2] Melmed S, et al. Guidelines for acromegaly management: An update. J Clin Endocrinol Metab, 2009

therapy are limited. However, in instances where surgery and radiation therapy are the primary treatment, medical therapies help to bridge the gap between surgery and the full effect of radiation therapy. The table below describes the available treatments for acromegaly.

Table 1. Available treatments for acromegaly

Name	Mechanism of action	Major side effects	Comments
Non-drug therapies			
Transphenoidal surgery	Removal of adenoma	Surgery related complications; pituitary hormone loss, vision damage	Higher cure rates with microadenomas; lower cure rates with macroadenomas. Experience of surgeon critical.
Radiation therapy	Adenoma cell death	Pituitary hormone deficiencies; rare cranial nerve palsies, blindness	Now used as supportive therapy in resistant cases as medical therapies have become more efficacious and with better safety profiles.
Approved drug therapies			
Octreotide	1st generation SSA	Diarrhea, nausea, gallbladder abnormalities	Hyperglycemia occurs in approximately 15% of patients. Tumor shrinkage observed with short and long acting formulations.
Lanreotide	1st generation SSA	Diarrhea, nausea, gallbladder abnormalities	
Pegvisomant	GH receptor antagonist	Liver toxicity; Concerns of adenoma growth	GH levels increase and not used for monitoring. As monotherapy or in combination with SSAs, has high rate of normalization of IGF-1.
Off-label drug therapies			
Dopamine receptor agonists -cabergoline	Inhibition of GH secretion	Nausea, lightheadedness, mental fogginess	Rare use as monotherapy; used in combination with SSAs.

SSA, somatostatin analogue
Reported cure rates are approximate as a) criteria for cure have varied over time, and b) study designs and populations differ

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in Signifor LAR, pasireotide, was approved in the US in the immediate-release product Signifor® for the treatment of Cushing's disease.

2.4 Important Safety Issues With Consideration to Related Drugs

The major safety concerns with octreotide LAR and lanreotide ATG, first generation SSAs, as listed in the "WARNINGS AND PRECAUTIONS" section of their labels include:

- Gallbladder: Gallstones may occur.
- Glucose metabolism: Hypo- or hyperglycemia may occur.
- Cardiac function: Bradycardia, arrythmias, or conduction abnormalities may occur.
- Thyroid function (octreotide LAR only): Hypothyroidism may occur.

In addition to the gallbladder and cardiac warnings above, the Signifor® label also includes the following safety issues in the "WARNINGS AND PRECAUTIONS" section of its label:

- Hypocortisolism: Decreases in circulating levels of cortisol may occur resulting in biochemical and/or clinical hypocortisolism. Signifor® dose reduction or interruption and/or adding a low-dose short-term glucocorticoid may be necessary.
- Hyperglycemia and Diabetes (occurs with initiation): Intensive glucose monitoring is recommended and may require initiation or adjustment of anti-diabetic treatment.
- Liver Test Elevations: Evaluate liver tests prior to and during treatment.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 74,642 for pasireotide LAR was submitted in 2007 and orphan designation was granted for treatment of acromegaly in August 2009. Pasireotide s.c. was approved in the EU for the treatment of Cushing's disease in April 2012, in Switzerland since November 2012, and in the U.S. in December 2012. (b) (4)

Three presubmission regulatory meetings took place prior to submission of this NDA 203255 for Signifor LAR. The clinical highlights of the meetings are described.

At the **End of Phase 2 meeting, October 15, 2007, (IND 74,642),** FDA advised the following:

- Exclude any patient who has received pituitary irradiation
- Evaluate the resected adenoma (in appropriate patients) by receptor subtype.
- Perform bloodwork every three months in patients with diabetes mellitus, optimize diabetes control, document changes in therapy, discontinue those patients in whom diabetes is uncontrolled (blood glucose > 200 mg/dl and/or HbA1c > 8% in spite of appropriate interventions
- Be aware that GH and IGF-1 secondary endpoints are considered exploratory and may not be discussed in labeling.
- Accept the definition of responder by 5-point mean GH and/or IGF-1 levels.
- Add GH level two hours after a 75g glucose load (OGTT) as an additional efficacy endpoint

- Recommend a one year as opposed to the proposed six month duration of pivotal trial to evaluate efficacy and safety
- Agreed with rationale for selecting doses for C2305 via comparison of trough concentrations at different doses from the Phase 1 pasireotide LAR 2110 study with the predicted median $C_{effective}$ dose from the Phase 2 pasireotide s.c. 2201 study

At the **Type B, Pre-NDA meeting, November 29, 2011**, FDA advised the following:

- Recommendation on labeling: pasireotide LAR should be specifically indicated for the "long term treatment in acromegalic patients who have had an inadequate response to surgery and/or for whom surgery is not an option." Labeling should also state that the pivotal trial excluded patients who previously received other acromegaly medical therapies or radiotherapy
- Provide comprehensive hepatic safety report; specify planned analyses to detect drug-induced liver injury
- Provide information on why additional lab work-up to determine etiology of abnormal liver function was not performed in all patients
- Agreed that no pooling of efficacy or safety data is required for the Summary of Clinical Efficacy (SCE) or Summary of Clinical Safety (SCS). However, FDA stated that discussions of important safety issues such as hepatic events, should include subjects in all trials and all indications

Novartis elected to delay the submission of the NDA until additional data were collected in an ongoing trial, C2402. Therefore they requested a **second, Type C, pre-NDA meeting in 2013**. Such meeting took place on September 9, 2013 at which time the FDA advice focused on how the existing data should be pooled and presented.

2.6 Other Relevant Background Information

Signifor® (pasireotide s.c.; NDA 200677) was the subject of a 2012 Endocrinologic and Metabolic Advisory Committee meeting. Issues presented to the committee were related to safety, in particular the hyperglycemia observed during the Signifor® clinical trials, as well as several cases of liver enzyme elevations that had not been extensively investigated by the applicant. The committee found that hyperglycemia was an acceptable risk for Cushing's disease patients given the high need of medical therapies for this disease and the availability of antihyperglycemic therapies.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no major issues with the overall quality of the application. Several inquiries were made regarding data clarification and several information requests were made during the review, to which Novartis replied in a time appropriate fashion.

3.2 Compliance with Good Clinical Practices

The pivotal clinical trials were in compliance with Good Clinical Practice (GCP) standards. Novartis identified and addressed several GCP violations and deviations that did not affect the overall results of the trials. Specifically, violations were identified and reported for two sites in Mexico (sites 730 and 731) which provided 22/358 patients in C2305. Novartis closed both of these sites prior to submission of the NDA. Areas of violation included: informed consent, source documents, adherence to the monitoring plan, protocol compliance, AE reporting procedures, and delegation and supervision of the study. Within the NDA submission, Novartis, appropriately provided the efficacy data with and without these two sites. The two analyses were consistent. FDA conducted independent sensitivity analyses of this data and verified Novartis's conclusion.

Visual inspection and comparison of the safety data, by this reviewer, with and without the aforementioned patients did not reveal notable differences.

In May 2014, during the review period, we received correspondence from Novartis regarding GCP violations at sites 901 and 904, which were identified in preparation for a site visit by FDA. Novartis reported that at both sites, staff members (one at 901 and two at 904) ended up performing both blinded and unblinded tasks. Nine and 12 patients from these sites were enrolled into C2305, respectively. Novartis reported that the results of the study would not be biased by this situation and did not perform sensitivity analyses with and without the patients from these sites. However, in an independent analysis of the data, FDA confirmed that the results of the primary efficacy and key secondary analyses of the study was not impacted by this violation. In addition, the FDA site inspection confirmed that there was no evidence of bias in the collection of information.

As part of the PDUFA pre-approval clinical investigation data validation, FDA conducted inspections at the following sites: 516 (USA), 681 and 771 (China) and, 151, 152, 901, and 904 (Brazil). The decision to conduct an inspection at sites 901 and 904 was made prior to the May 2014 correspondence from Novartis. Overall, the inspections did not reveal significant GCP issues. A detailed report on the results of the inspections is provided by Dr. Cynthia Kleppinger.

3.3 Financial Disclosures

Novartis collected financial disclosure data from all clinical investigators participating in Studies: SOM230B2113, SOM230B2124, SOM2302125, SOM230B2216, SOM230C2305, and SOM230C2402.

Three investigators had disclosable financial arrangements and interests requiring reporting.

Table 2. Investigator disclosures of financial arrangements

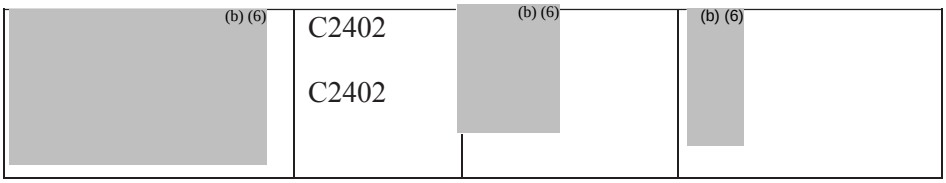
Investigator	Study No.	Center No./ # patients enrolled	Amount Disclosed	Category of Disclosure
(b) (6)	C2305	(b) (6)	$ 40, 571	Research grants
	C2402		$250,000	Research grants
	C2402		>$25,000 (as part of (b) (6) grant)	Research grants

Novartis reports that any bias from these arrangements is minimized by independent data monitoring, multiple investigators participating in the studies and double-blinded trials.

Investigators at various sites did not submit their financial disclosure forms as seen in the table below. This happened despite the fact that Novartis sent follow-up letters to the non-compliant physicians requesting their disclosure forms. All of the investigators who did not submit financial disclosure were sub-investigators.

Table 3. Investigators who did not submit financial disclosure forms

Investigator	Study No.	Center No.	# patients enrolled at site
(b) (6)	C2305	(b) (6)	(b) (6)
	C2305		
	C2305		
	C2305		
	C2305		



4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. Ravi Kasliwal's review for full details. Approval is recommended.

4.2 Clinical Microbiology

Please refer to Dr. Vinayak Pawar's review for full details. Approval is recommended.

4.3 Preclinical Pharmacology/Toxicology

Please refer to Dr. Miyun Tsai Turton's review for full details. Approval is recommended.

4.4 Clinical Pharmacology

Please refer to Dr. Sang Chung's review for full details. Approval is recommended.

All disciplines mentioned in sections 4.1 – 4.4 recommended approval without any postmarketing requirements.

4.4.1 Mechanism of Action

Somatostatin is a neuropeptide that exerts its metabolic effects via binding to somatostatin receptors (SSTRs). SSTRs are members of the G-protein-coupled receptor superfamily. There are five known SSTRs (1-5), each with a distinct activation profile and tissue distribution. Within the pituitary gland, somatostatin inhibits growth hormone (GH) release primarily via binding of SSTR 2 and 5. SSTR 2 and 5 are also found with high prevalence in pituitary tumors. Somatostatin has a short half-life (1-3 minutes) and therefore somatostatin analogues with longer duration of action have been developed for therapeutic purposes.

Octreotide and lanreotide, the currently marketed first generation SSAs, bind most strongly to SSTR 2 and moderately to the other receptors. In contrast, pasireotide, a second generation SSA, binds with high affinity to SSTR 2 as well as 1, 3 and 5. Pasireotide's enhanced binding profile

of SSTRs is believed to be the primary mechanism behind its increased effectiveness over first generation SSAs in the treatment of acromegaly.

Similar to natural somatostatin, which binds to all five SSTRs, pasireotide inhibits the secretion several hormones, including: GH and ACTH from the pituitary, corticosterone from the adrenal, and insulin, and glucagon from the pancreas. Activation of the SSTRs causes hyperpolarization of the cell by activating K+ channels and inhibiting Ca2+ channels causing reduced hormone secretion. In addition to its anti-secretory effects, pasireotide and other SSAs may have anti-proliferative tumor effects based on *in vitro* and *in vivo* study data. The mechanism responsible for the anti-proliferative effect is not yet known.

With regard to adverse effects, pasireotide is unique among the SSAs in its adverse effect on glucose metabolism. SSAs are reported to impair pancreatic beta-cell function leading to reduced insulin secretion. However, the degree of hypergycemia seen with pasireotide is much greater than that seen with other SSAs. Pasireotide has a strong binding affinity that surpasses that of octreotide for SSTR1, 3 and 5; however, the opposite is true for SSTR2 where octreotide has higher affinity. Based on nonclinical studies investigating glucose, insulin and glucagon levels, Novartis hypothesizes that the SSTR5 and SSTR 2 activation ratio is responsible for the hyperglycemia with pasireotide. In addition, binding of SSTR2 may counteract the hyperglycemic effect, explaining why octreotide treatment does not result in such dramatic hyperglycemia. Octreotide also has a stronger inhibitory effect on glucagon compared to pasireotide, which likely also contributes to the relative absence of hyperglycemia in octreotide treated patients.

4.4.2 Pharmacodynamics

Pasireotide 40 mg LAR was chosen as the starting dose for therapy in C2305. The rationale comes from PK and efficacy data in clinical trials C2110 and B2201, respectively. The trough concentrations of 20 mg, 40 mg and 60 mg of pasireotide LAR at steady state (Day 84) were 3.8 ± 2.1, 6.4 ± 3.1 and 13.7 ± 9.6 ng/mL, respectively. The trough concentrations of the 40 and 60 mg pasireotide LAR dose were higher than the median value of effective concentration of 4.35 ng/mL required for normalization in responders to pasireotide s.c. treatment.

4.4.3 Pharmacokinetics

For full details on the PK of pasireotide LAR, please refer to the clinical pharmacology review by Drs. Lian Ma and Sang Chung. In summary, data from healthy volunteers shows that subjects experience an initial burst of pasireotide LAR release on the injection day, followed by a dip from Day 2 to Day 7 and then a slow increase that peaks around Day 20. This is followed by a slow decline in concentration over the next seven weeks. PK exposure is approximately dose proportional in the evaluated dose range (20-60 mg) in both single dose and multiple dose evaluations. Trough concentrations reach steady state after three injections with low

accumulation. Pasireotide LAR has a large volume of distribution and low apparent clearance. PK is comparable between healthy volunteers and acromegaly patients.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A summary of the pivotal trials is presented in Table 4.

Table 4. Summary of pivotal trials

Trial	Description	Efficacy analysis set (N)	Assessment time points	Treatment duration	Dosing Regimen
C2305 **(pivotal trial)**	Phase III multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR versus octreotide LAR in patients with active acromegaly naïve to medical treatment; primary efficacy analysis performed at month 12 (end of core phase: extension up to 14+ months as well as option to cross over to other study treatment possible)	Core and Up to Crossover: Pasireotide LAR: 176 Octreotide LAR: 182 After crossover: Pasireotide LAR: 81 Octreotide LAR: 38	GH (5-point mean level) assessed from 2 hour profile prior to injection. IGF-1 assessed from single sample taken prior to injection	12 months (core), completed; Extension phase, completed; Open label extension phase (ongoing for patients treated with pasireotide LAR)	Pasireotide LAR: 40 mg q28d Octreotide LAR: 20 mg q 28d
C2402 **(pivotal trial)**	Phase III multicenter, randomized, parallel group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with	Pasireotide LAR 40 mg: 65 Pasireotide LAR 60 mg: 65 Octreotide LAR or lanreotide ATG: 68	GH (5-point mean level) assessed from 2 hour profile prior to injection. IGF-1 assessed from single sample	6 months core, completed; Blinded extension ongoing for patients treated with pasireotide LAR	Pasireotide LAR: 40 or 60 mg q28d Active control: Octreotide LAR: 30 mg q28d or

	inadequately controlled acromegaly; primary efficacy analysis performed at month 6 (end of core phase)		taken prior to injection		Lanreotide ATG: 120 mg q 28d

Source: Summary Clinical Efficacy, Table 1-1

Novartis has conducted several studies to understand the safety and efficacy of pasireotide. Studies specific to the acromegaly indication are listed in Table 5 below. Some were conducted with the immediate-release formulation, some with the long–acting formulation. Studies conducted in other indications are provided in the Appendix. Except for C2110, which is reviewed in Appendix 4, Dr. Naomi Lowy reviewed the aforementioned studies along with special safety reports for the glycemic, cardiovascular and hepatic effects of pasireotide in NDA 200677.

Table 5. Summary of supportive studies for pasireotide for the acromegaly indication

Study/ Patient Population	Design	# Patients	Treatment Duration	Assessment time points	Dosing regimen
B2201 **Acromegaly**	Phase 2, open-label, randomized, crossover study to assess efficacy, safety, and PK/PD relationship	60	Octreotide s.c. for 28 days followed by pasireotide s.c. 200 µg, 400 µg, or 600 µg bid for 28 days in Period 1; patients progressed to each remaining pasireotide s.c. dose in Periods 2 and 3	GH and PRL samples were taken 30 min and 1 min prior to the first pasireotide dose; and, 30, 60, 90, and 120 min after the first dose. IGF-1 samples were taken 30 min and 1 min before dosing	Octreotide s.c. 100 µg tid Pasireotide s.c. 200 µg bid, 400 µg bid, and 600 µg bid
B2201E1	Open-label extension to assess long-term safety, efficacy and PK	30	Dependent on clinical benefit		Pasireotide -escalation up to 900 µg bid permitted
C2110 **Acromegaly and carcinoid**	Phase 1, open-label, randomized study to assessing PK, safety	35 acromegaly 42 carcinoid	3 months*	GH and PRL samples were taken at 30 min, 1h, 1.5h and 2h. IGF-1 was	Pasireotide LAR q28d: 20 mg, 40 mg or 60 mg

	and tolerability profiles			assessed by using a single sample taken at a single time point prior to injection	
C2110E	Open-label extension of study C2110 to assess long term safety and PK/PD profiles	29		Dependent on clinical benefit	Pasireotide LAR q28d: 20 mg, 40 mg, or 60 mg
B2103 **Acromegaly**	Phase 2, double-blind, randomized, 3-way crossover, study in patients with acromegaly to assess efficacy	12	17 days: sequence with 3 single-dose injections of pasireotide s.c. or octreotide s.c. each separated by 6-day washout period	GH and PRL samples were taken 30 min and 1 min prior to dosing, hourly over 24h and at 48h after injection; IGF-1 samples were taken 30 min prior to dosing and 24 h and 48 h after dosing	Octreotide s.c. 100 µg single dose Pasireotide s.c. 100 µg single dose and 250 µg single dose

*for patients who did not previously receive pasireotide, 300 µg pasireotide s.c. single dose was given, followed by ≥ 5 days washout to ensure patient tolerance
Source: Summary of Clinical Safety Table 1-1, Summary of Clinical Efficacy, Table 1-1

5.2 Review Strategy

The primary focus of the efficacy and safety evaluation for this review was the phase 3, pivotal trial data. The 120-day clinical safety update data was reviewed as well to ensure that no new safety signals emerged. Last, information request responses from Novartis were reviewed.

The following reports were referenced during this review:

1) Phase 1 and 2 trials described in Table 5.

2) Clinical review for Signifor® (NDA 200677) by Dr. Naomi Lowy

3) Special safety reports by Novartis for hyperglycemia, cardiovascular and liver function

No compassionate use studies were provided for review.

5.3 Discussion of Individual Studies/Clinical Trials

The two pivotal trials CSOM 2305 and CSOM 2402 are presented below.

Study C2305 ***(First patient visit: Feb 2008; Data cut-off for current analysis: Dec 2011)***

Study C2305 (C2305) is a Phase III, multicenter, randomized, active controlled, blinded study of pasireotide LAR vs. octreotide LAR in patients with active acromegaly who had not previously received medical treatment. Patients were enrolled across 27 countries at 84 study centers.

The **primary objective of C2305** was to compare the proportion of patients who achieved biochemical control (defined as a reduction of mean growth hormone (GH) level <2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex adjusted) between pasireotide LAR and octreotide LAR after 12 months of treatment (CORE phase).

Key secondary objectives included comparisons of the effect of pasireotide LAR to octreotide LAR on each of the following: 1) reduction of GH to <2.5 µg/L, 2) normalization of IGF-1 and, 3) tumor volume.

There were nine other secondary objectives studied in the CORE phase:

- Proportion of patients with a reduction of mean GH level to <2.5 µg/L and normalization of IGF-1 (age and sex adjusted) at months 6 and 9
- Change from baseline in mean GH at 12 months
- Time to first achievement of mean GH <2.5 µg/L and IGF-1 to within normal limits (age and sex related)
- Symptoms of acromegaly: ring size, headache, fatigue, perspiration, paresthesia, osteoarthralgia at 12 months
- Health-related quality of life
- Prolactin level
- Duration of response for subjects who meet the primary objective
- Overall safety and tolerability
- Plasma exposure

In the extension phase, the effects of long term treatment and after crossover treatment with pasireotide LAR and octreotide LAR were evaluated. Specific objectives were to evaluate:

- Proportion of patients with a reduction of mean GH level to <2.5 µg/L and normalization of IGF-1 (age and sex adjusted) at Months 6 and 9 of the extension and at the end of the first year of the extension. This was also done for GH <2.5 µg/L and normalization of IGF-1 separately

- Change in 1) serum GH levels, 2) tumor volume, and 3) symptoms of acromegaly, health related quality of life and prolactin, from core baseline and extension baseline, respectively, over time
- Overall safety and tolerability

Exploratory objectives, not phase specific, were to:

- Explore patient demographics (e.g. age, body mass index (BMI), sex) as PK covariates on pasireotide/octreotide trough concentrations, if applicable
- Explore the correlation between pasireotide/octreotide trough concentrations and PD/safety markers, if applicable
- Explore the GH nadir post-oral glucose tolerance test (OGTT) with 75 g of glucose at 12 months and at the end of the first year of the extension (required only for US sites; any other sites who have the capacity to perform this test should also perform it. OGTTs will not be performed in patients with known glucose abnormalities.
- In patients who had previous pituitary surgery, correlate the expression of different somatostatin receptor subtypes with treatment response to pasireotide LAR or octreotide LAR. Tissue samples had to be available, the patient had to provide consent and local legislation had to allow shipment of samples to the central facility

Study Design

Patients were stratified by the following two criteria: 1) patients who had undergone one or more pituitary surgeries but had not been treated medically, and 2) de-novo patients presenting a visible pituitary adenoma on MRI or who refused or were not eligible for pituitary surgery.

Randomization was stratified as described above and treatment assignment was balanced by country.

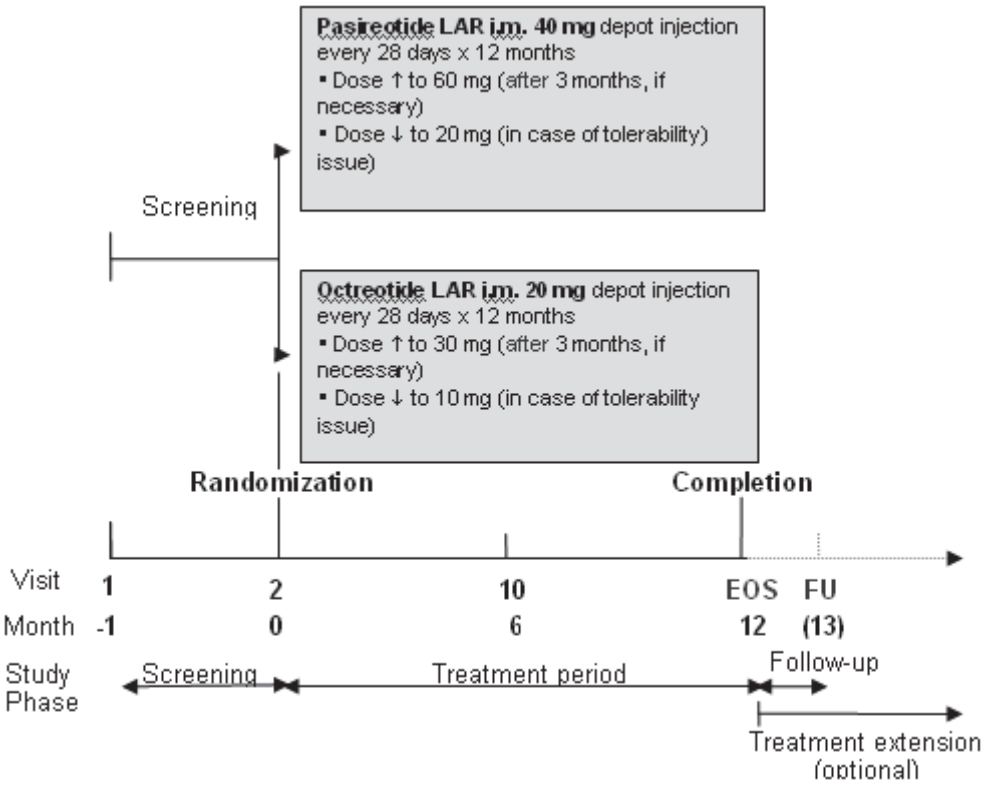
As the appearance of the pasireotide LAR and octreotide LAR intramuscular (IM) depot injections are different, a true double blind treatment was not possible. Subjects, investigators and Novartis personnel, were blinded to the study drug, however, an unblinded nurse/coordinator administered the assigned LAR treatment to the subject.

During the screening phase, abnormal GH and IGF-1 levels were documented and informed consent was provided for each patient. If eligible, patients entered a 12 month CORE phase. (Figure 1). In the CORE phase, patients were randomized 1:1 to pasireotide LAR 40 mg or octreotide LAR 20 mg injections starting with the first dose on study day (Day) 1 in study month (Month) 0. Study drug injections were given once a month, defined as every 28 days (± 2 days). All patients were blinded in this phase. Patients who completed the core phase of the study were given their last (12^{th}) injection at month 11.

Prior to month 12, treatment could be discontinued for lack of efficacy, unacceptable toxicity, protocol deviation, subject withdrawal of consent, or other safety concerns. All patients had to

have follow-up evaluation 28 days after the End of the Study (56 days after the last dose of study medication). Unacceptable toxicity was defined as an adverse event of CTCAE (CTC) ≥ 3 and assessed as study drug related. If this occurred, a protocol was in place to reduce dosage, followed by re-challenge and/or discontinuation.

Figure 1. Core phase study design (incorporates amendment 4)



Source: Figure 9-1, Clinical Study Report C2305

Participation in the extension phase (Figure 2) of the trial was an option for subjects who completed the core phase. In the original protocol, subjects on pasireotide LAR with a GH < 2.5 µg/L and normalization of IGF-1 (responder) or who were considered as benefiting from pasireotide LAR at core completion, could continue on pasireotide LAR unblinded. Those who did not respond to or who were not benefiting from octreotide LAR therapy were offered the option to switch to pasireotide LAR unblinded. Subjects who did not respond to pasireotide LAR and those showing response to octreotide LAR were not eligible for the extension.

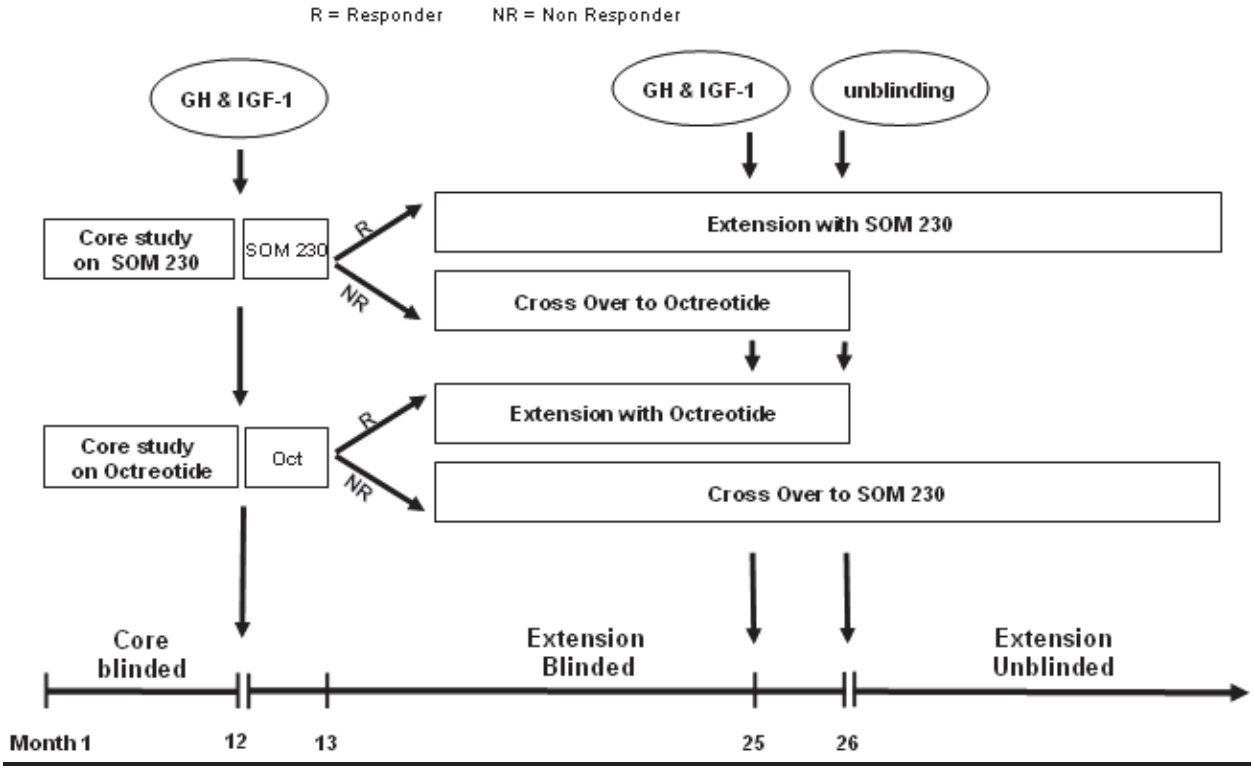
This extension design was modified in protocol amendment four implemented in April 2009. With this amendment, upon completion of the core phase, responders to octreotide LAR with a GH < 2.5 µg/L and normalization of IGF-1 or those who showed benefit per the investigator, were allowed to continue octreotide LAR during the extension. Non-responders or those not

showing benefit from pasireotide LAR were offered the option to switch to octreotide LAR. Implementation of amendment 4 reinstated the double blind design of the trial in the extension phase.

Under amendment 4, as a bridge to the extension phase, subjects received a 13th injection (study month 12) of the same blinded study drug received during the core phase. Results of study month 12 assessment determined whether a subject would remain on the same treatment as in the core or crossover to the opposing drug. The extension phase consisted of 13 additional injections of the determined study drug with the first injection given at study month 13. Treatment was unblinded at study month 26 after 12 injections in the core, 1 bridging injection and 13 injections of the determined crossover treatment. Only subjects on pasireotide LAR were followed after study month 26.

Thirty-four subjects were enrolled into the extension prior to amendment 4. These subjects received unblinded pasireotide LAR starting at study month 12 and are allowed to continue it until the medication becomes commercially available or the pasireotide development program is complete. Note, subjects in the UK were not allowed to participate in the extension and stopped treatment at month 12 regardless of response status. Some cases were considered for compassionate use.

Figure 2. Extension phase study design (incorporating amendment 4)



SOM 230 = pasireotide LAR
Source: Figure 9-2, Clinical Study Report C2305

Subjects

Patients had to fulfill all inclusion criteria and none of the exclusion criteria to participate.

Inclusion criteria (key criteria listed), C2305:

1. Male or female patients of at least 18 years of age

2. Patients with active acromegaly demonstrated by:

    - a lack of suppression of GH nadir to <1 µg/L after an oral tolerance test with 75 g of glucose (OGTT) (not applicable for diabetic patients) **or** a mean GH concentration of a 5-point profile within a 2 hour time period of >5 µg/L
    - elevated circulating IGF-1 concentration (age and sex adjusted)

3. Patients who have undergone one or more pituitary surgeries, but have not been treated medically, or de-novo patients presenting with a visible pituitary adenoma on MRI and who refuse pituitary surgery or for whom pituitary surgery is contraindicated.
4. Patients with a known history or new diagnosis of impaired fasting glucose or diabetes mellitus could be included, however blood glucose and anti-diabetic treatment had to be monitored closely throughout the trial and adjusted as necessary.

Major Exclusion Criteria (key criteria listed):

1. Patients who were being or were treated with octreotide, lanreotide or dopamine agonists with the exception of a single dose of short-acting octreotide or short –acting dopamine agonists. In case of a single dose of short-acting octreotide, the dose should not be used to predict the response to the octreotide treatment. The single dose of short acting octreotide or short-acting dopamine agonists should not have been administered in the 3 days prior to randomization
2. Current or prior treatment with GH antagonists
3. De-novo patients not having a visible pituitary adenoma on MRI
4. Received pasireotide prior to randomization
5. Surgical intervention for relief of any sign or symptom associated with tumor compression
6. Any surgical therapy within 4 weeks of visit 1
7. Except for pituitary irradiation, any radiation therapy within 4 weeks of visit 1 from which side effects had not resolved
8. Pituitary irradiation within 10 years prior to visit 1
9. Inadequately or untreated hypothyroidism
10. Diabetic patients on anti-diabetic medications whose fasting blood glucose was poorly controlled as evidenced by HbA1c >8%
11. Symptomatic cholelithiasis
12. Abnormal coagulation parameters

13. Congestive heart failure (NY Heart Association Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction within six months preceding enrollment
14. Risk factors for torsades de pointes
15. Diabetes insipidus or confirmed hypothyroidism, hypoadrenalism, and/or hypogonadism of a central etiology, unless adequately treated with stable doses of hormone replacement therapy for a minimum of three months prior to study entry (first dose of study medication) except in cases where hormone therapy might not be indicated (hypogonadism)
16. Patients with liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis, or patients with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) more than 2x ULN, serum bilirubin > 2x ULN, serum albumin < 0.67 x lower limit of normal (LLN)
17. Serum creatinine > 2.0x ULN
18. Abnormal hematological parameters (WBC, Hgb, platelets)
19. Pregnant, lactating or of childbearing potentially and not practicing medically acceptable method of birth control
20. History of immunocompromise or presence of any cytopenia

Note: At End of Phase 2 meeting, October 15, 2007, FDA recommended exclusion of any patient who had received pituitary irradiation: Novartis chose to use a history of pituitary irradiation within 10 years (criterion #8).

Criteria for drug withdrawal (key criteria listed), C2305:

Subjects **had** to be withdrawn from the trial for the following reasons:

- Uncontrolled study drug toxicity
- Uncontrolled diabetes mellitus, defined as blood glucose values consistently in excess of 200 mg/dl or HbA1c value ≥ 8 % in spite of continuous, appropriate therapeutic intervention(s)
- QTc prolongation
    - Confirmed QTcF > 470 ms and discontinuation recommended by cardiologist
    - Mean QTcF > 500 ms as measured by triplicate ECGs
    - Significant arrhythmia findings from Holter monitoring such as:
        - Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic response
        - Sustained ventricular tachycardia (lasting > 30 s) irrespective of symptoms
        - Recurrent non-sustained VT (≥ 3 beats) during any 24 hour monitoring period
        - Torsades de pointes
        - Cardiac arrest

    - Pause > 5 sec
    - Second or third degree atrioventricular block
- New occurrence of clinically significant bradycardia
- Increased risk of QT prolongation by use of QT prolonging medication
- Hypokalemia (<3.5 mmol/L) or hypomagnesemia (<0.7 mmol/L)
- Pregnancy
- Patient withdrawal of consent

Subjects **could** be withdrawn for any of the following reasons:

- Lack of efficacy: no reduction in biochemical endpoints compared to baseline (Visit 2) after more than 3 months of treatment with the highest dose of study medication
- AEs
- Significant abnormal laboratory or test procedure result(s)
- Protocol deviation

Protocol Amendments, C2305:

Seven amendments were incorporated into C2305 clinical protocol. The first patient visit was February 11, 2008. Amendments of interest are as follows:

Amendment 1: Increases the duration of the study from six to 12 months; modifies and clarifies various inclusion and exclusion criteria and timing of certain laboratory measurements; adds a few more secondary and exploratory endpoints. Released Feb 18, 2008.

Amendment 4: Modified the design of the extension period (described above, under the Trial Design section). Released April 23, 2009

Amendment 5: Incorporates one additional visit 20 days after injection for ECG recording and PK sampling based on results from thorough QT/QTc (TQT) study (CSOM230B2113). The visit was scheduled as soon as amendment was approved at site. Released May 3, 2010.

Amendment 7: Includes additional hepatic-related safety measures and discontinuation criteria as a result of an internal hepatic medical review. Released December 12, 2011. The algorithm for additional liver testing is seen in Figure 4.

Clinical Protocol C2402 *(First patient visit: Jul 2010; Completion of CORE phase: Jan 2013)*

Study C2402 (C2402) is a Phase III, multicenter, randomized, parallel group, double-blind, three-arm study of pasireotide LAR 40 and pasireotide LAR 60 mg versus open-label octreotide LAR 30 mg and lanreotide autogel (ATG) 120 mg in patients with inadequately controlled acromegaly. The study has a core and extension phase, however, only the CORE phase (July 19-2010 – January 22, 2013) is represented in the Clinical Study Report.

Objectives C2402:

The primary objective of this study was to compare the proportion of patients achieving biochemical control (defined as mean GH levels < 2.5 µg/L and normalization of sex- and age-adjusted insulin-like growth factor (IGF-1) at 24 weeks (CORE phase) with pasireotide LAR 40 mg and 60 mg, separately, versus continued treatment with octreotide LAR 30 mg or lanreotide ATG 120 mg.

The key secondary objective was to compare the proportion of patients achieving normalization of sex- and age adjusted IGF-1 at 24 weeks.

Key additional secondary objectives included comparison of the effect of pasireotide LAR (40 and 60 mg separately) versus continuation of same treatment on:

- Proportion of patients achieving biochemical control (defined above) at 12 weeks
- Proportion of patients achieving GH levels < 2.5µg/L at 12 and 24 weeks
- Proportion of patients achieving normal sex- and age-adjusted IGF-1 at 12 weeks
- Proportion of patients achieving GH levels < 1.0µg/L and normal sex- and age-adjusted IGF-1 at 12 and 24 weeks
- Proportion of patients achieving GH levels < 1.0µg/L at 12 and 24 weeks.
- Proportion of patients achieving a tumor volume reduction > 25% assessed by pituitary MRI at 24 weeks
- Percent change of tumor volume assessed by pituitary MRI from baseline to 24 weeks
- Health related quality of life using the acromegaly quality of life (AcroQoL) instrument
- Overall safety and tolerability as well as the pharmacokinetics of pasireotide LAR 40 and 60 mg

Exploratory objectives, C2402:
(The term "study drugs" will be used in place of "pasireotide LAR, octreotide LAR and/or lanreotide ATG)

- To assess whether baseline tumor (where tissue sample available) and/or blood biomarkers may be predictive of response to study drugs
- To assess on repeated blood samples whether there were any effects of study drugs on potential response biomarkers over time
- To assess on repeated blood samples the correlation between potential response biomarkers and response to study drugs
- To perform exploratory, optional pharmacogenetic assessments in order to explore whether individual variations in genes relating to drug metabolism, acromegaly, and/or the drug target pathways conferred differential response to study drugs
- To perform exploratory, optional biomarker assessments related to study drugs, acromegaly and/or other endocrine diseases on remaining biomarker samples to assess additional hypotheses which may arise from internal or external research activities

- To explore the relationship between pasireotide LAR 40 and 60 mg separately and levels of pharmacodynamics (PD) (GH/IGF-1) and safety markers (e.g. glucose, insulin, electrocardiogram (ECG)
- To explore the effect of demographics (e.g. age, gender, bodyweight, race) on PK and PD parameters of pasireotide LAR 40 mg and 60 mg, separately

Study Design C2402:

Core phase:

After a four week screening period where inclusion and exclusion criteria were assessed, patients were randomized to receive either pasireotide LAR 40 mg or 60 mg (double blind) or continue on the same treatment on the maximum indicated dose of octreotide LAR 30 mg or lanreotide ATG 120 mg as before randomization in an open-label, active control arm. If necessary, study medication doses could be titrated to a lower dose; otherwise, up titration was not permitted in the CORE phase. Total treatment time was 24 weeks; total study duration including the four week screening period was 28 weeks.

Patients were stratified according to previous treatment (octreotide LAR or lanreotide ATG) and GH levels (<2.5µg/L and ≤ 10 µg/L; and > 10 µg/L) at their screening visit (Visit 1).

Extension phase:

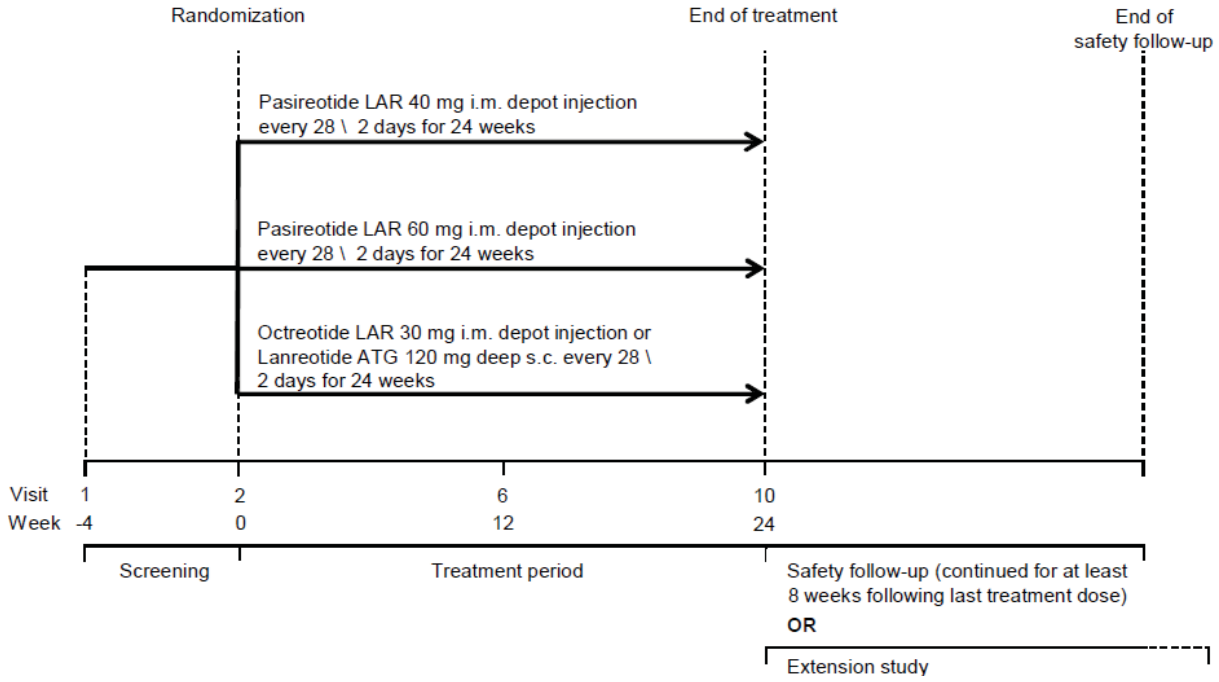
At the end of the 24 week core phase, patients who achieved biochemical control on pasireotide LAR 40 or 60 mg could continue on the same dose in a blinded fashion.

Patients who did not achieve biochemical control on pasireotide LAR 40 or 60 mg could start open label pasireotide LAR 60 mg, per investigator's judgment.

Patients who did not achieve biochemical control while on octreotide LAR or lanreotide ATG were offered pasireotide LAR 40 mg, with a dose increase to 60 mg if biochemically uncontrolled after three injections, in the extension.

Patients who achieved biochemical control continued on their previous treatment of octreotide LAR or lanreotide ATG and did not participate in the extension.

Figure 3. Study design of core and extension phase in C2402



Source: Figure 9-1, Clinical Study Report C2402

Subjects:

All patients needed to meet the following inclusion and none of the exclusion criteria. A full listing of these criteria is found on pages 51-53 of the Clinical Study Report for CSOM 2402.

Inclusion criteria (key criteria listed):

- Male and female patients ≥ 18 years of age
- Patients with inadequately controlled acromegaly as defined by:
  - A mean GH concentration of a 5-point profile over a 2 hour period > 2.5 µg/L
  - And, sex- and age adjusted IGF-1 >1.3 x upper limit of normal (ULN)
- Patients treated with maximum indicated doses of octreotide LAR or lanreotide ATG given as monotherapy for at least six months prior to Visit 1 (Screening visit). Maximum indicated doses were 30 mg for octreotide LAR and 120 mg for lanreotide ATG.
- Patients with diagnosis of pituitary micro-or macro-adenoma (patients could have been previously submitted to surgery)

For C2305, a GH level of > 5 µg/L was required for inclusion, which is different than the GH < 2.5 µg/L presented above for C2402. In C2305, patients were not actively being treated thus it is possible Novartis chose a GH > 5µg/L to help ensure active disease. In C2402, patients were receiving medical treatment at the time of enrollment. One of the goals of medical therapy, at the time this study was designed, was to achieve GH levels < 2.5 µg/L, thus, a level > 2.5 µg/L is considered "inadequate control".

Exclusion criteria:

The full list of exclusion criteria for studies CSOM 2402 and CSOM 2305 are the same with a few exceptions detailed below. With the exception of the key exclusion criterion inherent to the study design of C2402, the other differences in criteria are minor and were not expected to affect the efficacy results.

Key exclusion criterion specific to C2402:

1. Concomitant treatment with growth hormone receptor (GHR)-antagonist or dopamine agonists, unless concomitant treatment was discontinued eight weeks prior to Visit 1 (Screening) (8 week washout period). Such patients must have been treated with octreotide LAR 30 mg or lanreotide ATG 120 mg monotherapy continuously for a minimum of six months prior to starting combination therapy and they should have been inadequately controlled on monotherapy.

Exclusion criteria listed in C2402 but not in C2305:

1. History of syncope or family history of idiopathic sudden death
2. Sustained or clinically significant cardiac arrhythmias
3. Concomitant disease(s) that could have prolonged the QT interval, such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism, or cardiac failure
4. Concomitant medications (s) known to increase the QT interval

Exclusion criteria listed in CSOM 2305 but modified for CSOM 2402:

Amendment 4 in C2402 incorporated additional hepatic-safety measures as a result of the internal hepatic medical review of pasireotide trials. Amendment 4 in C2402 is equivalent to amendment 7 in C2305. The changes below reflect the incorporation of amendment 4 into C2402.

1. Patients with known gallbladder or bile duct disease, acute or chronic pancreatitis (patients with asymptomatic cholelithiasis and asymptomatic bile duct dilation could have been included). Before amendment 4, this exclusion criteria stated "patients with symptomatic cholelithiasis." Therefore, this exclusion criterion was not ensured for all patients.

2. Patients with liver disease or history of liver disease, such as cirrhosis, chronic active hepatitis B and C or chronic persistent hepatitis, or patients with ALT and/or AST more than 2 x ULN, total serum bilirubin > 1.5x ULN, or serum albumin <0.67x LLN. Before

amendment 4, this exclusion criterion did not specify "or history of liver disease, hepatitis "B and C", and "total" bilirubin was ">2"x ULN. Therefore, this exclusion criterion was not ensured for all patients.

3. Patients with a history of recurrent alcohol or drug misuse/abuse in the 12 month period prior to Visit 1 (Screening). This exclusion criterion did not specify "or recurrent," or "misuse", and the 12 month period was "6 month period". Therefore, this exclusion criterion was not ensured for all patients. In addition, the following exclusion criteria were added after Amendment 4 and were not applied to patients before Amendment 4: 1) presence of hepatitis B surface antigen, 2) presence of hepatitis C antibody test.

Criteria for drug withdrawal for C2402:

Patients were withdrawn from the study if any of the following occurred (italic font indicates difference when compared to C2305):

- Patients experienced unacceptable toxicity
- *Uncontrolled diabetes and/or blood glucose values consistently in excess of 240 mg/dL despite appropriate therapeutic interventions and/or if the HbA1c value was ≥ 10%*
- *Confirmed QTcF > 480 ms and discontinuation recommended by a cardiologist*
- *Onset of angina pectoris*
- Increased risk of QT prolongation by use of QT prolonging medication
- Vomiting and/or diarrhea and electrolyte imbalances (K^+, Na^+, Ca^{2+}, Mg^{2+})
- New occurrence of clinically significant/symptomatic bradycardia
- Hypokalemia (<3.5 mmol/L) or hypomagnesemia (<0.5 mmol/L) confirmed by repeat testing that was either a new finding or accompanied by vomiting or diarrhea and not corrected by treatment
- Pregnancy
- Patient withdrew informed consent
- Patient lost follow-up
- Death
- *Patients experiencing*
    - *ALT or AST >3x ULN and total bilirubin (TB) ≥ 2x ULN and alkaline phosphatase < 2x ULN*
    - *ALT or AST >5x ULN and ≤ 8 x ULN persistent for more than 2 weeks*
    - *ALT or AST >8x ULN*

  If any of these three discontinuation criteria were met, study medication should have been discontinued immediately. In addition, proper safety follow-up management should have been performed as written in the protocol (Appendix 16.1.1-Protocol-Section 7.5.2.3). Re-challenge of study medication was prohibited once discontinuation criteria were met.

Differences in drug withdrawal criteria between C2305 andC2402

The differences in the withdrawal criteria between the two pivotal trials are noted by italic font. In particular, there were several specific QTc prolongation related adverse events cited in C2305 as withdrawal criteria, which were not specified in C2402. Similarly, in C2402, "onset of angina pectoris is listed as a criterion of withdrawal and this is not mentioned in C2305. We inquired about these differences and Novartis indicated that the QT prolongation criteria were stricter for C2305 because of increased concern about this AE at trial start. However, following an internal review and expert cardiovascular consultation of the safety data, less restrictive criteria could be applied for C2402. Regarding "onset of angina pectoris", this exclusion criterion was part of an internal Novartis guidance that was implemented in 2012.

Similarly, the glucose withdrawal criteria in C2402 allow for worse glucose values and HbA1c before requiring withdrawal compared to C2305. When asked about this, Novartis responded that the medically naïve patients enrolled into C2305 were expected to have more preserved beta cell function and better glucose homeostasis than the inadequately controlled patients enrolled into C2402 who had already been exposed to somatostatin analogues (SSAs). SSAs are reported to impair beta-cell function. Therefore, Novartis expected C2402 patients to have a higher incidence of impaired glucose tolerance, impaired fasting glucose, and diabetes.

The hepatic discontinuation criteria were implemented as part of Amendment 4.

Concomitant Medications for C2305 and C2402:

Patients could not be taking the following medications at the time of study start for C2305 and C2402:

1. Any other investigational drug
2. Any drug known to affect GH or IGF-1 levels
3. Any drug known that might prolong the QT interval
4. Anti-coagulants were to be avoided

Protocol Amendments, C2402:

Five protocol amendments were incorporated into the C2402 protocol over the course of the study. Amendment 4 regarding hepatic safety measures is described above. The other four amendments incorporate various changes and improvements to the protocol that do not reflect major changes to the study design, the primary efficacy endpoint or major safety measures; therefore, they will not be discussed in detail in this review.

Special Safety Monitoring for C2305 and C2402

Glucose metabolism:

Subjects with prior history or new diagnosis of impaired fasting glucose, impaired glucose tolerance or diabetes mellitus or at risk for these conditions were recommended to monitor blood glucose by fingerstick twice daily (fasting and 2 hours post-prandial). Subjects were encouraged to keep a blood glucose log for appropriate management of their disease by their physician/diabetes specialist. This data was not collected by Novartis.

Any patient with a fasting glucose of > 130 mg/dl (7.2 mmol/L) or 2-hour post-prandial capillary glucose ≥ 180 mg/dl (10 mmol/L) on two consecutive measurements at least 14 days apart and/or HbA1c > 7% should be evaluated by a diabetes specialist for appropriate treatment (consistent with ADA's Position Statement 2008[3]). These patients were to be given information on diabetes management and, at the discretion of the diabetes specialist, recommended therapy at the earliest manifestation of glucose abnormality. Withdrawal criteria for glucose abnormalities are stated above (page 23).

These practices were the same in study CSOM 2402. However, Position Statement ADA 2011 is cited rather than 2008.

QT-related cardiology consultation/Holter monitoring:

Amendment 5 in study CSOM 2305 modified the study discontinuation criteria and implemented one additional ECG recording and PK sampling. This action was taken after review of ECG results of study CSOM230B2113 (one of two dedicated TQT studies) showing a slight increase in the QTcF interval compared with placebo as well as bradycardia in the pasireotide group. A summary of the amendment follows:

If at any visit a QTcF > 500 msec is observed, triplicate ECGs, each 2-3 minutes apart need to be taken approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If the mean QTcF is > 500 msec, study treatment is postponed until a cardiologist has re-evaluated the ECG (at most within 7 days of initial ECG). If cardiology confirms a mean QTcF > 500 msec, the patient had to discontinue the study.

If at Day 21 visit, a QTcF/mean QTCF is > 470 msec but ≤ 500 msec is observed for the first time for a patient at a given dose level, the following steps need to be taken:

Cardiology consultation within at least 7 days of the initial abnormal ECG.

If QTcF > 470 msec not confirmed, no further action needs to be taken.

[3] ADA (2008) "Position statement: Standards of medical care in diabetes 2008" diabetes care; 31 Suppl 1:12-54.

If QTcF > 470 msec confirmed, cardiologist must assess patient for acute cardiovascular safety risk. If confirmed, patient must be discontinued from study. If there is **not** an cardiovascular safety risk, the patient may continue to receive study medication. However, a 24 hr. Holter monitor must be recorded and evaluated prior to the next injection of pasireotide/octreotide LAR and a trough sample will be taken. The study drug injection must be postponed with a maximal permissible delay of 7 days until the Holter-ECG results are available. If it is determined that the study drug injection may be given, a second Holter-ECG must be done on the day of the LAR injection and a pre-dose PK sample must be taken.

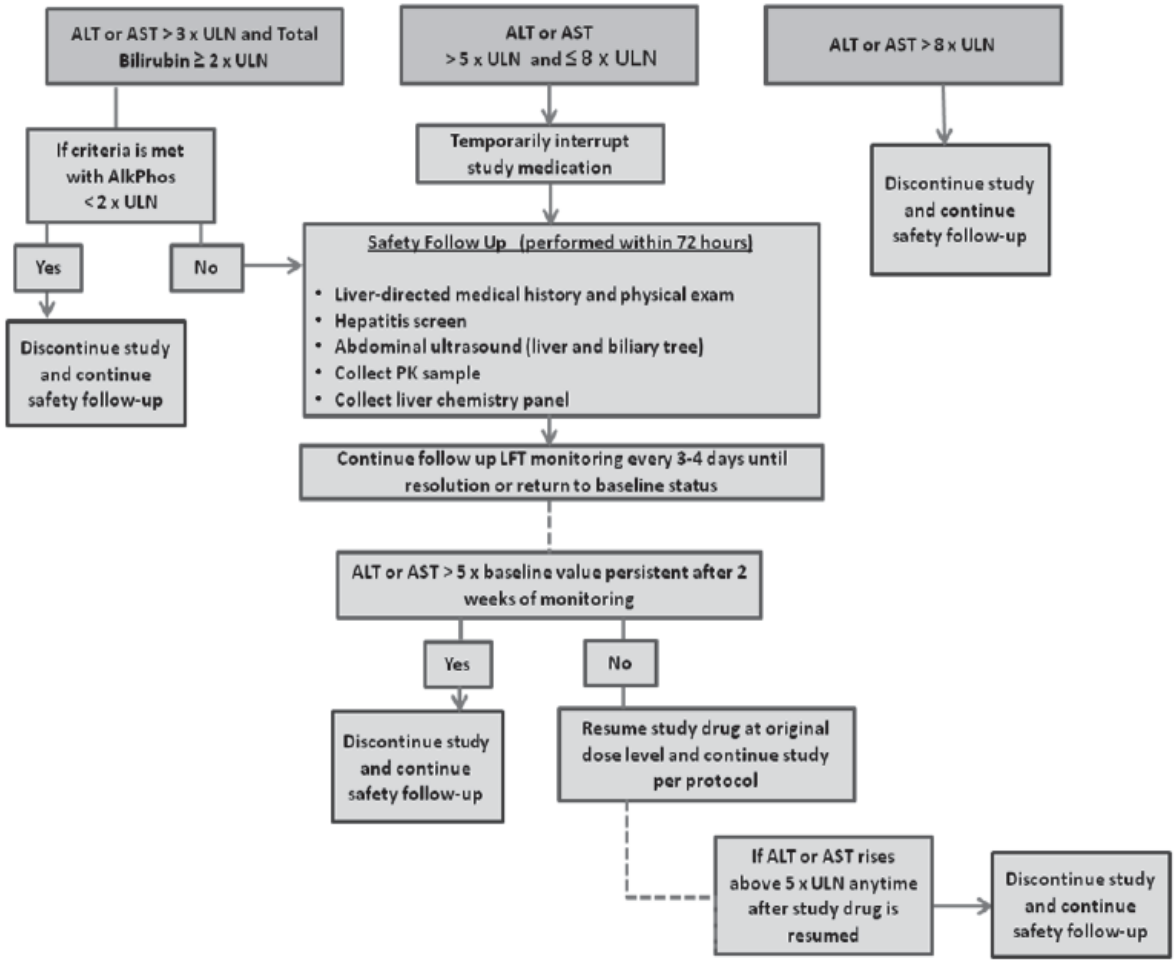
In study CSOM 2402, QT-related cardiology evaluation was triggered if QTcF > 480 msec at visit 4, 5, 6, 8, 9 (10) prior to pasireotide LAR injection. Further cardiology evaluation was similar to that performed in study CSOM 2305.

Hepatic Safety:

Specific hepatic safety management algorithm was instituted after an internal hepatic medial review of pasireotide trials. The results of this review were published in a dedicated Hepatic Report submitted with NDA 200,677 for Signifor®. The liver function test management algorithm provided below is in the final version of the C2305 protocol, however, it was incorporated as part of Amendment 7 in December 2011, the same month of the data cut-off for this NDA review. Similarly, patient enrollment for C2402 started in July 2010. Therefore, the algorithm was not in place and recommended management cannot be ensured for the majority of patients in the CORE study of C2305 and patients who enrolled into C2402 prior to December 2011. .

One minor difference between the two studies was that total bilirubin >1.5x ULN in CSOM 2305 versus > 2.0x ULN in CSOM 2402 triggered fractionation to direct and indirect bilirubin.

Figure 4. Hepatic algorithm



Source: Adapted from amended protocol version 05 study C2402, page 4597, Clinical Study Report C 2402

Pre-Specified Analysis Plan

C2305:

The primary objective was to compare the proportion of patients with a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 to within normal limits (age and sex adjusted) at 12 months between the two treatment groups.

The primary variable was defined as the proportion of patients with a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 (age and sex adjusted) at 12 months.

Secondary and exploratory objectives were also pre-specified and are described earlier on page 21.

Analysis sets:

Full analysis set (FAS): all patients randomized into the study. Patients were analyzed according to the treatment assigned at randomization.

Per protocol set (PP): a subset of the patients in the FAS who did not have any major protocol deviation by Month 12 (end of CORE phase) and completed a minimum exposure requirement (80% of randomized treatment during the CORE study). Patients were analyzed according to the treatment assigned at randomization.

Safety analysis set (SAS): all patients who received any study medication with a valid post-baseline assessment. Patients were analyzed according to treatment they first received.

Crossover analysis set (CAS): all patients whose first treatment in the extension was different from the first dose in the CORE. CAS was used for both efficacy and safety analyses.

Second PP analysis set: subset of patients in the CAS who did not have protocol deviation.

PK and extension PK analysis set: all patients with at least one LAR injection and one trough concentration assessment in the CORE, extension (PK) or in the extension after crossover (extension PK).

Two patients randomized to the octreotide LAR arm erroneously received pasireotide LAR as their first dose. These two patients were included in the octreotide LAR group for the FAS and the pasireotide LAR group for the safety analysis set.

Table 6. Analysis sets, C2305

Analysis population	Pasireotide LAR	Octreotide LAR	All patients
Up to Crossover –n (%)	**N=176**	**N=182**	**N=358**
Full analysis set (FAS)	176 (100.0)	182 (100.0)	358 (100.0)
Safety analysis set (SAS)	178 (101.1)	180 (98.9)	358 (100.0)
Per protocol (PP) set	161 (91.5)	171 (94.0)	332 (92.7)
PK analysis set	172 (97.7)	178 (97.8)	350 (97.8)
After Crossover – n (%)	**N = 81**	**N = 38**	**N = 119**
Crossover analysis set	81 (100.0)	38 (100.0)	119 (100.0)
Second (PP) set	75 (92.6)	37 (97.4)	112 (94.1)
Extension PK analysis set	78 (96.3)	38 (100.0)	116 (97.5)

CORE phase analysis sets are the same as those listed for Up to Crossover; however, cut-off dates are different.
Source: Table 2-1, Summary of Clinical Efficacy

Statistical Analysis Plan:

For a detailed review of the statistical analysis plan, please refer to Dr. Jennifer Clark's (FDA statistician) review. The plan as described by Novartis is briefly summarized here.

For C2305, Novartis describes the null hypothesis as no difference in the response rates between the pasireotide LAR and octreotide LAR groups. The alternative hypothesis is that the response rates are different between the two groups. A two-sided Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification factor was used to test the null hypothesis at the significance level of 0.0499. The response rate was calculated along with the 95% confidence interval by treatment group. The primary efficacy analysis was conducted on the FAS set and repeated on the PP analysis set. Sensitivity analyses in which a patient with missing values of mean GH or IGF-1 at 12 months or who withdrew from the study prior to month 12 were considered as non-responders.

The last observation at or after month six was carried forward for the primary efficacy variable when a month 12 assessment was not available (LOCF).

The key secondary efficacy analyses were also performed on the FAS. If the result of the primary analysis was statistically significant favoring Pasireotide LAR, the key secondary efficacy variables were then tested using the closed multiple testing method based on the weighted version of Simes test to control the overall type I error rate at 5%.

The statistical analysis plan for the other secondary efficacy analyses was reviewed and determined to be appropriate. The detailed plan will not be discussed in this review.

Extension phase data were analyzed separately by Novartis. These analyses will not be reviewed here as these data are not the primary focus of the review or approval.

C2402

The primary study objective was to compare the proportion of patients achieving biochemical control (defined as mean GH levels < 2.5 µg/L) and normalization of sex and age adjusted IGF-1 at 24 weeks with pasireotide LAR 40 mg and pasireotide LAR 60 mg separately versus continued treatment with octreotide LAR 30 mg or lanreotide autogel (ATG) 120 mg.

The primary efficacy variable was the proportion of patients achieving biochemical control at 24 weeks.

Pre-specified secondary and exlporatory objectives are described earlier on page 28.

C2402 consisted of FAS, PP, safety and PK analysis sets. These sets carry the same definition as the corresponding analysis set defined for C2305. In the PP set, however, C2402 patients only had to have one dose of study treatment.

Table 7. Analysis sets, C2402

	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68

	n (%)	n (%)	n (%)
Full analysis set (FAS)	65 (100.0)	65 (100.0)	68 (100.0)
Safety analysis set* (SAS)	63 (96.9)	62 (95.4)	66 (97.1)
Per-protocol set (PP)	54 (83.1)	50 (76.9)	59 (86.8)
PK set	63 (96.9)	62 (95.4)	NA

Seven patients were excluded from the SAS because they never received treatment or did not have post-baseline safety assessment
Source: Table 11-1, Clinical Study Report C2402

The primary efficacy analysis was performed on the FAS and repeated on the PP set. The statistical null hypotheses of the primary efficacy variable were:

H1: The response rate in the pasireotide LAR 40 mg group was ≤ to the active control group.

H2: The response rate in the pasireotide LAR 60 mg group w was ≤ to the active control group.

An exact logistic regression model that adjusts for the randomization stratification factors was used to test the null hypothesis. The exact two-sided 95% and 97.5% confidence intervals (CI) for the common odds ratio (OR) were calculated. A common OR > 1 indicated an increased odds for the pasireotide LAR (40 mg or 60 mg) group compared to the active control group.

The key secondary analysis was analyzed by the exact logistic regression described above. A gatekeeping procedure was used that combined hierarchical (i.e. primary objective and key secondary objective) and simultaneous testing based on the Simes inequality. This approach allowed for control of multiple comparisons.

6 Review of Efficacy

Efficacy Summary

The primary objective of the main pivotal trial, C2305, was to show superiority of pasireotide LAR to octreotide LAR in achieving biochemical control in medically naïve patients with acromegaly. Biochemical control was defined as a GH level < 2.5 µg/L and normalization of age and sex adjusted IGF-1 (IGF-1). As a treatment for acromegaly, the results support pasireotide LAR as a more effective treatment compared to octreotide LAR with 31.3% versus 19.2% patients, respectively, achieving biochemical control. Stratification of the population into those with a history of prior pituitary surgery compared to those with de novo diagnoses showed that post-surgery patients had higher rates of response in both treatment groups. Further analysis showed that post-surgery patients had lower mean GH and IGF-1 levels compared to their de novo counterparts. Similarly, analysis of dose response in all pasireotide LAR subjects showed that patients with higher versus lower baseline GH and IGF-1 levels have less response to pasireotide LAR.

Key secondary endpoints included the effect of pasireotide LAR to a) reduce GH levels to < 2.5 µg/L and, b) normalize IGF-1 levels. There was no significant difference on reduction of GH

levels to < 2.5 µg/L between the two study groups. The data suggest that the ability of pasireotide LAR to meet the primary endpoint comes from its effect on IGF-1 levels where 38.6% of pasireotide LAR subjects versus 23.6% of octreotide LAR subjects normalize levels.

A third key secondary endpoint was to evaluate tumor volume between the two treatment arms. Both study drugs were able to substantially reduce tumor volume compared to baseline but not with significant difference form each other.

C2402 is a "supportive" pivotal trial. The results of this trial are more supportive of the safety of pasireotide LAR than for its effectiveness. Patients were not blinded to the control arm, which was open-label. The primary objective of this trial was to show superiority of pasireotide LAR 40 mg and 60 mg, separately, in achieving biochemical control in inadequately controlled acromegaly patients. Patients had been on maximum doses of either octreotide LAR or lanreotide ATG therapy for at least six months prior to the first visit of C2402. Patients were randomized to pasireotide LAR 40 mg, 60 mg or active control (i.e. staying on their current regimen of octreotide or lanreotide). Patients in the active control group were unlikely to achieve biochemical control with an additional six months of the same therapy. The results show that some patients who are unresponsive to octreotide LAR and lanreotide ATG achieved biochemical control on pasireotide LAR, giving hope to patients with resistant cases of acromegaly.

6.1 Indication

Novartis proposes pasireotide LAR injection for the treatment of patients with acromegaly (b) (4)

6.1.1 Methods

Novartis seeks to prove their claim of efficacy with data from two pivotal trials C2305 and C2402. Data from Phase 2 and 3 studies were not pooled for efficacy or safety analyses because of differences in study design.

Please see information on the study design including the statistical analysis plan in section 5.2.

6.1.2 Demographics

In C2305, the largest race groups were Caucasian (60.3%) and Asian (22.9%) with most of the Asian patients being Chinese. Mean age was 45.4 years and the proportion of females to males was approximately 50% although the proportion of males was higher in those that crossed over to pasireotide LAR (53.1%) than to octreotide LAR (42.1%).

Table 8. C2305 demographic summary, full analysis set

	Pasireotide LAR N=176	Octreotide LAR N=182	All patients N=358
Age (years)			
n	176	182	358
Mean (standard deviation)	45.1 (12.37)	45.6 (12.97)	45.4 (12.67)
Median	46.0	45.0	46.0
Range	18 to 80	19 to 85	18 to 85
Age category (years)			
<65	168 (95.5%)	167 (91.8%)	335 (93.6%)
≥ 65	8 (4.5%)	15 (8.2%)	23 (6.4%)
Sex			
Male	85 (48.3%)	87 (47.8%)	172 (48.0%)
Female	91 (51.7%)	95 (52.2%)	186 (52.0%)
Race			
Caucasian	105 (59.7%)	111 (61.0%)	216 (60.3%)
Asian	39 (22.2%)	43 (23.6%)	82 (22.9%)
Other	23 (13.1%)	19 (10.4%)	42 (11.7%)
Native American	6 (3.4%)	5 (2.7%)	11 (3.1%)
Black	3 (1.7%)	4 (2.2%)	7 (2.0%)
BMI (kg/m^2)			
n	175	181	356
Mean (standard deviation)	28.8 (4.58)	28.7 (5.17)	28.7 (4.88)
Median	28.1	27.8	28.0
Range	19.0 to 44.4	19.5 to 55.8	19.0 to 55.8

Source: Table 11-2 Clinical Study Report C2305

In C2402, demographic characteristics were also well-balanced between the treatment groups. Again, the largest race group was Caucasian, however, the Asian population was not as prevalent in this trial.

Table 9. C2402, demographic summary, full analysis set

	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
Age (years)			
n	65	65	68
Mean (SD)	42.9 (14.05)	45.8 (14.07)	46.2 (13.11)
Median	46.0	45.0	46.5
Min - max	18 - 80	20 - 83	18 - 74
Age category (years), n (%)			
<65	62 (95.4)	57 (87.7)	63 (92.6)
≥ 65	3 (4.6)	8 (12.3)	5 (7.4)
Gender, n (%)			
Female	38 (58.5)	35 (53.8)	38 (55.9)
Male	27 (41.5)	30 (46.2)	30 (44.1)
Race, n (%)			
Caucasian	53 (81.5)	52 (80.0)	56 (82.4)
Black	3 (4.6)	8 (12.3)	4 (5.9)
Asian	3 (4.6)	1 (1.5)	0
Other	4 (6.2)	3 (4.6)	7 (10.3)
Native American	2 (3.1)	1 (1.5)	1 (1.5)
Body mass index (kg/m^2)			
n	62	64	67
Mean (SD)	29.1 (4.97)	29.8 (6.20)	29.5 (5.69)
Median	28.4	27.5	28.2

Source: Table 11-2 Clinical Study Report C2402

Disease characteristics for both pivotal trials are provided below. Baseline disease history was well balanced between the two study arms of C2305. Median time since diagnosis for all patients was 6 months, and more than 80% of all patients had been diagnosed within 24 months of study start. No patient in the pasireotide LAR group had previous pituitary radiation therapy. One patient in the octreotide LAR group received pituitary radiation treatment 7.5 years prior to study start and was reported as a protocol violation. Less than half of patients in both randomized groups had prior pituitary surgery.

In addition to elevated IGF-1 levels, active acromegaly was also defined by a 5-point mean GH level > 5 µg/L or post-OGTT GH level > 1 µg/L. However, performance of baseline OGTT was required only in the U.S. whereas it was optional outside of the U.S. The majority (90%) of U.S. patients had a baseline OGTT compared to 43% in countries outside the U.S. Therefore, OGTT results are not presented here. Thirteen of 358 patients did not have mean 5-point GH levels at baseline. All of these patients had GH nadir > 1.0 µg/L post-OGTT at baseline, however.

Review of Table 10 also shows that some patients had GH levels < 5 µg/L and IGF-1 levels in the normal range. Patients with low GH levels are reported as protocol deviations (see Table 14). In a response to clinical information request, Novartis reported that the patients with normal IGF-1 levels at baseline did have elevated IGF-1 levels at the screening visit. Some variability in levels was expected between visits and only patients who had normal levels at both screening and baseline visits were not eligible to participate.

Table 10. Disease history and baseline characteristics by randomized group, FAS, C2305

	Pasireotide LAR	Octreotide LAR
Time (months) to first pasireotide LAR dose since diagnosis		
N	176	182
Mean (SD)	20.1 (45.7)	19.6 (41.5)
Median	5.6	6.4
Range	0.4, 357.5	0.4, 377.1
Previous surgery	71 (40.3%)	80 (44.0%)
Time since surgery (months)		
N	71	80
Mean	27.9 (50.2)	29.2 (56.3)
Median	9.5	6.2
Range	1.6, 328.8	1.2, 377.1
Previous radiation		
External beam	0	0
gamma-knife	0	1 (0.5%)
Baseline 5-point mean GH (µg/L)		
N	167	178
Mean (SD)	21.9 (32.1)	18.8 (26.0)
Median	8.8	10.1
Minimum	0.8	0.6
Maximum	200.0	170
Baseline mean IGF-1 (standardized)*		
N	176	182
Mean (SD)	3.1 (1.3)	3.1 (1.2)
Median	2.9	2.9
Minimum	0.9	0.8
Maximum	6.9	7.3

Source: Tables 11-3 and 14.1-3.2.1, 14.2-2.9, and 14.2-2.13 Clinical Study Report C2305
*Absolute values of IGF-1 normal range vary by age and gender; IGF-1 is expressed as times upper limit normal and referred to as "standardized"

In C2305, 13 (18.3%) versus 20 (25%) of patients on pasireotide LAR versus octreotide LAR had pituitary surgery < 3 months before enrolling into the study. After surgery, it can take up to 3-6 months for IGF-1 levels to decrease and reach steady state. Therefore, making a decision on the success of surgery before 3 months time can be premature. In response to a clinical information request, Novartis reported that the number of patients who underwent surgery < 3 months before entering the study was greater in the octreotide LAR arm and, as such, would not favor the results for pasireotide LAR.

Disease characteristics in C2402 were also well balanced between the three treatment arms. The median time since diagnosis of acromegaly was approximately 50 months in each arm. The patients had been treated, on average, for more than six years. Most patients had undergone prior pituitary surgery as well.

Table 11. Disease history and baseline characteristics by treatment, C2402

	Pasireotide LAR 40 mg (N=65)	**Pasireotide LAR 60 mg (N=65)**	**Active Control (N=68)**
Time (months) to first pasireotide LAR dose since diagnosis			
N	65	65	68
Mean (SD)	66.4 (61.0)	75.0 (65.5)	80.1 (75.6)
Median	50.0	54.5	53.8
Range	10.1 - 336.9	7.9 - 356.6	8.1 - 357.4
Previous surgery	50 (76.9%)	41 (63.1%)	41 (60.3%)
Time since surgery (months)			
N	50	41	41
Mean	58.3 (64.9)	73.9 (51.3)	69.9 (66.3)
Median	32.0	66.0	43.7
Range	3.5 - 336.9	20.5 - 228.8	5.1 - 239.7
Previous radiation N (%)			
External beam	2 (3.1)	2 (3.1)	5 (7.4)
Gamma-knife	0	1 (1.5)	0
Baseline mean GH (µg/L)			
N	65	65	68
Mean (SD)	17.6 (35.8)	12.1 (21.8)	9.5 (12.0)
Median	7.1	5.3	6.1
Range	0.98 - 200.0	1.4 - 113.8	0.96 - 92.4
Baseline mean IGF-1 (standardized)			
N	65	65	68

Mean (SD)	2.6 (1.1)	2.8 (1.1)	2.9 (1.1)
Median	2.3	2.6	2.9
Range	0.93 - 6.2	1.1 - 6.7	1.1 - 6.0
Randomization stratification factors N (%)			
Octreotide LAR	50 (76.9)	50 (76.9)	51 (75.0)
Lanreotide ATG	15 (23.1)	15 (23.1)	17 (25.0)
GH>2.5 to ≤10 µg/L	47 (72.3)	47 (72.3)	48 (70.6)
GH > 10 µg/L	18 (27.7)	18 (27.7)	20 (29.4)

Source: Tables 11-2 and 11-3, Clinical Study Report C2402

The majority of patients had relevant medical history and continuing medical conditions. This is not unexpected given the mean age of patients enrolled in C2305 and C2402, and the known co-morbidities associated with a diagnosis of acromegaly. An exhaustive list of baseline medical conditions is beyond the scope of this review. However, on visual inspection of Tables 14.1-3.3 in the clinical study reports of both C2305 and C2402, striking differences in the prevalence of the baseline medical conditions that might impact the efficacy and safety of pasireotide LAR were not observed.

The table below summarizes baseline medical history of study subjects by SOC/PTs relevant to the diagnosis of acromegaly and assessment of safety of the somatostatin analogues. If the number of patients with a specific condition was "0" in the pasireotide LAR group, it is not listed in Table 10.

Table 12. Relevant baseline medical diagnoses in patient populations for C2305 and C2402, full analysis sets

	C2305		C2402		
SOC/PT	Pasireotide LAR (N=176)	Octreotide LAR (N=182)	Pasireotide LAR 40 mg (N=65)	Pasireotide LAR 60 mg (N=65)	Active Control (N=68)
Blood and lymphatic system disorders	16 (9.1)	13 (7.1)	12 (18.5)	6 (9.2)	11 (16.2)
-all anemia	11 (6.3)	10 (5.5)	12 (18.5)	4 (6.2)	9 (13.2)
Cardiac disorders	35 (19.9)	30 16.5)	7 (10.8)	11 (16.9)	14 (20.6)
-all bradycardia	7 (3.9)	5 (2.7)	2 (3.1)	0	1 (1.5)
Endocrine disorders	54 (30.7)	55 (30.2)	37 (56.9)	40 (61.5)	50 (73.5)
-all AI	6 (3.4)	6 (3.3)	9 (13.8)	11 (16.9)	13 (19.1)
-hyperprolactinemia	2 (1.1)	1 (0.5)	5 (7.7)	5 (7.7)	3 (4.4)
-all hypothyroidism	18 (9.6)	8 (4.4)	16 (24.6)	14 (21.6)	16 (23.5)
-goiter	24 (13.6)	21 (11.5)	9 (13.8)	14 (21.5)	23 (33.8)
-hypopituitarism	0	3 (1.6)	7 (10.8)	4 (6.2)	5 (7.4)
-all hypogonadism	14 (8.0)	9 (4.9)	9 (13.8)	11 (16.9)	11 (16.9)
GI disorders	47 (26.7)	46 (25.3)	12 (18.5)	19 (29.2)	19 (27.9)
-all abdominal pain	5 (2.8)	5 (2.6)	1 (1.5)	1 (1.5)	2 (2.9)
-diarrhea	2 (1.1)	2 (1.1)	-	-	-
-nausea	1 (0.6)	3 (1.6)	-	-	-

Hepatobiliary disorders	33 (18.8)	46 (25.3)	15 (23.1)	25 (38.5)	24 (35.3)
-cholelithiasis	11 (6.3)	25 (13.7)	12 (18.5)	17 (26.2)	20 (29.4)
Investigations	36 (20.5)	47 (25.8)	5 (7.7)	8 (12.3)	7 (10.3)
-glucose increased	1 (0.6)	0	1 (1.5)	1 (1.5)	0
-HbA1c increased	4 (2.3)	5 (2.7)	-	-	-
-QT prolongation	2 (1.1)	1 (0.5)	-	-	-
Metabolism and nutrition disorders	80 (45.5)	88 (48.4)	41 (63.1)	40 (61.5)	44 (64.7)
-IFG/IGT	17 (9.6)	7 (3.8)	12 (18.5)	11 (16.9)	14 (20.6)
-all diabetes mellitus	23 (13)	46 (25)	24 (36.9)	20 (30.7)	20 (29.4)
-Hyperglycemia	8 (4.5)	3 (1.6)	0	0	2 (2.9)
Musculoskeletal and connective tissue disorders	55 (31.3)	62 (34.1)	14 (21.5)	12 (18.5)	20 (29.4)
Nervous system disorders	51 (29.0)	63 (34.6)	20 (30.8)	11 (16.9)	11 (16.2)
-headache	28 (15.9)	35 (19.2)	4 (6.2)	3 (4.6)	1 (1.5)
Psychiatric disorders	34 (19.3)	36 (19.8)	12 (18.5)	12 (18.5)	9 (13.2)
-all anxiety	10 (5.6)	9 (4.9)	2 (3.1)	3 (4.5)	3 (4.4)
-depression	11 (6.3)	13 (7.1)	7 (10.8)	2 (3.1)	4 (5.9)
-insomnia	9 (5.1)	13 (7.1)	2 (3.1)	4 (6.2)	1 (1.5)

*"all" = closely related PTs were combined by this reviewer; AI, adrenal insufficiency; GI, gastrointestinal; IFG, impaired fasting glucose; IGT, impaired glucose tolerance DM, diabetes mellitus; "-", term not listed in data table provided by Novartis
Source: Table 14.1-3.3 in both Clinical Study Reports C2305 and C2402

In patients entering C2305, the most commonly prescribed medications prior to study start were anti-hypertensives (50% in pasireotide LAR and 60% in octreotide LAR groups) followed by corticosteroids (dermal>intranasal>oral) and glucose lowering drugs (12.4% in pasireotide LAR and 22.2% in octreotide LAR groups). The use of glucose lowering drugs at baseline and throughout the study is discussed in detail in section 7.3.5. The use of thyroid hormones was 9.1 and 9.9 % in pasireotide LAR and octreotide LAR groups, respectively. There were no striking differences in the medication categories between pasireotide LAR and octreotide LAR on visual inspection of Table 14.3-1.3 of the C2305 clinical study report.

In patients entering C2402, the most commonly prescribed medications prior to study start were anti-hypertensives (50% combined total for both pasireotide LAR groups and 75% in active control group) followed by corticosteroids (dermal>intranasal>oral) and thyroid hormone drugs (34.4% combined total for both pasireotide LAR groups and 33.2% in octreotide LAR group). The use of glucose lowering drugs was 28.8% in the pasireotide LAR groups (data combined) and 30.3% in the active control group.

6.1.3 Subject Disposition

In Study C2305, 80% of patients in the pasireotide LAR and 86% in the octreotide LAR group completed the CORE phase of the study. Subject disposition is detailed in the following table.

Table 13. Patient disposition by treatment, CORE phase, full analysis set, C2305

Disposition Reason	Pasireotide LAR N=176 n (%)	Octreotide LAR N=182 n (%)
Patients randomized	176 (100.0)	182 (100.0)
-treated	176 (100.0)	182 (100.0)
Patients treated, completed Month 12 (core phase)	141 (80.1)	156 (85.7)
-did not enter extension	29 (16.5)	29 (15.9)
-entered extension, crossed over	38 (21.6)	81 (44.5)
-entered extension, continued same treatment	74 (42.0)	46 (25.3)
Discontinued prior to Month 12	35 (19.9)	26 (14.3)
-adverse event(s)	14 (8.0)	6 (3.3)
-protocol deviation	7 (4.0)	8 (4.4)
-unsatisfactory therapeutic effect	5 (2.8)	8 (4.4)
-subject withdrew consent	5 (2.8)	3 (1.6)
-administrative problems	2 (1.1)	0
-abnormal laboratory value(s)	1 (0.6)	0
-lost to follow-up	1 (0.6)	0
-death	0	1 (0.5)

Death includes only those patients for whom death was reported as the primary reason for discontinuation therapy.
Source: Table 14.1-1.1.6, Clinical Study Report C2305

The percentage of patients who discontinued prior to Month 12 was higher in the pasireotide LAR versus octreotide LAR groups. Of the 35 patients in the pasireotide LAR group that discontinued the study, 13 (37%) discontinued by month 3 and 14 (40%) discontinued between Months 6 – 12. Fourteen (40% of 35 or 8% of 176) discontinued due to an adverse event. Four of the five patients who discontinued because of unsatisfactory therapeutic effect did so between Months 6 – 12.

Protocol Deviations

The table below describes protocol deviations during the CORE phase of C2305. The most common deviation in both randomized groups was that patients did not complete three months of treatment.

Table 14. Protocol deviations by treatment, CORE phase, C2305

	Pasireotide LAR N=176 n (%)	Octreotide LAR N=182 n (%)
Any protocol deviation	15 (8.5)	11 (6.0)
Any inclusion criteria deviation -GH 5 point mean lower than 5 µg/L or not done, and OGTT-GH < 1 µg/L or not done at V1 and V2	6 (3.4)	4 (2.2)
Any exclusion criteria deviation -prior SSA, dopamine agonist, GH antagonist treatment received	2 (1.1)	0
Other deviation	10 (5.7)	9 (4.9)
-Frequency of treatment different from as randomized prior to cross-over	0	1 (0.5)
-Not completed 3 months of treatment	10 (5.7)	8 (4.4)
-Patient did not receive at least 80% of randomized treatment	0	1 (0.5)

Source: Table 10-4, Clinical Study Report C2305

Subject Disposition and Protocol Deviations for C2402

A total of 198 patients were randomized to one of the three treatment arms. Six patients did not receive study treatment. Two patients had incorrect data listed in the dosing case report form and therefore, are listed as treated in the table below.

Table 15. Patient disposition by treatment, full analysis set, C2402

Disposition Reason	Pasireotide LAR 40 mg N=65 n (%)	Pasireotide LAR 60 mg N=65 n (%)	Active Control N=68 n (%)
Patients randomized			
-Not treated	2 (3.1)	1 (1.5)	1 (1.5)
-Treated	63 (96.9)	64 (98.5)	67 (98.5)
Completed CORE phase	59 (90.8)	57 (87.7)	65 (95.6)
-Extension – no	3 (4.6)	4 (6.2)	3 (4.4)
-Extension – yes	56 (86.2)	53 (81.5)	62 (91.2)
Discontinued in CORE phase	6 (9.3)	8 (12.3)	3 (4.4)
-AEs	2 (3.1)	4 (6.2)	0
-Withdrew consent	2 (3.1)	2 (3.1)	2 (2.9)
-Administrative	2 (3.1)	1 (1.5)	0

-Protocol deviation	0	1 (1.5)	1 (1.5)

One patient in pasireotide LAR 60 mg group and one in the active control group are counted in the Treated group, when they should be counted in the Not treated group
Source: Table 10-1, Clinical Study Report C2402

Protocol deviations in C2402 occurred in 25 patients in the pasireotide LAR groups and eight patients in the active control group. Details are provided in the table below.

Table 16. Protocol deviations, CORE phase, C2402

	Pasireotide LAR 40 mg N=65 n (%)	**Pasireotide LAR 60 mg N=65 n (%)**	**Active Control N=68 n (%)**
Any protocol deviation	**11 (16.9)**	**14 (21.5)**	**8 (11.8)**
Any eligibility criteria deviation	**4 (6.2)**	**9 (13.8)**	**4 (5.9)**
-GH 5 point mean ≤2.5 µg/L or IGF-1 ≤ 1.3 x ULN	1 (1.5)	3 (4.6)	0
-GHR-antagonist or dopamine agonists taken < 8 weeks prior to randomization	1 (1.5)	3 (4.6)	0
-Less than 6 months of treatment with max indicated dose of octreotide LAR or lanreotide ATG up to Visit 1 or treatment discontinued for more than 42 days before Visit 1.	3 (4.6)	4 (6.2)	4 (5.9)
Any other deviation	**7 (10.8)**	**5 (7.7)**	**4 (5.9)**
-In appropriate breaking of blind*	1 (1.5)	0	0
-Incorrect dispensing of pasireotide LAR, octreotide LAR, or lanreotide ATG	2 (3.1)	0	0
-Missed injection of study medication	1 (1.5)	1 (1.5)	1 (1.5)
-OGTT performed	3 (4.6)	3 (4.6)	3 (4.4)

before or at the same time as the 5-point mean GH profile			
-Patient failed screening but was randomized in error and did not receive study medication	2 (3.1)	1 (1.5)	0

*patient given incorrect dose of study medication; data safety monitoring committee informed investigator of medication given
Source: Table 10-2, Clinical Study Report C2402

6.1.4 Analysis of Primary Endpoint(s)

C2305

The primary efficacy endpoint was the proportion of responders with GH level < 2.5 µg/L and normalized IGF-1 at Month 12. The number of patients who met the primary endpoint was greater in the pasireotide LAR versus octreotide LAR groups. Of note, patients with a history of previous pituitary surgery had a higher rate of response to both drugs than patients with de novo disease.

Table 17. Proportion of patients meeting primary endpoint by stratum and treatment, LOCF, FAS, C2305

Stratum	Pasireotide LAR N =176 n/N (%) (95% CI)	Octreotide LAR N =182 n/N (%) (95% CI)	Between treatment	
			OR (95% CI)	P-value
Overall	55/176 (31.3) (24.5, 38.7)	35/182 (19.2) (13.8, 25.7)	1.94 (1.19, 3.17)	0.007
Post-surgery	28/71 (39.4) (28.0, 51.7)	17/78 (21.8) (13.2, 32.6)	2.34 (1.14, 4.80)	-
De novo	27/105 (25.7) (17.7, 35.2)	18/104 (17.3) (10.6, 26.0)	1.65 (0.85, 3.23)	-

Post-surgery = medical treatment naïve after surgery; De novo = naïve to all treatments.
P-value based on 2-sided Cochran-Mantel Hansel test
GH assessment based on mean of 5-point 2-hour profile
Source: Table 11-4, Clinical Study Report C2305

The primary efficacy analysis for the PP set was consistent with the primary efficacy analysis for the FAS and showed a significantly greater treatment effect for pasireotide LAR (Table 18). Similarly, results of the primary analysis where patients with missing data were considered non-responders also showed a treatment effect (P = 0.009) in favor of pasireotide LAR. These results were confirmed by the statistical analysis performed by the FDA.

Table 18. Proportion of patients meeting primary endpoint at Month 12 by stratum and treatment, LOCF, PP, C2305

Stratum	Pasireotide LAR N =161 n/N (%) (95% CI)	Octreotide LAR N =171 n/N (%) (95% CI)	Between treatment	
			OR (95% CI)	P-value
Overall	54/161 (33.5) (26.3, 41.4)	34/171 (19.9) (14.2, 26.7)	2.1 (1.25, 3.39)	0.004
Post-surgery	27/65 (41.5) (29.4, 54.4)	16/71 (22.5) (13.5, 34)	2.34 (1.16, 5.14)	-
De novo	27/96 (28.1) (19.4, 38.2)	18/100 (18.0) (11.0, 26.9)	1.78 (0.91, 3.51)	-

Source: Table 14.2-1.2, Clinical Study Report 2305

Exploratory analysis of additional response categories at Month 12, C2305

In the primary efficacy analysis performed for C2305, patients defined as "over-responders" (i.e. GH < 2.5 µg/L and IGF-1 < LLN) were analyzed as non-responders. Similarly, partial responders, i.e. not full response but with GH < 5 µg/L and IGF-1 ≤ 1.3x upper limit of normal (ULN), were considered non-responders in the primary efficacy analysis. The table below displays the numbers for each responder group, which is helpful in understanding the range of effect of pasireotide LAR.

Table 19. GH and IGF-1 response status at Month 12 by treatment, LOCF, FAS, C2305

Stratum	Response status	Pasireotide LAR n/N (%)	Octreotide LAR n/N (%)
Overall	Full response	63/176 (35.8)	38/182 (20.9)
	Per-protocol	55/176 (31.3)	35/182 (19.2)
	Over-response	8/176 (4.5)	3/182 (1.6)
	Partial response	24/176 (13.6)	33/182 (18.1)
	No response	89/176 (50.6)	111/182 (61.0)

Full response, combines per-protocol and over-response categories
Source: Table 11-5, Clinical Study Report C2305

Taking full response and partial response together, **49.4% of** patients in the pasireotide LAR group had a positive response compared to **39.0%** in the octreotide LAR group.

Dose increase and response categories, C2305

In all patients, the proportion of patients that required a dose increase was lower in the pasireotide LAR versus octreotide LAR groups. This statement was also true for patients with a full response, whereas in patients with a partial response, the proportion of patients requiring a dose increase was higher in the pasireotide LAR arm.

Table 20. Patients with dose increase during CORE phase by GH and IGF-1 response at Month 12, LOCF, FAS, C2305

	Pasireotide LAR		Octreotide LAR	
Response status	Total	Dose increase n (%)	Total	Dose increase n (%)
Overall	176	89 (50.6)	182	123 (67.6)
Full response	63	11 (17.5)	38	11 (28.9)
Partial response	24	16 (66.7)	33	18 (54.5)
No response	89	62 (69.7)	111	94 (84.7)

LOCF, last observation carried forward
Source: Table 11-6, Clinical Study Report C2305

C2402

While the results of C2402 reach statistical significance in of support of the primary endpoint, it should be noted that this is a selected population. The patient population in C2402 was inadequately controlled on somatostatin analogues; therefore, the expectation that GH and IGF-1 levels could be further lowered by the same therapy during the trial was low. However, the study does show that patients with a history of being unresponsive to 1st generation SSAs, may still respond to pasireotide LAR therapy, Table 21.

Table 21. Proportion of patients meeting the primary endpoint at Week 24, FAS, C2402

Category	Pasireotide LAR 40 mg N = 65	Pasireotide LAR 60 mg N = 65	Active Control N = 68
n (%)	10 (15.4)	13 (20.0)	0
95% CI for %	[7.6, 26.5]	[11.1, 31.8]	[0, 5.3]
OR versus active control	16.6	23.0	
- 95% CI for OR	[3.3, infinity]	[4.7, infinity]	
- 97.5% CI for OR	[2.6, infinity]	[3.7, infinity]	
- p-value*	0.0006	<0.0001	
- adjusted p-value**	0.0006	<0.0001	

Discontinued patients were considered non-responders
*p-value, one sided and calculated using stratified exact logistic regression
**adjusted p-value, based on trimmed version of the weighted Simes test
Source: Table 11-4, Clinical Study Report C2402

Per protocol analysis support the results shown in the above table.

Subgroup analyses, albeit with small numbers, are provided in Table 22. When stratified by previous treatment, an increased response to pasireotide LAR 60 mg compared to 40 mg was seen for patients previously on lanreotide ATG. Patients with higher baseline GH levels appear to have less response to pasireotide LAR. While this subgroup analysis has small numbers, the FDA clinical pharmacology team also found that patients with higher GH and IGF-1 levels at baseline have a weaker response to pasireotide LAR.

Table 22. GH and IGF-1 response at Week 24 by stratum and treatment, FAS, C2402

Stratum	Pasireotide LAR 40 mg n/N%	Pasireotide LAR 60 mg n/N%	Active control
Octreotide LAR	9/50 (18.0)	9/50 (18.0)	0
Lanreotide ATG	1/15 (6.7)	5/15 (33.3)	0
GH >2.5 to ≤10 µg/L	8/47 (17.0)	13/47 (27.7)	0
GH > 10 µg/L	2/18 (11.1)	1/18 (5.6)	0

Source: Table 11-9, Clinical Study Report C2402

Exploratory analysis of additional response categories at Month 6, 2402

There was only one patient in C2402 who was classified as an over-responder. Exclusion of this patient from the primary efficacy analysis did not change the results.

Dose increase and response categories, C2402

Dose increases were not permitted in C2402.

Analyses excluding sites with GCP violations

Analyses done excluding sites 730, 731, 901 and 904 with GCP violations did not change the significance of the results as reported by Dr. Jennifer Clark, FDA statistics team.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary objectives in C2305 were to compare the effect of pasireotide LAR versus octreotide LAR at 12 months, on:

1) the reduction of GH to < 2.5 µg/L
2) normalization of IGF-1 (age and sex adjusted)
3) tumor volume

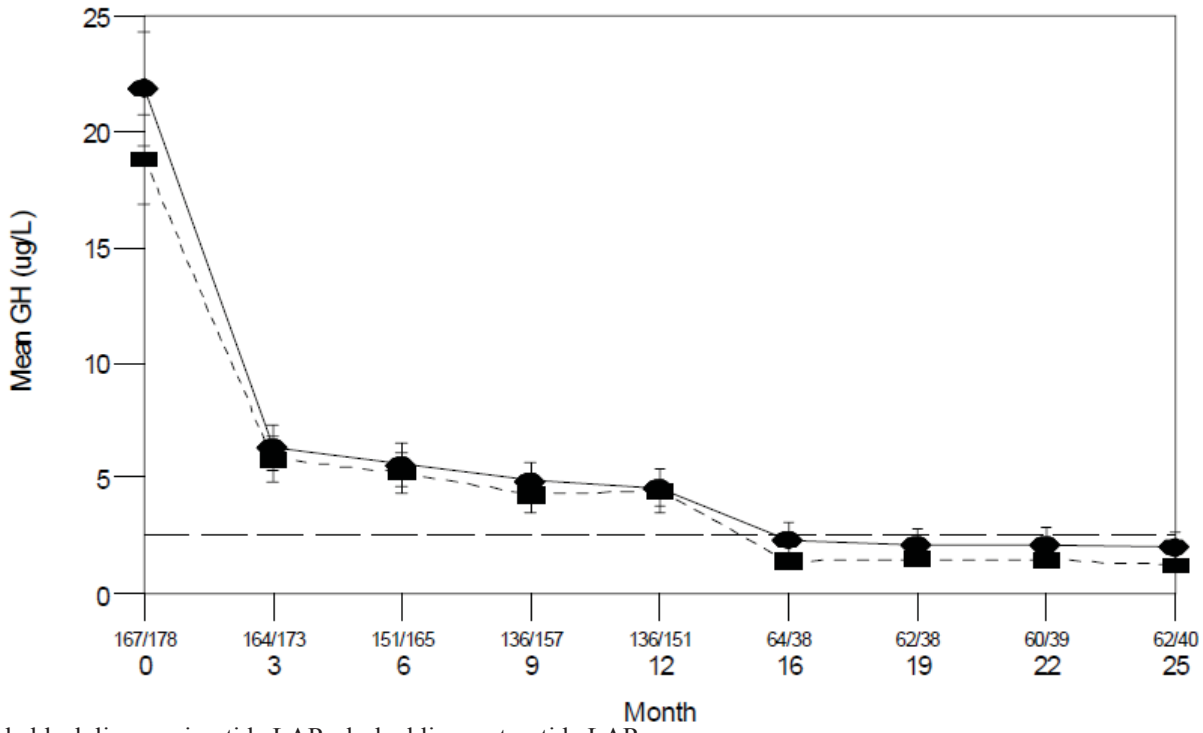
In C2402, the key secondary objective was to evaluate the proportion of patients achieving normalization of IGF-1 at 24 weeks between the three study arms. This, along with evaluation of GH response in the trial are the only two secondary objectives that will be discussed in this

review. Additional secondary and exploratory objectives were reviewed and determined not to provide information that would further support or deny approvability of pasireotide LAR.

1) Reduction of GH to < 2.5 µg

Although the efficacy of pasireotide LAR was greater than octreotide LAR using the combined GH and IGF-1 primary endpoint, the ability of pasireotide LAR to reduce GH to < 2.5 µg/L at Month 12 was not statistically significantly greater than octreotide LAR (48.3% versus 51.6%, OR 0.877, 95% CI [0.58, 1.33], P = 0.54 (Figure 5).

Figure 5. Mean (+/-) of GH level by visit and treatment, data up to crossover, FAS, C2305



Single black line, pasireotide LAR; dashed line, octreotide LAR
Source: Figure 11-3, Clinical Study Report C2305

Per protocol results were consistent with the FAS results presented above.

In C2402, the percentage of patients reaching a GH level < 2.5 µg/L was highest in the pasireotide LAR 60 mg group (43.1%) followed by the 40 mg group (35.4%). The active control group had a significantly lower rate of response at 13.2%. A per protocol analysis for this endpoint in C2402 was not provided.

2) Normalization of IGF-1

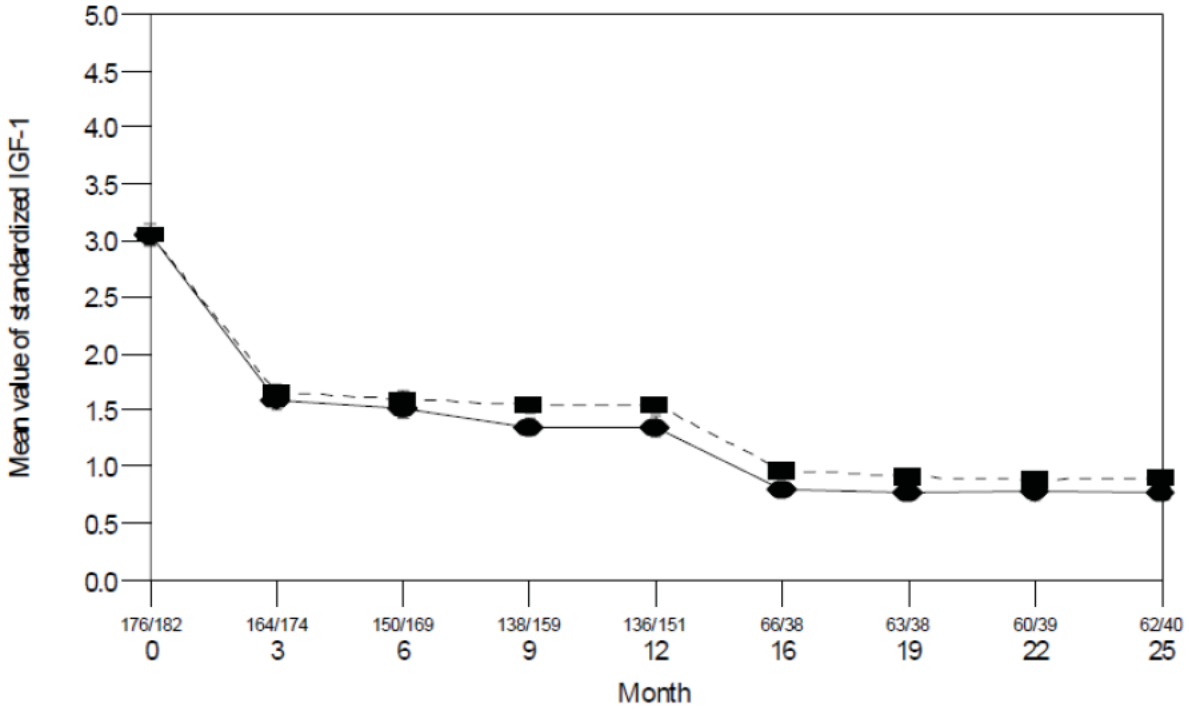
The proportion of patients with normalization of IGF-1 alone was significantly greater for those in the pasireotide LAR versus octreotide LAR group, which appears to be driven by the response of the post-surgery patients. FAS and PP results were consistent (Table 23 and Figure 6).

Table 23. Proportion of patients with normalization of IGF-1 at Month 12 by stratum and treatment, LOCF, FAS, C2305

Stratum	Pasireotide LAR N=176 n/N (%) (95% CI)	Octreotide LAR N=176 n/N (%) (95% CI)	Between treatment		
			Odds ratio (95% CI)	p-value	adjusted p-value
Overall	68/176 **(38.6)** (31.4, 46.3)	43/182 **(23.6)** (17.7, 30.5)	2.1 (1.3, 3.3)	0.002	0.007
Post surgery	36/71 **(50.7)** (38.6, 62.8)	21/78 **(26.9)** (17.5, 38.2)	2.8 (1.4, 5.5)	-	-
De novo	32/105 **(30.5)** (21.9, 40.2)	22/104 **(21.2)** (13.8, 30.3)	1.6 (0.88, 3.1)	-	-

p-value, based on 2-sided Cochran-Mantel-Haenszel test, adjusting for randomization stratification factor
Adjusted p-value, based on weighted Simes test
Source: Table 11-8, Clinical Study Report C2305

Figure 6. Mean of standardized IGF-1 level by visit and treatment, data up to crossover, FAS, C2305



Single black line, pasireotide LAR; dashed line, octreotide LAR
Source: Figure 11-4, Clinical Study Report C2305

In C2402, the key secondary objective was to evaluate the proportion of patients achieving normalization of IGF-1 (age and sex adjusted) at 24 weeks between the three study arms. The proportion of patients who achieved normalization of IGF-1 at Week 24 was higher in both pasireotide arms compared to active control **(24.6% and 26.2% [40 mg and 60 mg, respectively], responders compared to zero in the active control group**) as well. Although an unconfirmed observation, there appears to be a dose dependent response for pasireotide LAR on GH levels that is not seen on IGF-1 levels in the C2402 population. A per protocol analysis was not provided.

Results of IGF-1 response by stratum (background therapy and baseline GH levels) are provided below.

Table 24. Proportion of patients with normalization of IGF-1 at Week 24 by stratum and treatment, FAS, C2402

Stratum	Pasireotide LAR 40 mg n/N%	Pasireotide LAR 60 mg n/N%	Active control
Octreotide LAR	12/50 (24.0)	11/50 (22.0)	0
Lanreotide ATG	4/15 (26.7)	6/15 (40.0)	0
GH >2.5 to ≤10 µg/L	11/47 (23.4)	14/47 (29.8)	0
GH > 10 µg/L	5/18 (27.8)	3/18 (16.7)	0

Source: Table 14.2-2.2, Clinical Study Report C2402.

3) Tumor volume

Tumor volume decreased substantially in both the pasireotide LAR and octreotide LAR groups; however, there was not a significant difference between the treatment groups. The mean decrease was 987.1 mm3 (39.7% reduction) in the pasireotide LAR group and 801.2 mm3 (38% reduction) in the octreotide LAR groups. Similar results were seen in the post-surgery and de novo groups. Per protocol analysis showed similar results as well.

6.1.6 Other Endpoints

There were nine other secondary objectives specifically relating to the CORE phase in which pasireotide LAR and octreotide LAR were compared in C2305. Brief comments regarding each are provided.

1. Proportion of patients with a reduction of mean GH level to <2.5 µg/L and on the normalization of IGF-1 to within normal limits (age and sex related) at months 6 and 9.

-The proportion of responders varies slightly over time, but, is greater in the pasireotide LAR vs. octreotide LAR group at months 6, 9 and 12. The difference is only statistically significant at months 6 and 12.

2. Change from baseline in mean GH at 12 months.

   -In section 6.1.5 of the this review, Figure 5 shows comparable reductions in GH in both the pasireotide LAR and octreotide LAR groups in the CORE phase.

3. Time to first achievement of mean GH <2.5 µg/L and IGF-1 to within normal limits.

   -The median time to first response using the up to crossover data was comparable for pasireotide LAR, 12.6 weeks, and octreotide LAR, 12.4 weeks. The results were similar when divided into post surgery and de novo groups. The median time to first response for GH and IGF-1 separately was approximately 12 weeks for each parameter in both treatment groups. Please see figures 5 and 6 in Section 6.1.5 of this review.

4. Symptoms of acromegaly: ring size, headache, fatigue, perspiration, paresthesia, osteoarthralgia at 12 months.

   -Treatment with pasireotide LAR and octreotide LAR resulted in improvements in the severity of acromegaly symptoms within each group; however, there was no significant difference found between the two treatment arms. An analysis comparing acromegaly symptoms in responders and non-responders within and between arms was not conducted. An analysis comparing symptoms between post-surgery and de novo patients also revealed comparable results between the treatment arms.

5. Health related quality of life.

   -Acromegaly quality of life was measured by the AcroQol, which consists of a total score comprised of four subscores: physical, pyschological, psychological/appearance, and pyschological/personal. Higher scores indicated increased quality of life. Percent increase in total scores was greater in the pasireotide LAR (+28.4%) compared to octreotide LAR (+15.8%), however, the scores were not statistically significantly different. Similarly, the percent increase in sub-scores was greater in the pasireotide LAR group, but did not reach statistical significance when compared to octreotide LAR. As with the symptom analysis, a comparison between responders and non-responders within and between arms was not reported.

6. Prolactin level.

   -The assessment of prolactin levels in this study is not of substantial value. The patient population is not known to have pituitary adenomas with concomitant production of growth hormone and prolactin. The mean baseline levels of prolactin were not elevated

(20.6 µg/L, pasireotide LAR and 15.8 µg/L); therefore, the statistically significant reduction in prolactin levels favoring use of pasireotide LAR does not add value to our knowledge of the study drug at this time.

7. Duration of response for subjects who meet the primary objective.

   - The median duration of response was comparable between pasireotide LAR and octreotide LAR at 64.4 and 64.6 weeks, respectively. Novartis states most patients who lost response after Month 12 did so due to small variations in GH and IGF-1 levels and remained close to the criteria for biochemical control. Tachyphylaxis was not evident.

8. Overall safety and tolerability.

   -Safety and tolerability are discussed in section 7.0, review of safety.

9. Plasma exposure.

   - *Please see section 6.1.8 below.*

6.1.7 Subpopulations

Most subgroup analyses are discussed in the sections above. However, the efficacy of pasireotide LAR stratified by age and gender are reviewed in detail in Dr. Jennifer Clark's, FDA statistician, review. The results of the analysis show that pasireotide LAR might have greater efficacy in patients < 65 y (n=161) versus > 65 y (n=17) although there is a striking imbalance in the number of patients between the two groups. Efficacy between females and males is approximately the same. C2305 and C2402 were not powered to study these variables as determinants of efficacy; thus, the results should be considered preliminary at best.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A large dose ranging study was not performed for pasireotide LAR. As discussed in sections 7.2.1 and 7.2.2, the dose for pasireotide LAR was determined by PK/PD models compared to pasireotide s.c. and has been determined to be acceptable by the FDA.

A detailed review of plasma exposure and clinical endpoints in relation to dosing recommendations is provided in the clinical pharmacology review. In summary, there is no evident relationship between exposure and response for efficacy in C2305. However, subjects were not randomized to dose in C2305 as it was a dose titration study. In C2402, patients were randomized to either 40 mg or 60 mg of pasireotide LAR allowing for a more robust evaluation of exposure and dose response. Although not statistically significant, there is a trend that advocates for higher probability of response with increased exposure. Dose-response analysis provided similar results.

During the CORE phase of C2305, 15 patients were down titrated from a dose of 40 mg to 20 mg of pasireotide LAR and 75 patients had dose increases to 60 mg. The majority of dose increases were prescribed at Month 4 of the CORE phase. Dose increases were not because of decreased exposure. The majority of patients who required dose increase had higher baseline GH and IGF-1 levels.

In the pasireotide LAR arm, response rates were higher in the 30-50 mg average dose category (41 of 69 patients, 59.4%) compared to the > 50 mg average dose (7/81, 8.6%). In addition, two of four patients with an average dose of < 30 mg were responders. In those receiving octreotide LAR, 21/57 (36.8%) were responders in the 15-25 mg average dose group compared to 9/100 (8.2%) in the > 25 mg dose group. These data suggest, although dose was not randomized, that non-responders required larger doses.

Taken together, the dosing recommendations to start at 40 mg pasireotide LAR and titrate up to 60 mg over time appear quite reasonable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please see section 6.1.6, number 9, where duration of response is discussed.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

Pasireotide LAR is a somatostatin analogue (SSA) that has a safety profile similar in many respects to other drugs in its class. GI-related adverse events, including diarrhea, abdominal pain and nausea were experienced most commonly in all treatment groups. Gallbladder and biliary system-related events were also common as expected.

Significant hyperglycemia (primary system organ class, metabolism and nutrition disorders), as learned with Signifor®, occurred in approximately 60-70% of patients in all pasireotide LAR groups compared to approximately 30-35% in the active control groups. Glucose related abnormalities accounted for 5/23 (21.7%) of serious adverse events (SAEs) and 5/14 (35.7 %) drug discontinuations in the pasireotide LAR group, CORE phase, of C2305. In C2402, glucose related abnormalities accounted for 2/8 (25%) of SAEs and 5/6 (83.3%) drug discontinuations (data combined for pasireotide LAR 40 and 60 mg) in the CORE phase.

In contrast, glucose related abnormalities accounted for no SAEs and 1/6 discontinuations in the octreotide LAR group of C2305 and no SAEs or discontinuations in the active control group of C2402.

There were four deaths (includes CORE and extension phase) in C2305 that do not appear to be study drug related. There were no deaths in C2402 in the CORE phase and one death reported in the 120 day clinical safety update, which also does not appear to be study drug related.

Hepatic and cardiac (QT prolongation) safety was thoroughly evaluated as concerns were raised about these issues with the Signifor® application. The amendment incorporating additional hepatic safety measures was not finalized until the end of the data cut-off period for C2305. Therefore, patients in the CORE and early extension phase of this trial might not have had as complete a work-up for liver function abnormalities as patients in the later phases of both trials. Regardless, the frequency and severity of liver function abnormalities seen in both C2305 and C2402 does not further intensify concern for drug induced liver injury at this time. Similarly, no new cardiac concerns were identified in this safety review.

With the exception of hyperglycemia, the overall safety profiles of pasireotide LAR and the active control groups are similar.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The two pivotal trials used to evaluate safety for pasireotide LAR are described in sections 5.1 and 5.3 of this review. The focus of this safety review is review of pivotal trial C2305. C2402 was also a pivotal trial and has been reviewed, however, the data are viewed as supportive to the main findings of C2305.

The up to crossover and after crossover analyses for C2305 were the focus of the safety review conducted by Novartis. However, the primary focus of this review is of the CORE phase data as this represents the randomized, double blind, active control phase of the study.

7.1.2 Categorization of Adverse Events

Adverse event (AE) monitoring started with signing of the consent form and continued until four weeks after (eight weeks for serious adverse event, SAE) the last dose of study treatment. AE coding for the submitted data utilized the medical dictionary for regulatory activities (MedDRA) version14.1 for C2305 and 16.0 for C2402. Adverse event severity was graded according to CTCAE 3.0 (CTC).

In the safety sections of the clinical study reports, Novartis captured and provided data on adverse events of special interest (AESI; see section 7.2.6). These AESI reflect specific safety concerns related to either pasireotide LAR or the class of somatostatin analogues. Many of the AESI reviewed in this application were also evaluated in the NDA review for Signifor® and are discussed in detail below. Of note is that many preferred terms related to the AESI were recorded in an effort to identify any safety signal associated with the AESI in question. For example, rhabdomyolysis is an AESI. In the pasireotide LAR group, 12.9% of patients had "rhabdomyolysis related events". However, no patient actually experienced a true case of rhabdomyolysis. The "rhabdomyolysis related events" category includes the preferred term "blood creatinine phosphokinase increase", which is, in fact, what all 12.9% of the patients experienced. Awareness of this definition of an AESI must be taken into consideration when interpreting the percentages of AESI in the tables below.

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

Data from C2305 and C2402 were not pooled for the CORE efficacy or safety analyses. The populations and duration of study for the CORE period are different between the two studies. However, safety data from C2402 and the after crossover data from C2305, both representing inadequately controlled acromegaly, were pooled in the ISS/Summary of clinical safety. Data from the blinded and open-label time periods of the study were pooled for analyses that included the extension period for patients who continued on the same treatment.
Data from C2305 and C2402 were not pooled with the phase 1 and 2 studies because of significant differences in study design (Tables 4 and 5).

7.2 Adequacy of Safety Assessments

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

In C2305 the mean duration of exposure for patients who participated in the CORE and extension (on the same study drug) was longer in the pasireotide LAR versus octreotide LAR group. Prior to amendment 4, patients on octreotide LAR could not continue study treatment beyond month 12; in addition, data was not collected for octreotide LAR patients beyond month 26. These factors contribute to the difference in exposure duration.

In the CORE phase alone, mean (SD) duration of exposure to pasireotide LAR was 300.8 (89.2) days, which was similar to 315.7 (71.6) days for octreotide LAR. Median duration of exposure to both drugs was 336 days.

In C2402 the mean (SD) duration of exposure to pasireotide LAR 40 mg was 165.7 (17.2); to pasireotide LAR 60 mg it was 163 (24.3), and to active control 171.2 (18.1) days. Exposure by number of injections is provided in the table below for C2305 and C2402.

Table 25. Duration of exposure by study drug in C2305 and C2402, SAS, CORE phases, n(%)

Number of Injections	Pasi LAR	Octreo LAR	Pasi LAR 40 mg	Pasi LAR 60 mg	Active Control
1 injection	9 (5.1)	6 (3.3)	0	1 (1.6)	0
>1 - ≤ 3	4 (2.2)	2 (1.1)	2 (3.2)	2(3.2)	1 (1.5)
>3 - ≤ 6 (<6 for C2402)	7 (3.9)	4 (2.2)	3 (4.7)	2 (3.2)	1 (1.5)
6 injections (C2402)	-	-	58 (92.1)	57 (91.9)	51 (77.3)
>6 - ≤ 9 (>6 for C2402)	12 (6.7)	7 (3.9)	0	0	13 (19.7)
>9 - ≤12	144 (80.9)	155 (86.1)	-	-	-
>12 - ≤15	2 (1.1)	6 (3.3)	-	-	-

Pasi, pasireotide; Octreo, octreotide
Source: Table 12-1 in Clinical Study Report C2305 AND C2402

7.2.2 Explorations for Dose Response

The effect of pasireotide s.c. and LAR formulations is characterized well by the same PK/PD model indicating that the PD effect of pasireotide is independent of the formulation administered and dependent on the intrinsic factors of the molecule of pasireotide itself. Therefore, results from the PK analysis for study B2201 (pasireotide s.c., Table 5) and C2110 (pasireotide LAR, appendix 4) were used to determine the starting dose of pasireotide LAR for C2305 and C2402. For further discussion on dose dependent adverse events, please refer to section 7.5.1. Please see the clinical pharmacology review as part of this NDA review, 203255, as well as for NDA 200677.

7.2.3 Special Animal and/or In Vitro Testing

All animal toxicity data were reviewed in the Signifor® application (NDA 200,677). Supportive (not pivotal) in vitro testing was provided with this application. No new signals related to the LAR dose or formulation were noted. Please see the nonclinical review by Dr. Miyun Tsai-Turton for full details.

7.2.4 Routine Clinical Testing

The routine clinical testing conducted in C2305 and C2402 was generally adequate to address the safety issues of somatostatin analogues as well as hyperglycemia for pasireotide. In NDA 200677 for Signifor® (pasireotide s.c.), a hepatic algorithm to identify the source of liver function test abnormalities was not in place. The lack of an algorithm made it difficult to

elucidate the underlying etiology of the liver function abnormalities seen in the Signifor® application. Novartis implemented a hepatic algorithm in December 2011; however, this was not applied to the patients in C2305 CORE and the early part of the extension phases or in the first 1.5 years of C2402.

7.2.5 Metabolic, Clearance, and Interaction Workup

This is discussed in section 4.4.

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

Based on known AEs associated with the somatostatin analogues as well as pasireotide specific AEs, Novartis created a group of "adverse events of special interest (AESI)". Each AESI consists of one AE category and several PTs that are related to it. For example, "bradycardia related events" is an AESI. Preferred terms included in this category are bradycardia, sinus bradycardia, atrioventricular block first, conduction disorder, etc. Nineteen other AESI were identified and include: hyperglycemia, diarrhea, gallbladder and biliary, nausea, pancreatitis, rhabdomyolysis, low blood cell, liver safety, QT prolongation, constipation, hypothyroidism, injection site reaction, hypocortisolism, coagulation, GI bleeding, hypocalcemia, growth hormone deficiency, and hypotension related AEs.

Novartis provides all of the preferred terms used for each AE category in the Summary of Clinical Safety, appendix five.

7.3 Major Safety Results

7.3.1 Deaths

Four deaths occurred during the clinical program of C2305, two in pasireotide- and two in octreotide-treated patients. In the pasireotide group one of the deaths was due to a rupture of an aortic aneurysm in a 74 year-old male and the other to suicide and depression. None was suspected to be related to the study drug.

Table 26. Deaths, C2305

Demographics	Treatment/Phase/Cause of death reported/Study Day number (D)	Comments
58y female 0506-00002	Octreotide /Core/ Heart attack D = 256	Died 3 days after 10th injection; hospitalized due to myocardial infarction and died same day.
45y male 0912-00008	Pasireotide/Extension/ Psychotic depression	Patient committed suicide 9 days after onset of episode of severe

	D = 361	psychotic depression that was precipitated by external circumstances.
33y female 0903-00009	Octreotide/Extension/ Sepsis D = 421	Patient hospitalized with diarrhea and symptoms of sepsis; subsequently diagnosed with acute renal failure and lung infiltration. Despite treatment, patient experienced multiple organ failure and death.
74y male 0102-0001	Pasireotide/Crossover/ Aortic aneurysm Rupture Day = 931	Patient with history of CAD/arterial stent, hypertension, DM2 and COPD and died after receiving 20th injection of crossover treatment.

Source: Modified from Table 12-13, Clinical Study Report C2305

There were no deaths in the CORE phase of study C2402.

7.3.2 Nonfatal Serious Adverse Events

The number of patients with AEs, serious adverse events (SAEs), and discontinuations due to AEs in the core, up to crossover, and after crossover period are provided below in Table 27. Evaluation of the data did not raise concerning differences between rates of these events across the different phases.

Table 27. Classification of adverse events and drug discontinuations in all phases, SAS, C2305

	Pasi/core N=178 n (%)	**Octre/core N=180 n (%)**	**Pasi/CO N=178 n (%)**	**Octre/CO N=180 n (%)**	**Pasi/AC N=81 n (%)**	**Octre/AC N=38 n (%)**
Mean Duration of Exposure (days ± SD)	301 ± 89	316 ±72	527±334	415±190	450±247	342±72
Patients w/ AEs	168 (94.4%)	163 (90.6)	172 (96.6)	165 (91.7)	77 (95.1)	34 (89.5)
Grade 3 or 4 AEs	49 (27.5)	38 (21.1)	63 (35.4)	46 (25.6)	23 (28.4)	8 (21.1)
Discontinuations due to AEs	14 (7.9)	6 (3.3)	16 (9.0)	9 (5.0)	13 (16.0)	0
Deaths	0	1 (0.6)	1 (0.6)	2 (1.1)	1 (1.2)	0
Patients w/ SAEs	23 (12.9)	19 (10.6)	35 (19.7)	27 (15.0)	8 (9.9)	6 (15.8)

Discontinuations due to SAEs	8 (4.5)	0	9 (5.1)	0	2 (2.5)	0

Pasi, pasireotide LAR; octre, octreotide LAR; w/, with; n (%) does not apply to row indicating exposures
CO, up to crossover, AC, after crossover
Source: Modified from Tables 12-4, 12-5, and 12-6 Clinical Study Report C2305.

In the CORE phase, there is an increased rate of events in all categories except death in the pasireotide LAR versus octreotide LAR group. As will be further discussed below, this might be because of the number of subjects who developed hyperglycemia.

This trend continues in the up to crossover and after crossover groups as well. Although, the percent of SAEs in the group that crossed to octreotide LAR is much higher than in those who crossed to pasireotide LAR.

In study CSOM 2402, study drug exposures across groups are similar. The number of total adverse events is lower in the active control group, however, the patients in this arm had already been on drug for at least six months during which time adverse event and drop out data were not collected.

Table 28. Classification of adverse events and drug discontinuations, SAS, C2402

	Pasi 40 mg N=63 n (%)	**Pasi 60 mg N=62 n (%)**	**Active control N=66 n (%)**
Mean Duration of Exposure (days)	165.7 (17.2)	163 (24.3)	171.2 (18.1)
Patients w/ AEs (Grade 3 or 4)	58 (92.1) 11 (17.5)	53 (85.5) 12 (19.4)	49 (74.2) 5 (7.6)
Discontinuations due to AEs	3 (4.8)	4 (6.5)	0
Deaths	0	0	0
Patients w/ SAEs Grade 3 or 4	6 (9.5) 2 (3.2)	2 (3.2) 2 (3.2)	3 (4.5) 2 (3.0)
Discontinuations due to SAEs	1 (1.6)	0	0

Source: Modified from Table 12-1 and 12-2, Clinical Study Report C2402; w/, with; n (%) does not apply to row indicating exposures.

Review of the adverse event tables for studies C2305 and C2402 shows a similar percentage of adverse events between studies. However, the number of grade 3 or 4 adverse events and number of discontinuations due to adverse events is lower in the CSOM 2402 patient population.

Serious adverse events for studies CSOM 2305 and 2402 are tabulated below followed by narratives of interest.

Table 29. SAEs in the CORE phase, described by SOC/PT and study drug, CORE phases, C2305 and C2402

Primary SOC Preferred term	Pasireotide LAR N=178	Octreotide LAR N=180	Pasireotide LAR 40 mg N=63	Pasireotide LAR 60 mg N=62	Octreotide LAR and Lanreotide ATG N=66
Metabolism and nutrition disorders G3/4	**4 (2.2)**	2 (1.1) **1 (0.6)**	1 (1.6)	**1(1.6)**	0
Diabetes mellitus	**3 (1.7)**	0	-	-	-
Hyperglycemia	**1 (0.6)**	0	1(1.6)	**1(1.6)**	0
Decreased appetite	0	1 (0.6)	-	-	-
Hypoglycemia	0	**1 (0.6)**	-	-	-
Neoplasms benign, malignant and unspecified G3/4	**3 (1.7)**	4 (2.2) **1 (0.6)**	**1 (1.6)**	0	0
Acute myeloid leukemia	**1 (0.6)**	0	-	-	-
Mixed hepatocellular cholangiocarcinoma	**1 (0.6)**	0	-	-	-
Thyroid cancer	**1 (0.6)**	0	-	-	-
Benign breast neoplasm	0	1 (0.6)	-	-	-
Lung neoplasm	0	1 (0.6)	-	-	-
Pituitary tumor benign	0	**1 (0.6)**	-	-	-
Renal oncocytoma	0	1 (0.6)	-	-	-
Colon cancer	-	-	**1 (1.6)**	0	0
Renal and urinary disorders	**3 (1.7)**	**1 (0.6)**	-	-	-
Nephrolithiasis	**2 (1.1)**	0	-	-	-
Urinary incontinence	**1 (0.6)**	0	-	-	-
Hydronephrosis	0	**1 (0.6)**	-	-	-
General disorders and administration site	**3 (1.7)**	3 (1.7)	-	-	-

conditions					
Concomitant disease progression	**2 (1.1)**	0	-	-	-
Fatigue	**1 (0.6)**	0	-	-	-
Chills	0	1 (0.6)	-	-	-
Hernia	0	1 (0.6)	-	-	-
Pyrexia	0	1 (0.6)	-	-	-
Gastrointestinal disorders **G3/4**	2 (1.1) **1 (0.6)**	5 (2.8) **2 (1.1)**	0	**1 (1.6)**	0
Anal fissure	1 (0.6)	0	-	-	-
Hemorrhoids	**1 (0.6)**	0	-	-	-
Pancreatitis, acute	1 (0.6)	0	-	-	-
Abdominal pain	0	1 (0.6)	-	-	-
Abdominal pain, upper	0	**1 (0.6)**	-	-	-
Colonic polyp	0	1 (0.6)	-	-	-
Gastritis	0	1 (0.6)	-	-	
Intestinal obstruction	0	**1 (0.6)**	-	-	-
Irritable bowel syndrome	0	1 (0.6)	-	-	-
Pancreatic cyst	0	1 (0.6)	-	-	-
Sigmoiditis	0	1 (0.6)	-	-	-
Inguinal hernia	-	-	0	**1 (1.6)**	0
Hepatobiliary disorders **G3/4**	2 (1.1) **1 (0.6)**	2 (1.1) **1 (0.6)**	-	-	-
Cholelithiasis	2 (1.1) **1 (0.6)**	2 (1.1) **1 (0.6)**	-	-	-
Infections and infestations **G3/4**	2 (1.1) **1 (0.6)**	5 (2.8) **2 (1.1)**	0	**1 (1.6)**	0
Febrile infection	1 (0.6)	0	-	-	-
Urinary tract infection	**1 (0.6)**	1 (0.6)	-	-	-
Gastroenteritis	0	**1 (0.6)**	-	-	-

Pyelonephritis	0	1 (0.6)	-	-	-
Rectal abscess	0	1 (0.6)	-	-	-
Renal abscess	0	**1 (0.6)**	-	-	-
Abdominal abscess	-	-	0	**1 (1.6)**	0
Cardiac disorders	1 (0.6)	**1 (0.6)**	**0**	**1 (1.6)**	**0**
Atrial fibrillation	1 (0.6)	0	-	-	-
Cardiovascular disorder	1 (0.6)	0	-	-	-
Myocardial infarction	0	**1 (0.6)**	-	-	-
Atrial flutter	-	-	-	**1 (1.6)**	-
Musculoskeletal and connective tissue disorders	**1 (0.6)**	2 (1.1)	1 (1.6)	**1 (1.6)**	**2 (3.0)**
Intervertebral disc protrusion	**1 (0.6)**	0	0	0	**1 (1.5)**
Musculoskeletal pain	**1 (0.6)**	0	0	**1 (1.6)**	0
Pain in extremity	**1 (0.6)**	0	-	-	-
Tendonitis	**1 (0.6)**	0	-	-	-
Back pain	0	1 (0.6)	1 (1.6)	**1 (1.6)**	**1 (1.5)**
Osteoarthritis	0	1 (0.6)	-	-	-
Injury, poisoning and procedural complications **G3/4**	**1 (0.6)**	3 (1.7) **1 (0.6)**	-	-	-
Subdural hematoma	**1 (0.6)**	0	-	-	-
Kidney rupture	0	**1 (0.6)**	-	-	-
Road traffic accident	0	1 (0.6)	-	-	-
Tibia fracture	0	1 (0.6)	-	-	-

Blood and lymphatic system disorders	**1 (0.6)**	0	1 (1.6)	0	0
Neutropenia	**1 (0.6)**	0	-	-	-
Anemia	-	-	1 (1.6)	0	0
Nervous system disorders **G3/4**	2 (1.1) **1 (0.6)**	1 (0.6) 0	0	0	1 (1.5)
Diabetic hyperglycemic coma	**1 (0.6)**	0	-	-	-
Dizziness	1 (0.6)	0	-	-	-
Migraine	0	1 (0.6)	-	-	-
Intracranial aneurysm	-	-	0	0	1 (1.5)
Psychiatric disorders	**1 (0.6)**	0	-	-	-
Catatonia	**1 (0.6)**	0	-	-	-
Reproductive system and breast disorders	1 (0.6)	0	1 (1.6)	0	0
Uterine prolapse	1 (0.6)	0	-	-	-
Dysfunctional uterine bleeding	-	-	1 (1.6)	0	0
Skin and subcutaneous tissue disorders	0	1 (0.6)	-	-	-
Schamberg's disease	0	1 (0.6)	-	-	-
Vascular disorders	**0**	**1 (0.6)**	**1 (1.6)**	0	0
Arteriovenous fistula	0	**1 (0.6)**	-	-	-
Deep vein thrombosis	-	-	**1 (1.6)**	0	0
Ear and labyrinth disorders	**1 (0.6)**	**0**	-	-	-
Hypoacusis	**1 (0.6)**	0	-	-	-

Investigations	**0**	**2 (1.1)**	1 (1.6)	0	0
Blood creatine phosphokinase increased	0	**2 (1.1)**	-	-	-
Blood glucose increased	-	-	1 (1.6)	**0**	**0**
Surgical and medical procedures	-	-	0	0	1 (1.5)
Hip arthroplasty	-	-	0	0	1 (1.5)

Adapted and modified from Table 14.3.1-3.1.3 and Table 14.3.1-2.1, Novartis Clinical Study Reports C2305 and 2402; G3/4, grade 3 or 4; bolded numbers signify G3/4 event; "-" signifies a heading not in the listing; orange highlight indicates a hyperglycemia related SAEs

Notable CORE serious adverse events in the **pasireotide LAR group** in CSOM 2305 are discussed here. Summaries of octreotide LAR SAEs are not provided in this review.

Glucose related SAEs

1) **Patient C2305-0277-00006:** 59y Asian female diagnosed with acromegaly in June 2008. Patient had diabetes mellitus since March 2005. Baseline fasting glucose was 92 mg/dl and HbA1c was 6.3%. **By Day 15 fasting blood glucose increased to 228 mg/dl and by Day 29 up to 395 mg/dl.** Patient started treatment with glimeprimide-metformin. On Day 37, patient presented with lack of energy and was hospitalized. The pre-existing diabetes mellitus worsened to Grade 3, however, no glucose parameters are reported. The patient was treated with metformin hydrochloride, voglibose and insulin glargine. By Day 55, the event had resolved and on Day 56, blood sugar was 170 mg/dl. The pasireotide dose was **reduced to 20 mg**. The patient completed the CORE phase of the study and continued on pasireotide 20 mg in the extension phase.

   On Day 449, the patient's fasting blood glucose was normal but HbA1c was high at 10.9%. By Day 463, her diabetes mellitus worsened with "beta cell dysfunction to Grade 3", and she was hospitalized. Pasireotide LAR was **discontinued** due to the event, diabetes mellitus. Last injection was received on Day 449.

2) **Patient C2305 0605-00008:** 18y Black male diagnosed with acromegaly August of 2009. Patient had increased blood sugar and HbA1c and increased CPK since Sept 2009. Baseline blood glucose was 152 mg/dl, HbA1c 7.0% and CPK 279 UI/L (range: 40-250). On Day 15, patient was "diagnosed with diabetes mellitus" with a fasting glucose of 441 mg/dl and HbA1c 8.2%. CPK had increased to 1335 UI/L. **By Day 23, patient was**

hospitalized due to increasing blood sugar values. Treatment included insulin glargine, insulin aspart, and metformin. The event was considered resolved by Day 33 and Pasireotide LAR was **discontinued.**

3) **Patient C2305-0912-00002:** 39y male (race: Other) diagnosed with acromegaly in April 2008. Baseline fasting blood glucose and HbA1c "were normal". By Day 14, patient's blood glucose increased to 114 mg/dl and by Day 56 up to 131 mg/dl, diet modifications were recommended. On Day 168, blood glucose was 125 mg/dl and HbA1c 6.7%. Metformin treatment started. By Day 177, **blood glucose rose to 360 mg /dL** and patient was hospitalized for four hours. Treatment with gliclazide started. On Day 178, the event, diabetes mellitus, was reported as resolved.

4) **Patient C2305-0904-00016:** 50y Black female diagnosed with acromegaly Nov 2009. Relevant medical history includes impaired fasting glucose. Baseline fasting blood glucose was 100 mg/dl and HbA1c was 6.5%. By Day 31, **blood glucose rose to 283 mg/dl** and by Day 65 further worsened (no values reported) requiring **discontinuation** of pasireotide LAR. Last dose of study medication received on Day 59.

5) **Patient C2305-0840-00008:** 53y Caucasian female diagnosed with acromegaly June 2009. Baseline fasting blood glucose, HbA1c and gallbladder ultrasound were normal. On Day 85, patient's fasting blood glucose and HbA1c measured 392 mg/dL and 9.2%. On the same day gallbladder ultrasound showed sludge in gallbladder lumen and urinalysis showed 4+glucose, 1+protein. By Day 88, patient was hospitalized and diagnosed with **diabetic hyperglycemic coma** with a blood glucose level of 359 mg/dL; the event resolved on Day 89 and patient was discharged from the hospital. Core phase completed. Patient continued to receive pasireotide LAR 60 mg in the extension phase. On Day 671, patient diagnosed with **acute cholecystitis** and underwent laparoscopic cholecystectomy. Patient continued pasireotide LAR.

Non-glucose related SAEs C2305

1) **Patient C2305-0602-00010:** 49y Caucasian menopausal female diagnosed with acromegaly in October 2009. Patient had been on pasireotide LAR for 113 days when patient presented with **neutropenia** and leukopenia. By day 157, the patient was diagnosed with **acute myeloid leukemia**. Pasireotide LAR was **discontinued** on day 141.

2) **Patient C2305-0176-00008**: 43y Caucasian male diagnosed with acromegaly in 1990. On study day 90, patient was diagnosed with **mixed hepatocellular cholangiocarcinoma**. Pasireotide LAR was permanently **discontinued**.

3) **Patient C2305-0602-00003:** 37y Caucasian female diagnosed with acromegaly in August 2008. On study day 187, patient was diagnosed with a hepatic adenoma and **papillary thyroid carcinoma**. Pasireotide LAR was permanently **discontinued**.

4) **Patient C2305-0661-00002**: 55y Caucasian male diagnosed with acromegaly in February 2008. On study day 141, patient experienced agitation and confusion. Symptoms worsened and patient was hospitalized for **catatonic psychosis**. Pasireotide LAR was permanently **discontinued**.

Review of SAEs that occurred in the up to crossover or after crossover extension phases did not reveal unusual or increased frequency of events in the pasireotide LAR group compared to what was seen in the core phase. Of note, a 45 y female (Patient 0363-00002) taking pasireotide LAR in the core and extension phase was diagnosed with infiltrating ductal carcinoma of the breast during the extension phase. Pasireotide LAR was not discontinued. This patient received a total of 22 injections (611 days exposure). Breast cancer was diagnosed on study day 434.

In addition, one patient who crossed over to pasireotide experienced an SAE of adrenal insufficiency. This occurred after receiving the last dose of octreotide LAR and before receiving the first dose of pasireotide LAR. All cases of adrenal insufficiency are reviewed in section III of section 7.3.5.

Notable CORE serious adverse events in the pasireotide LAR group in C2402 are discussed here. There were two hyperglycemia related SAEs.

Of note is that Novartis provided nine SAE narratives; however, only eight SAEs are presented in the tables and discussion in the safety section. The ninth narrative is for an SAE of hypertension in patient **C2402-0344-00005**. When asked about this discrepancy, Novartis replied (response to information request received by FDA April 4, 2014) that a narrative was prepared for this patient as the patient experienced the AE of hypoglycemia. In order to provide a complete description of the patient's course in the study, the SAE hypertension, which occurred in the screening phase, was included in the narrative. In the absence of the AE of special interest, no narrative would have been provided. Therefore, hypertension is not included as an SAE as it was not treatment emergent.

There were three SAEs in the active control group, none because of glucose related abnormalities (Table 29) that will not be discussed here.

Glucose related SAEs C2402

1) **Patient C2402-0301-00002**: 48y Caucasian male diagnosed with acromegaly in August 2005 and treated with lanreotide, octreotide and pegvisomant. Relevant medical history includes impaired glucose tolerance. Baseline laboratories showed a fasting blood glucose of 114 mg/dL, HbA1c 5.5% and low hemoglobin at 10.5 g/dL. By Day 65, the hemoglobin level worsened to Grade 2 (level not reported). **Fasting blood glucose increased to 150 mg/dL and HbA1c to 6.3%.** Patient completed the core phase. After the last dose of pasireotide LAR, patient started on ferritin treatment and underwent colonoscopy. Approximately three months after discontinuation of pasireotide LAR, the anemia resolved with hemoglobin of 11.6 g/dL.

2) **Patient C2402-0344-00004**: 47y Caucasian male diagnosed with acromegaly in October 2010. Prior treatment included pituitary surgery in February 2011, octreotide and lanreotide. Relevant medical history includes type 2 diabetes mellitus treated with metformin. Screening visit fasting blood glucose measured at 122 mg/dL and HbA1c of 6.0%. **By Day 29, blood glucose rose to 172 mg/dL and on Day 58 remained at 169 mg/dL.** HbA1c on day 86 was 7.0%. Metformin dose was increased, but, ultimately changed to metformin hydrochloride-sitagliptin phosphate monohydrate (Ristfor). Patient completed core phase of the study.

Non-glucose related SAEs C2402

1) **Patient C2402-0301-00002**: 48y Caucasian male diagnosed with acromegaly in August 2005 and treated with lanreotide, octreotide and pegvisomant. Relevant medical history includes impaired glucose tolerance. Baseline laboratories showed a fasting blood glucose of 114 mg/dL, HbA1c 5.5% and low hemoglobin at 10.5 g/dL. By Day 65, the hemoglobin level worsened to Grade 2 (level not reported). **Fasting blood glucose increased to 150 mg/dL and HbA1c to 6.3%.** Patient completed the core phase. After the last dose of pasireotide LAR, patient started on ferritin treatment and underwent colonoscopy. Approximately three months after discontinuation of pasireotide LAR, the anemia resolved with hemoglobin of 11.6 g/dL.

2) **Patient C2402-0344-00004**: 47y Caucasian male diagnosed with acromegaly in October 2010. Prior treatment included pituitary surgery in February 2011, octreotide and lanreotide. Relevant medical history includes type 2 diabetes mellitus treated with metformin. Screening visit fasting blood glucose measured at 122 mg/dL and HbA1c of 6.0%. **By Day 29, blood glucose rose to 172 mg/dL and on Day 58 remained at 169**

mg/dL. HbA1c on day 86 was 7.0%. Metformin dose was increased, but, ultimately changed to metformin hydrochloride-sitagliptin phosphate monohydrate (Ristfor). Patient completed core phase of the study.

3) Patient C2402-0151-00026: 49y Caucasian female diagnosed with acromegaly in October 2004. On Day 112, patient developed pain and edema in left lower limb, was admitted to the hospital and diagnosed with deep vein thrombosis in the left iliac vein. A recent long bus ride is the only risk factor identified by the investigator. Patient completed the core phase.

4) **Patient C2402-0221-00013**: 59y Caucasian male diagnosed with acromegaly in May 2001 and had been treated with octreotide acetate prior to the current study. On Day 30, colonoscopy revealed suspected **colonic neoplasia** and ultimately underwent colon surgery. Patient **discontinued** pasireotide LAR with last dose being on Day 59.

5) **Patient C2402-0402-00003**: 43y Caucasian female diagnosed with acromegaly in 1997. Prior treatment included pituitary surgery 1997, lanreotide, and bromocriptine. On Day 132, patient presented with **dysfunctional uterine bleeding** along with low hemoglobin 10.6 g/dL. Treatment was given. Patient completed core phase. One day after the last dose of pasireotide LAR, patient underwent curettage of uterine cavity and ultimately was diagnosed with glandular hyperplasia of endometrium.

6) **Patient C2402-0502-00003:** 51y Caucasian female diagnosed with acromegaly in April 2009. Prior treatment included pituitary surgery in June 2009 and lanreotide acetate. Patient entered the study in active atrial flutter and first degree 2:1 AV block (both grade 1). Prior to study treatment, HbA1c was 7.8% and fasting blood glucose measured at 138 mg/dL. By days 83 and 113, **fasting blood glucose values increased** to a high of 249 mg/dL) and HbA1c to 11.4%. By Day 116, patient presented with **acute cardiac failure due to worsened atrial flutter (grade 3)**. Patient was hospitalized and underwent cardiac ablation surgery. Patient completed core phase of study. On the day of the last pasireotide LAR injection, patient presented with **abdominal abscess** due to liraglutide injections and was hospitalized for incision and drainage.

7.3.3 Dropouts and/or Discontinuations

Study C2305

All dropouts and discontinuations were due to adverse or serious adverse event occurrence. Of 16 patients who discontinued pasireotide LAR, nine discontinued due to SAEs, eight occurred in the core phase: (n=1 per diagnosis) fatigue, catatonia, acute pancreatitis, thyroid cancer, acute myeloid leukemia and mixed hepatocellular cholangiocarcinoma; and glucose related

abnormalities (n=2) (Table 30). The ninth subject discontinued in the extension phase due to diabetes.

The remaining seven of 16 patients discontinued pasireotide LAR due to AEs (n=6, CORE phase; n=1, extension) of which three were related to glucose metabolism and two to transaminase abnormalities (Table 30).

Six patients discontinued octreotide LAR in the CORE phase due to the following AEs: glucose abnormalities (n=1) and the remaining experienced (n=1 per diagnosis) Schamberg's disease, upper abdominal pain, blood creatinine phosphokinase increased, QT prolongation, fatigue/muscular weakness.

One subject on octreotide LAR in the CORE phase experienced an SAE of Schamberg's disease, i.e. required hospitalization. The SAE resolved, but, the adverse event of Schamberg's disease continued leading to discontinuation of octreotide LAR.

Study drug dose adjustments/interruptions were more frequent in the pasireotide LAR group (n=13) in the core phase with 5/13 (38%) because of glucose abnormalities. In contrast, of nine patients who required adjustment in the octreotide LAR group, only one did so because of glucose abnormalities. Differing patterns were not seen in the up to crossover or after crossover data.

Table 30. Summary of discontinuations/drop-outs in pasireotide LAR group, up to crossover, C2305

Subject ID	PT_TXT	AE Type	DC-CORE	DC-EXTN	Exposure to Pasireotide LAR # Inj (# days)
0714_00004	AST increased	AE	-	Yes	18 (533)
	Insulin-like growth factor decreased	-	-	-	-
0731_00005	Blood bilirubin increased	AE	Yes	-	1 (28)
	Transaminases increased	-	-	-	-
0771_00033	Alopecia	AE	Yes	-	8 (224)
	Non-cardiac chest pain	-	-	-	-
0161_00007	Diabetes mellitus	AE	Yes	-	7 (198)
0178_00002	Decreased appetite	AE	Yes	-	3 (84)
0704_00008	Type 2 diabetes mellitus	AE	Yes	-	4 (113)
0770_00001	HgbA1c increased	AE	Yes	-	4 (115)
0605_00008	Diabetes mellitus	SAE	Yes	-	1 (28)
	Hyperglycemia	-	-	-	-
0277_00006	Diabetes mellitus	SAE	-	Yes	12 (335)

	Concomitant disease progression	-	-	-	-
0602_00010	Acute myeloid leukemia	SAE	Yes	-	6 (168)
	Anemia	-	-	-	-
0176_00008	Mixed HCC	SAE	Yes	-	7 (201)
0322_00003	Pancreatitis acute	SAE	Yes	-	11 (311)
0602_00003	Thyroid cancer	SAE	Yes	-	8 (217)
0661_00002	Catatonia	SAE	Yes	-	6 (168)
0802_00008	Fatigue	SAE	Yes	-	7 (196)
0904_00016	Hyperglycemia	SAE	Yes	-	3 (86)

Source: Datasets AAEV and ADARSUM provided by Novartis.
PT_TXT, adverse event description; AE, adverse event; DC, discontinuation; EXTN, represents those who were on Pasireotide LAR in the core and continued it in extension phase; #Inj, number of injections received of Pasireotide LAR; # days, duration of days exposed to pasireotide LAR

Of those that crossed over to pasireotide LAR, 13 subjects discontinued the drug. Eleven patients had an adverse event related to glucose metabolism and two experienced an SAE related to glucose metabolism (diabetic ketoacidosis and diabetes mellitus).

Study C2402

Seven patients discontinued pasireotide LAR in C2402 (three in the 40 mg and four in the 60 mg group) of which six discontinued (n=5 CORE; n= 1 extension) due to hyperglycemia related events.

There were no study drug discontinuations in the active control group.

Table 31. Summary of discontinuations, pasireotide LAR group, C2402

Subject ID	PT_TXT	AE Type	DC-CORE	DC-EXTN	Exposure to Pasireotide LAR # Inj (# days)-dose
0151-00036	Hyperglycemia	AE	Yes	-	3 (87) – 60 mg
0151-00043	Hyperglycemia	AE	Yes	-	2 (50) – 40 mg
0480-00001	Hyperglycemia	AE	Yes	-	4 (97) – 60 mg
0480-00002	Hyperglycemia	AE	Yes	-	3 (68) – 60 mg
0224-00005	Hyperglycemia	AE	Yes	-	6 (139) – 60 mg
0461-00005	Diabetes Mellitus	AE	-	Yes	7 (168) – 40 mg
0223-00013	Colon Cancer	SAE	Yes	-	3 (78) – 40 mg

PT_TXT, adverse event description; AE, adverse event; DC, discontinuation; EXTN, represents those who were on Pasireotide LAR in the core and continued it in extension phase; #Inj, number of injections received of Pasireotide LAR; # days, duration of days exposed to Pasireotide LAR.

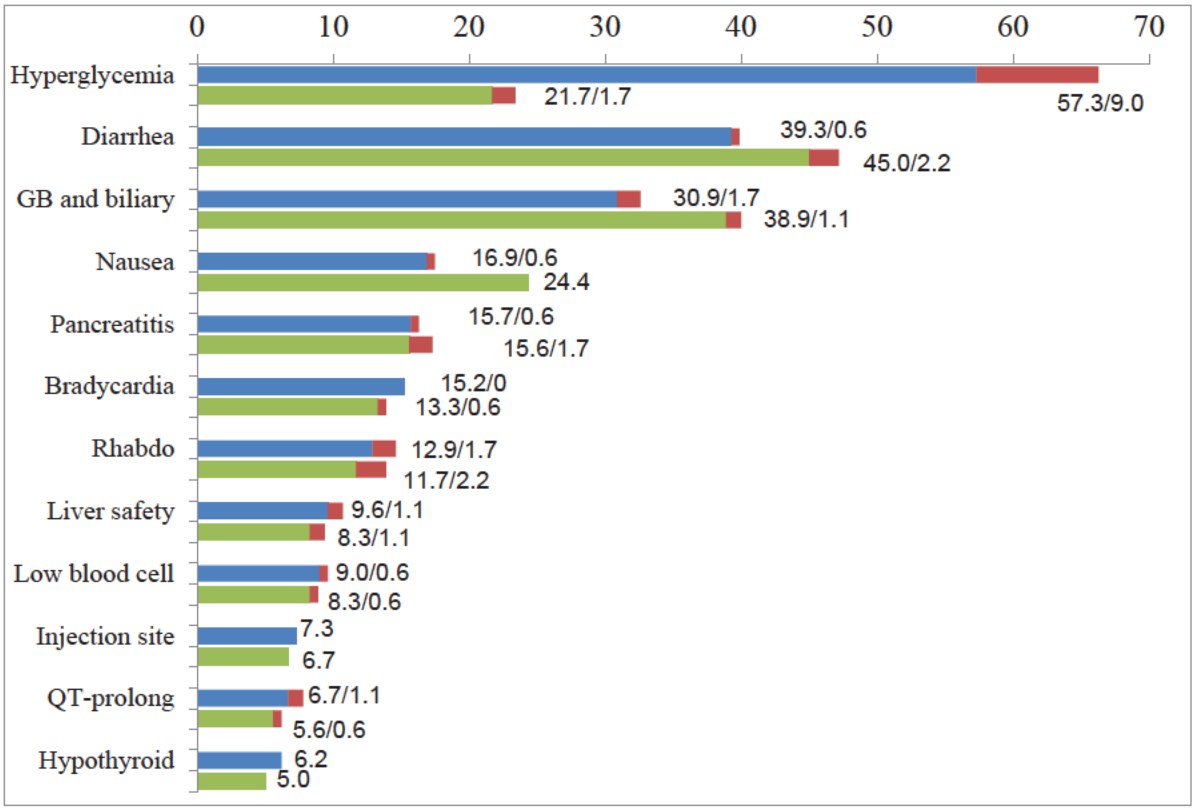
It is notable that six of 74 (8.1%) who were on pasireotide LAR in the core and extension versus 12/81 (14.8%) patients who crossed over to pasireotide LAR from octreotide LAR discontinued the study drug due to glucose related abnormalities. Thus, the rate of discontinuation due to glucose abnormality is higher in the after crossover phase. One might hypothesize that prior treatment with octreotide LAR increases a patient's risk for glucose abnormalities with pasireotide LAR. Somatostatin analogues as a class are reported to impair beta-cell secretion. However, the rates of discontinuation of pasireotide LAR due to glucose related abnormalities in C2402 are 4.7% in the 40 mg and 6.4% in the 60 mg groups, which would not support the hypothesis. That being said, patients in C2402 were not medical treatment naïve. Patients with significant adverse events to somatostatin analogues may not have chosen to enroll in C2402 biasing the results.

7.3.4 Significant Adverse Events

Adverse events of special interest that occurred with at least a 5% difference and with a higher incidence in the pasireotide LAR group were all hyperglycemia-related (57.3% vs. 21.7%). Using the same criteria, diarrhea-related, gallbladder and biliary-related, and nausea related AEs occurred with higher frequency in the octreotide LAR group (Figure 7). The rates of AE occurrence in the remainder of the categories seen in Figure 7 were not different by more than 2% between pasireotide LAR and octreotide LAR.

The data for the up to crossover and after crossover phases are comparable. In the after crossover phase, there was an increased frequency of rhabdomyolysis related events (15.8% octreotide LAR vs. 8.6% pasireotide LAR) and pancreatitis (10.5% octreotide LAR vs. 3.7%) related AEs in those who crossed over to octreotide LAR. However, these frequencies were not more than what was seen in total in the CORE phase.

Figure 7. 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



All Y-axis headings are shortened to the main preferred term. The extended titles would add the term "related events", e.g. hyperglycemia related events, diarrhea related events, etc.
GB, gallbladder; Rhabdo, rhabdomyolysis
Source: Table 12-20 page 207, CSOM 2305 Clinical Study Report

Adverse events that required significant additional therapy with the highest incidences are provided in the table below. Significant therapy was defined by Novartis as requirement of any additional therapy.

Table 32. Adverse events requiring significant additional therapy, up to crossover, SAS, C2305

SOC/PT	Pasireotide LAR N=178 (%)	Octreotide LAR N=180 (%)
Total	83.7	76.7
Metabolism and nutrition disorders -hyperglycemia -diabetes mellitus	53.4	21.1
Investigations	18.0	8.9

-glucose related		
Musculoskeletal and connective tissue disorders -pain in extremity	23.0	17.8
Infections and Infestations -nasopharyngitis -influenza -upper respiratory tract infection	43.3	37.8

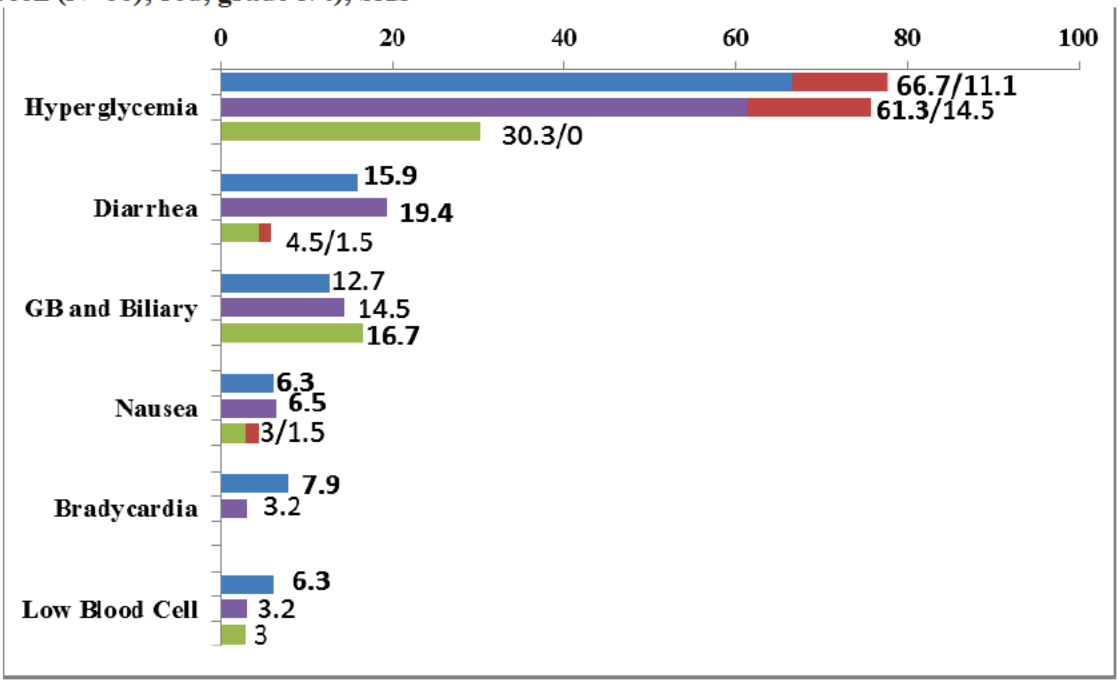
*SOC presented if rates ≥ 5% in pasireotide LAR versus octreotide LAR
Preferred terms provided represent the majority of adverse events requiring additional therapy under that SOC.
Source: Page 206, Clinical Study Report C2305

Study C2402

Adverse events of special interest that occurred with at least a 5% difference and with a higher incidence in the pasireotide LAR group were hyperglycemia and diarrhea related. Similar to C2305, gallbladder and biliary events occurred with increased frequency in the active control group. Nausea, bradycardia and low blood cell count occurred with greater frequency in pasireotide LAR vs active control with a 3-5% difference between groups (Figure 8).

The top four adverse event categories in both C2305 and C2402 are hyperglycemia, diarrhea, gallbladder and biliary and nausea related events; however, diarrhea and nausea occur with greater frequency in the octreotide LAR group in C2305 but in the pasireotide LAR group in C2402.

Figure 8. C2402 Percentage of patients with AEs of special interest (>5% shown) by treatment group (pasireotide LAR 40 mg (N=63), blue; pasireotide LAR 60 mg (N=62), purple, active control, green (N=66); red, grade 3/4), SAS



All Y-axis headings are shortened to the main preferred term. The extended titles would add the term "related events", e.g. hyperglycemia related events, diarrhea related events, etc.
GB, gallbladder; Rhabdo, rhabdomyolysis
Source: Table 12-9, Clinical Study Report C2402

Adverse events requiring significant additional therapy with the highest incidences are shown in the table below. Note that the SOC Infections and Infestations is not listed in the table as the difference between pasireotide LAR and active control was not at least 5%; however, the total incidence is notable at 17.5 and 17.7%, pasireotide LAR 40 and 60 mg, respectively and 13.6% for active control.

Table 33. Adverse events requiring significant additional therapy, SAS, C2402

SOC/PT	Pasireotide LAR 40 mg N=63 (%)	Pasireotide LAR 60 mg N=62 (%)	Active Control N=66 (%)
Total	77.8	62.9	43.9
Metabolism and nutrition disorders -hyperglycemia -diabetes mellitus	42.9	45.2	13.6
Gastrointestinal disorders -diarrhea -abdominal pain	15.9	8.1	7.6

Nervous system disorders -headache	9.5	1.6	4.5
Blood and lymphatic system disorders -anemia	6.3	1.6	1.5

*SOC presented if rates ≥ 5% in pasireotide LAR versus octreotide LAR
Preferred terms provided represent the majority of adverse events requiring additional therapy under that SOC.
Source: Table 14.3.1-8.1, Clinical Study Report C2402.

Comparison of different pasireotide LAR populations

The "after crossover" population in C2305 is most comparable to the C2402 population as both represent inadequately controlled disease while on medical treatment. Table 34 below compares the common adverse events in the CORE phase of C2305 versus the inadequately controlled groups.

The most commonly experienced AEs in **all those** who received pasireotide LAR included hyperglycemia, gallbladder and biliary disease and diarrhea. Nausea occurred frequently in the C2305 CORE and after crossover phase but less so in C2402 overall. A slight increase in low blood cell count is seen in the C2305 after crossover phase compared to the CORE phase and to C2402, the significance of this is not clear.

The rate of adverse events is generally higher in C2305 CORE than in the C2305 after crossover and C2402 groups. As mentioned earlier, what might explain the lower rates of adverse events in the C2402 population is: 1) patients with significant adverse events to somatostatin analogues may not have chosen to enter this study; and 2) patients experiencing adverse events on octreotide LAR or lanreotide ATG may have sought treatment or experienced spontaneous resolution of the event before enrolling into C2402.

Otherwise, there is no obvious pattern of AE differences in between the medically naïve group (C2305) and those with prior medical treatment for acromegaly (C2402).

Table 34. AEs of special interest in C2305 and C2402 (frequency >5%) in pasireotide LAR, all grades shown, SAS

Category	C2305 CORE Pasireotide All grades (G3/4) (%)	C2305 Crossed to Pasireotide All grades (G3/4) (%)	C2402 Pasireotide 40 mg All grades (G3/4) (%)	C2402 Pasireotide 60 mg All grades (G3/4) (%)
Hyperglycemia	57.3 (9.0)	67.9 (13.6)	66.7 (11.1)	61.3 (14.5)
Diarrhea	39.3 (0.6)	24.7 (0)	15.9 (0)	19.4 (0)
GB and Biliary	30.9 (1.7)	29.6 (2.5)	12.7 (0)	14.5 (0)
Nausea	16.9 (0.6)	11.1 (1.2)	6.3 (0)	6.5 (0)

Pancreatitis	15.7 (0.6)	3.7 (0)	3.2 (0)	0
Bradycardia	15.2 (0)	6.2 (1.2)	7.9 (0)	3.2 (0)
Rhabdomyolysis	12.9 (1.7)	8.6 (0)	0	1.6 (0)
Low blood cell	9.0 (0.6)	12.3 (0)	6.3 (0)	3.2 (0)
Liver Safety	9.6 (1.1)	6.2 (0)	3.2 (0)	1.6 (0)
Injection site	7.3 (0)	0	0	1.6 (0)
QT-prolongation	6.7 (1.1)	4.9 (2.5)	-	-
Hypothyroidism	6.2 (0)	3.7 (0)	-	-

Each category may represent one or more preferred terms; therefore, add "related events" to each term; "-" signifies that the term was not in the original table.
Source: Modified Tables 12-20 and 12-23, C2305 and Table 12-9, C2402 Clinical Study Reports.

7.3.5 Submission Specific Primary Safety Concerns

I. Glycemia Control

GH is a strong insulin antagonist and in excess leads to insulin resistance in either the liver or periphery and hyperinsulinemia. However, somatostatin analogues are known to impair pancreatic beta-cell function. In a phase 2 (study 2216) trial designed to elucidate the mechanism behind pasireotide induced hyperglycemia, investigators observed reductions in secretion of insulin, C-peptide, glucagon, GLP-1, and GIP in 45 healthy men. There was no evidence of a dose-dependent effect and the hyperglycemia was not associated with a decrease in insulin sensitivity in the liver or muscles (study 2216 reviewed by Dr. Naomi Lowy, NDA 200,677).

Throughout the safety sections of C2305 and C2402, multiple terms are used to represent glucose abnormalities. However, for purposes of describing "diabetes status" seen in the analysis below, Novartis used the following definitions:

- **Diabetic:** patients taking antidiabetic medication, or prior history of diabetes mellitus, or HbA1c $\geq$ 6.5% or FPG $\geq$ 126 mg/dL
- **Pre-diabetic:** patients not qualifying as diabetic, and 100 mg/dL $\leq$ FPG < 126 mg/dL or 5.7% $\leq$ HbA1c < 6.5%
- **Normal glucose tolerance:** patients not qualifying as diabetic or pre-diabetic, and with FPG < 100 mg/dL and/or HbA1c < 5.7%

Glycemic Control in C2305

As was learned with review of Signifor®, hyperglycemia was also a significant issue for pasireotide LAR. As shown below, the baseline combined rates of diabetes mellitus and impaired glucose tolerance was 68.0% in the pasireotide LAR group comparable to 72.3% observed in the octreotide LAR group. Although true prevalence rates of glucose abnormalities in acromegaly are not available, the diabetes mellitus and impaired glucose tolerance rates found

in C2305 appear to be consistent with the rates reported in the medical literature.[4] The figures below provide a detailed analysis of diabetic status over time in C2305. Interestingly, the proportion of diabetics at baseline was higher in the octreotide LAR group.

Figure 9. Diabetic status over time in the CORE phase, C2305 – pasireotide LAR group, SAS

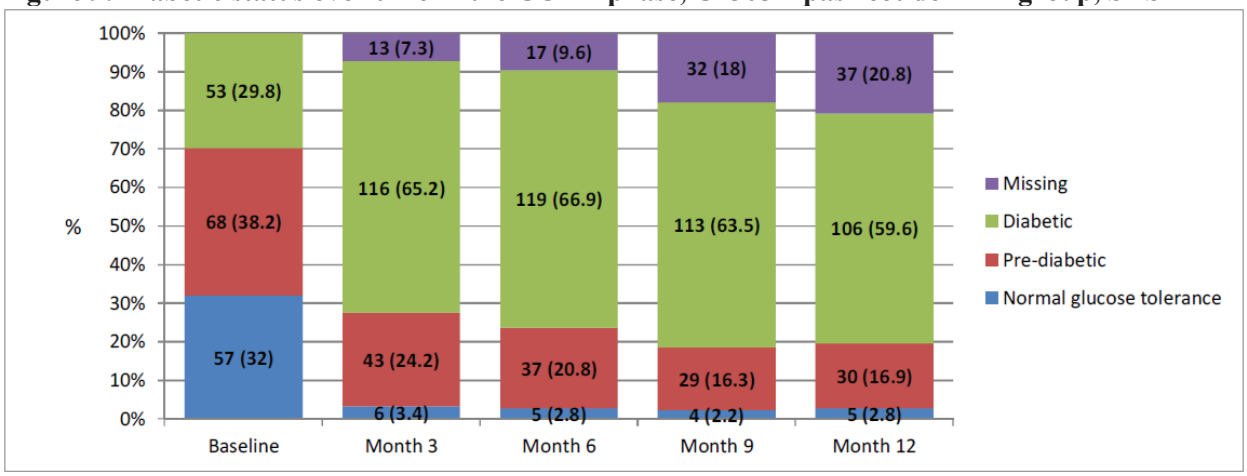
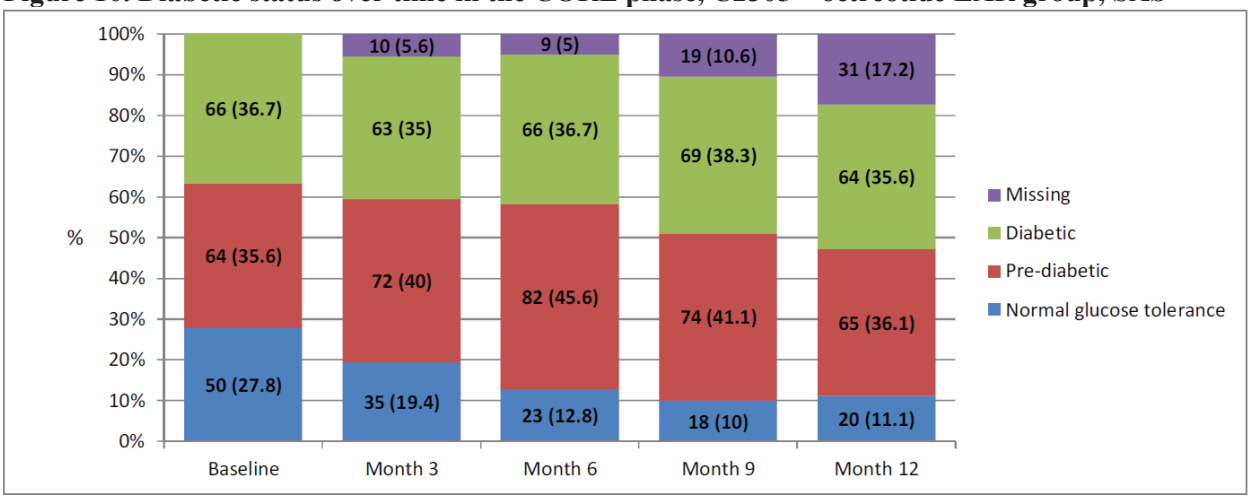


Figure 10. Diabetic status over time in the CORE phase, C2305 – octreotide LAR group, SAS



Source: Response to clinical information request received by FDA April 11, 2014

In a separate analysis (response to information request received April 11, 2014) of **completers (SAS; N = 143; pasireotide LAR)** of the CORE phase in C2305, the percentage of those with diabetes and pre-diabetes at 12 months is equally high. In the pasireotide LAR group, completers of the study showed an increase from 28.7% with diabetes at baseline to 74.1% at Month 12.

[4] Colao A, et al. Systemic complications of acromegaly: Epidemiology, pathogenesis, and management. Endo Rev., 2004.

Pre-diabetics accounted for 37.1% of the completers population at baseline and 21% at month 12. Completers with normal glucose tolerance accounted for 34.3% at baseline and 3.5% at month 12.

A text summary of changes in glycemia parameters (A-E) followed by graphical representations of this data is provided below.

A. Changes in glycemia parameters in those with **normal glucose tolerance** at baseline, C2305: (source: Tables 3.1-37 and 3.1-35, ISS)

Pasireotide LAR:

- Mean baseline **FPG** of 88 ± 8 mg/dl rose to a peak mean FPG of 113 ± 22 at month 4 representing a **28% increase**. Note: n = 56 at baseline and 45 by month 12.
- The mean percent increase at months 3, 6, 9 and 12 was approximately 26%.
- Mean baseline **HbA1c** values of 5.2 ± 0.4 rose to a peak HbA1c value of 6.1% at month 6 representing a **17.3%** increase.
- The range of percent increase of HbA1c was 13.5 - 15.4 % at months 3, 9 and 12.

Octreotide LAR:

- Mean baseline 86 ± 11 mg/dl rose to a peak mean FPG values of 94 ± 8 mg/dl at month 2. HbA1c changes from baseline to month 12 were minimal.

B. Changes in glycemia parameters in those with **pre-diabetes** at baseline, C2305: (source: Tables 3.1-37 and 3.1-35, ISS)

Pasireotide LAR:

- Mean baseline **FPG** of 97 ± 11 mg/dl rose to a peak mean FPG of 133 ± 51 mg/dl at month 3 representing a **37%** increase. Note: n = 68 at baseline down to 53 at month 12.
- Percent increases in mean FPG declined to 31, 28, and 29% at months 6, 9 and 12, respectively.
- Mean baseline **HbA1c** of 5.8 ± 0.3% rose to a mean peak HbA1c of 6.7 ± 0.7 representing a **15.5%** increase.
- The percent increase in HbA1c at the 3, 9 and 12 month time points was 13.8%.

Octreotide LAR

- Mean baseline 97 ± 10 mg/dl rose to a peak mean FPG values of 104 ± 12 mg/dl at month 5. HbA1c changes from baseline to month 12 were minimal.

C. Changes in glycemia parameters in those with **diabetes** at baseline, C2305: (source: Tables 3.1-37 and 3.1-35, ISS)

Pasireotide LAR:

- Mean baseline **FPG** of 107 ± 20 mg/dl rose to a peak mean FPG of 164 ± 76 mg/dl at month 2 representing a **53%** increase. Note: n=53 at baseline and decreased to 40 by month 12.
- At month 3, the percent increase dropped to 38% and by month 12, the percent increase was down to 21.5%.
- Mean baseline **HbA1c** of 6.3 ± 0.6% rose to a mean peak HbA1c of 7.6 ± 1.7 % at month 3 representing a **20.6%** increase.
- Percent increases dropped to 14.3, 11 and 11% at months 6, 9, and 12 respectively.

Octreotide LAR:

- Mean baseline FPG of 110 ± 25 mg/dl rose to a peak mean FPG values of 119 ± 34 mg/dl at month 11. HbA1c changes from baseline to month 12 were minimal.

D. Changes in glycemia parameters in **the intent to treat population (ITT, SAS) (N=178) in the CORE phase**, C2305: (source: Tables 14.3-2.17.1 and 14.3-2.18.1 , Clinical Study Report C2305)

Pasireotide LAR

- Mean baseline **FPG** rose from 97 ± 15.5 to a peak mean FPG at month 2 with a value of 131 ± 50 representing a **34%** change from baseline. Values plateaued by month 12 to a mean value of 123 ± 31 representing a 26.9% change. Note: n = 178 at baseline and decreased to 138 by month 12.
- **HbA1c** followed a similar pattern. Baseline mean HbA1c of 5.8 % ± 0.6 rose to a peak mean value of 6.7 ± 1.3% at month 3 with a slight plateau to 6.5 ± 0.9% by Month 12. Levels were only checked every 3 months from after baseline.

Octreotide LAR

- Mean baseline FPG rose from 98.5 ± 20 mg/dl to a mean peak FPG of 105 ± 25 mg/dl at month representing a 9% increase. HbA1c changes from baseline to month 12 were minimal.

E. Changes in glycemia parameters parameters in the **completer population (SAS) in the CORE (n=138)** phase: (source: response to FDA clinical information request received on April 11, 2014)

Pasireotide LAR

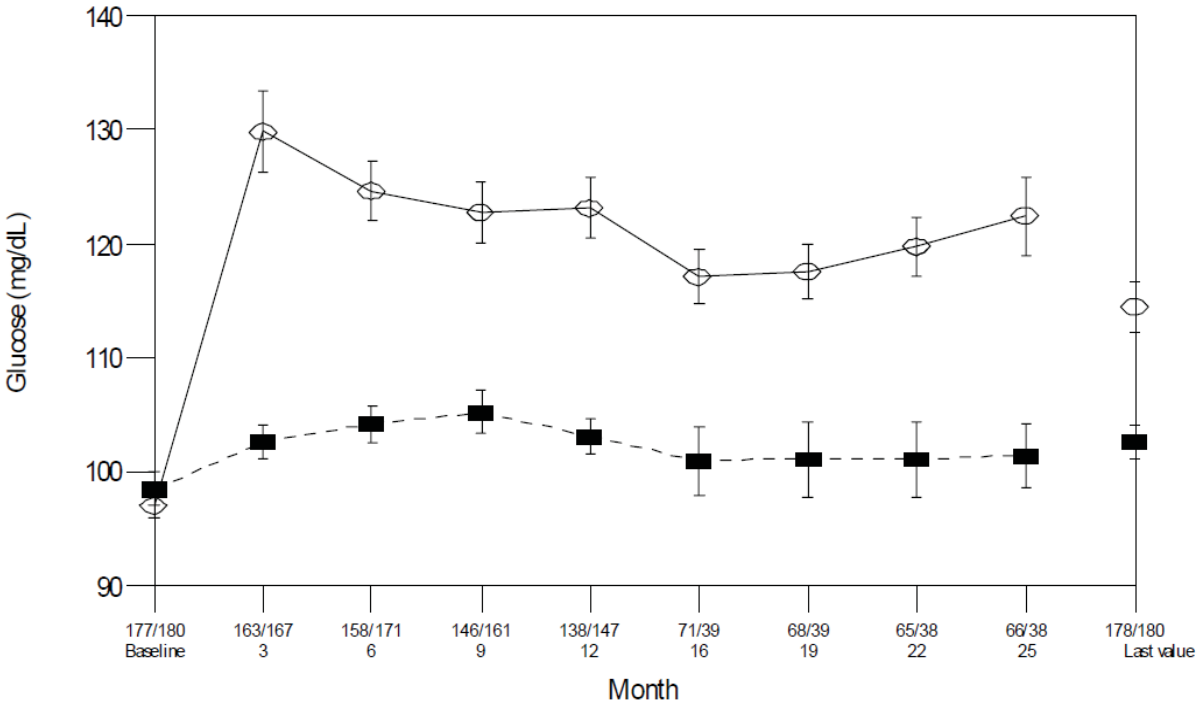
- Mean baseline **FPG** rose from 95.9 ± 14.1 mg/dl to a peak mean FPG of 127.5 ± 42.7 mg/dl at month 3 representing a **34%** change from baseline. Values plateaued by month 12 to a mean value of 123 ± 31mg/dl representing a 29.2% change.
- **HbA1c** followed a similar pattern. Baseline mean HbA1c of 5.7 ± 0.6% rose to a peak mean value of 6.6 ± 1.0% at month 6 (although value at month 3 was 6.56 ± 1.1%) remaining steady until month 12. Levels were only checked every 3 months from after baseline.

Octreotide LAR

- Mean baseline FPG rose from 97.5 ± 20 mg/dl to a mean peak FPG of 105.5 ± 25.5 mg/dl at month 11 representing a 10% increase. HbA1c changes from baseline to month 12 were minimal.

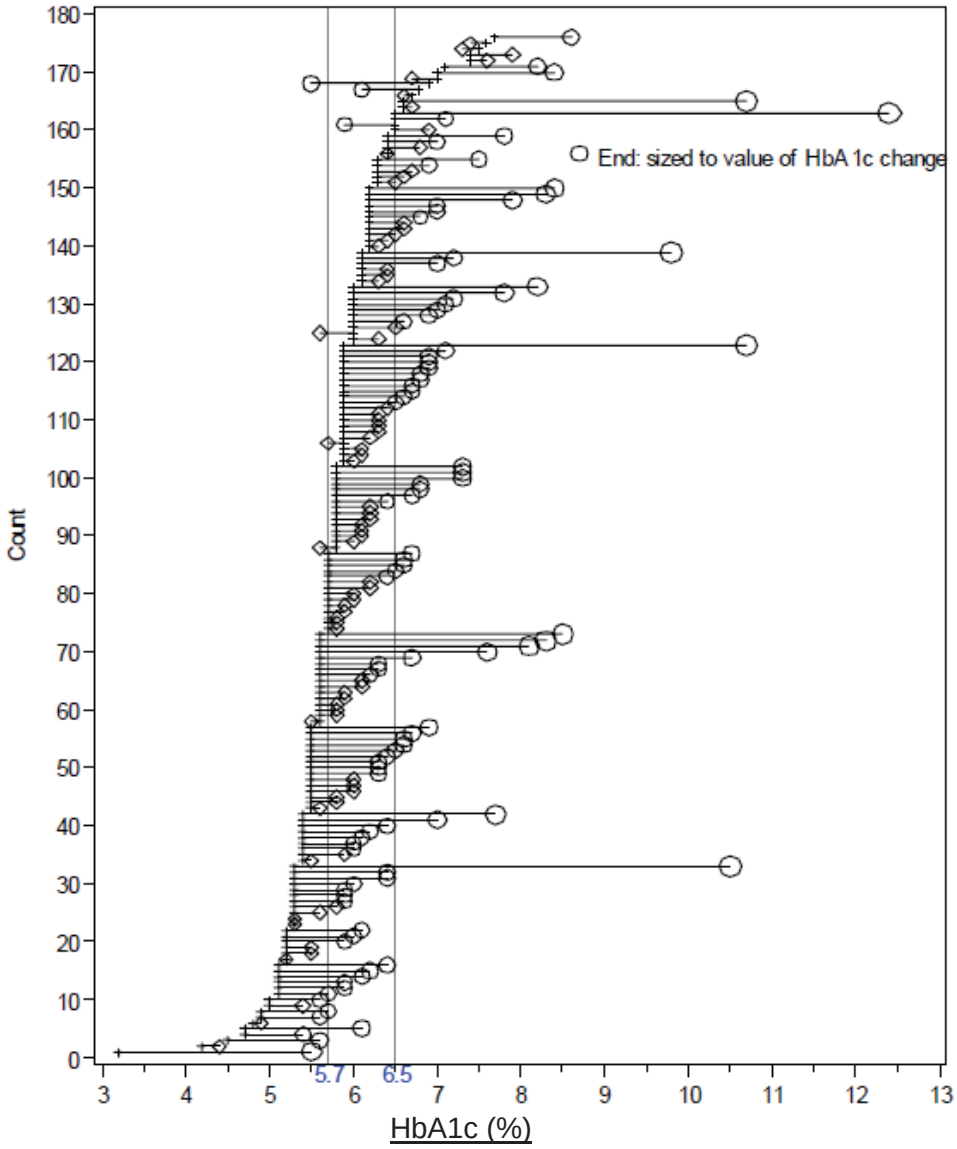
Figures 11-13, below, are graphical representations of glucose and HbA1c values over time in C2305.

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

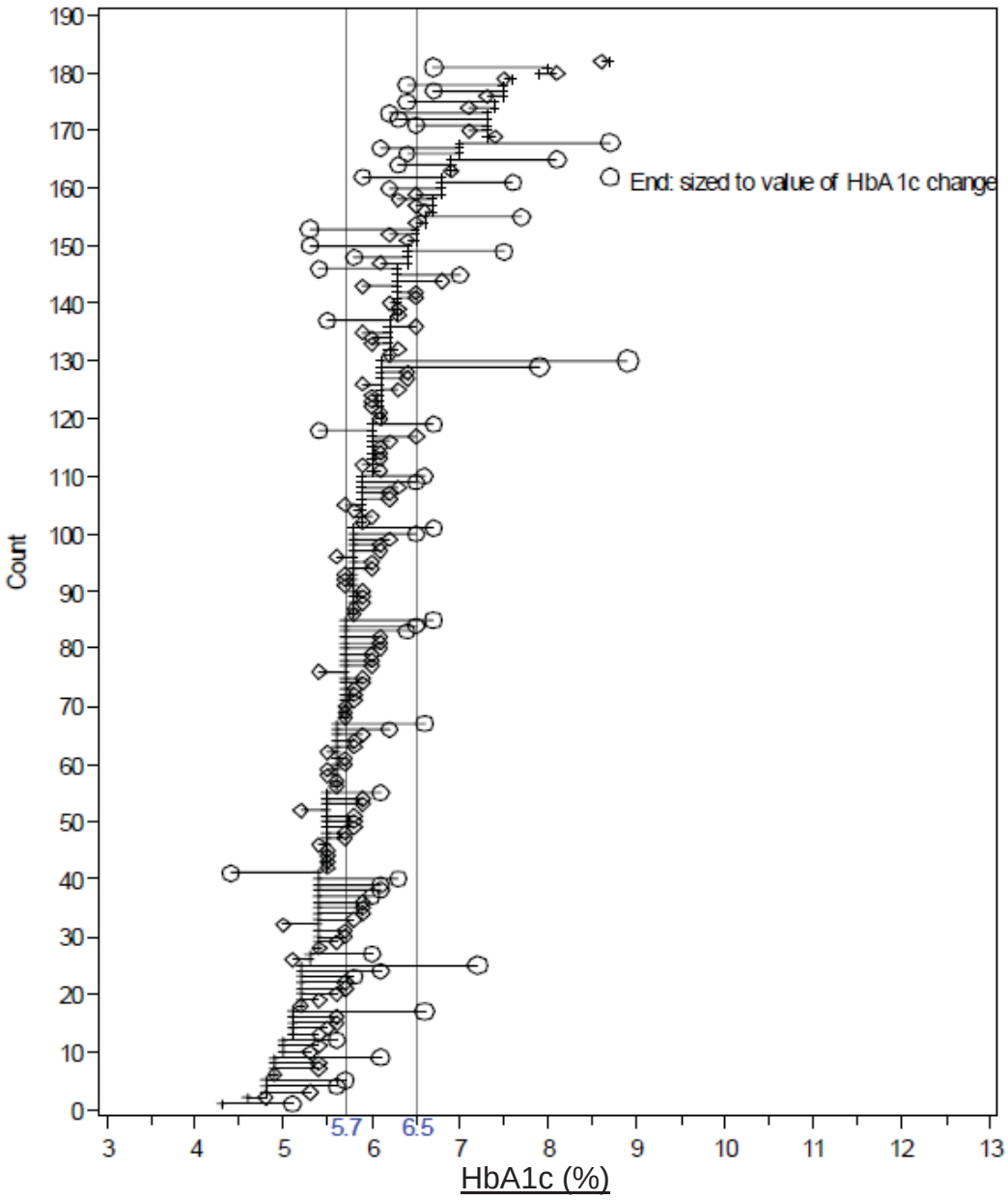
Figure 12. HbA1c from baseline to Month 12 (last available value), pasireotide LAR, C2305, FAS



Last value
No. with HbA1c<6.5%: 100/176(56.8%)
No. with HbA1c<7%: 138/176(78.4%)

Source: Response to clinical information request received by FDA April 11, 2014

Figure 13. HbA1c from baseline to Month 12 (last available value), octreotide LAR, C2305, FAS



Last value
No. with HbA1c < 6.5%: 144/182 (79.1%)
No. with HbA1c < 7%: 166/182 (91.2%)

Source: Response to clinical information request received by FDA April 11, 2014

Medication usage for glucose control, C2305

The table below summarizes anti-diabetic medication usage at baseline and at Month 12.

Table 35. Anti-diabetic usage over time in pasireotide LAR group, SAS, C2305

# Meds	Diabetic Status	Baseline n (%)	Started or Increased Usage by month 12, n (%)
No Med	Diabetes	31 (58.5)	22 (42)
	NGT	**57 (100.0)**	7 (12)
	Pre-Diab	68 (100.0)	24 (35)
One Med	Diabetes	16 (30.2)	10 (17.5)
	NGT	**0**	0
	Pre-Diab	**0**	0
Two Meds	Diabetes	5 (9.4)	4 (7.5)
	NGT	**0**	0
	Pre-Diab	**0**	0
3+ Meds	Diabetes	1 (1.9)	no change
	NGT	**0**	0
	Pre-Diab	**0**	0

Patients presented according to diabetes status at baseline: diabetes (N=53), normal glucose tolerance (N=57; bold), pre-diabetes (N=68).
Source: Response to clinical information request received by FDA April 11, 2014, Table HAQ002.1_1.1

In summary, 87.6%, (156/178) of all patients were not on anti-diabetic meds at the start of study C2305 and by Month 12 (67/178) 38 % of all patients started or had to intensify therapy.

In the octreotide LAR group, anti-diabetic medication usage did not change significantly from baseline to 6 and 12 (end of CORE) months. Similarly, there were no notable differences between those with diabetes, pre-diabetes and normal glucose tolerance.

Consistent with the intention-to-treat population, baseline anti-diabetic medication usage in the completer pasireotide LAR population (N = 143) increased from 10.5% to 42 % compared to a milder increase from 20.8% to 24.8% in the octreotide LAR group.

A breakdown of the different types of anti-diabetic medications used in study C2305 is provided in the table below.

Table 36. Anti-diabetic medications by visit and treatment, CORE phase, SAS, C2305

	Pasireotide LAR N = 178 n (%)			Octreotide LAR N = 180 n (%)		
ATC class	**Baseline**	**Month 6**	**Month 12**	**Baseline**	**Month 6**	**Month 12**
Insulin alone	1 (0.6)	1 (0.6)	3 (1.7)	3 (1.7)	3 (1.7)	2 (1.1)
Biguanides						

alone	**11 (6.2)**	**24 (13.5)**	**19 (10.7)**	**15 (8.3)**	**15 (8.3)**	**16 (8.9)**
Alpha glucosidase inhibitor alone	0	0	0	1 (0.6)	0	0
Glinides	1 (0.6)	1 (0.6)	0	0	0	0
Combination drugs	**6 (3.4)**	**29 (6.3)**	**34 (19.1)**	**19 (10.6)**	**18 (10.0)**	**18 (10.0)**

Source: Table 2-1, Response to clinical information request received by FDA May 16, 2014

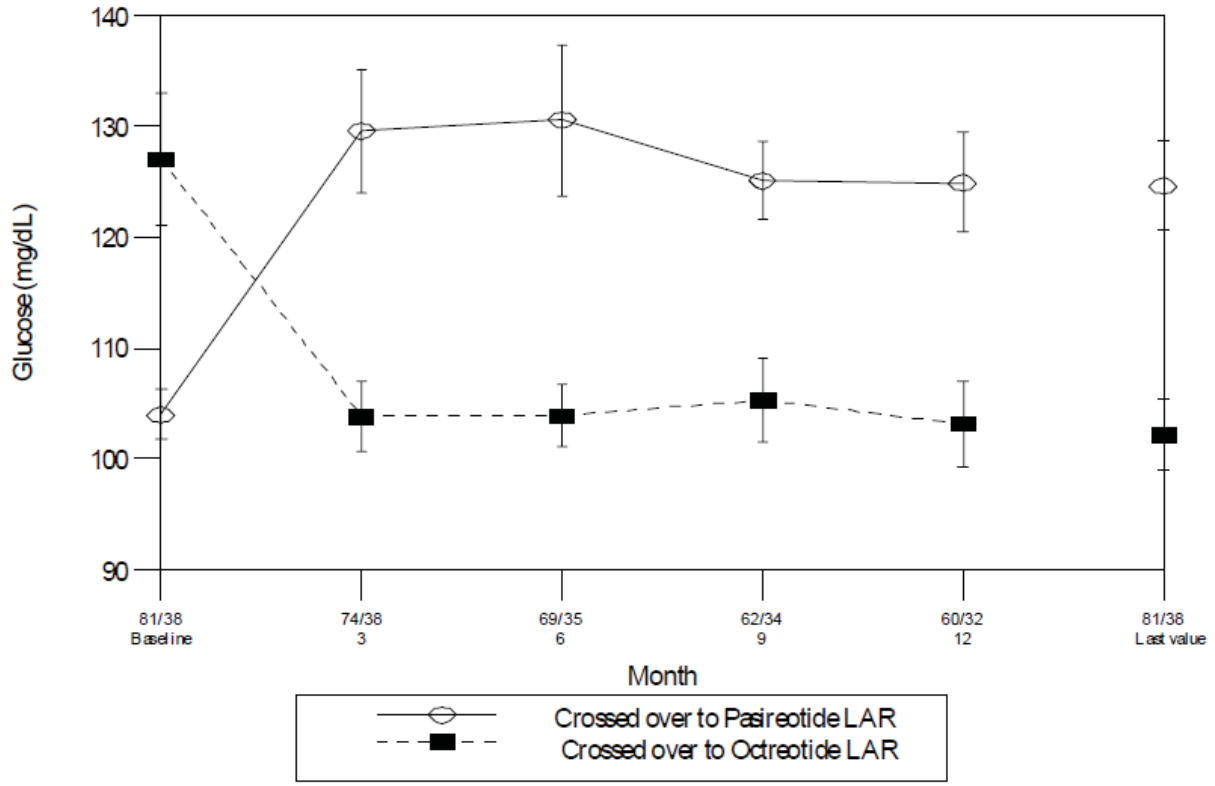
By month 12, combinations of anti-diabetic drugs and biguanide use alone were most the most commonly prescribed drug category in both treatment groups. However, the rates of biguanide use alone and combination drug use in the octreotide LAR groups are nearly equal, whereas in the pasireotide LAR group, greater use of combination drug therapy was needed. Detailed information on the drug combinations used is provided in appendix 2. In summary, in the pasireotide LAR group, with the exception of five patients, all combinations included a biguanide (metformin). Metformin was used in combination with a DPP4 inhibitor (marketed combination or separate prescriptions) in nine patients. Treatment with insulin plus one or more oral anti-diabetic drugs (none were a DPP4 inhibitor) was prescribed in 11 patients. The combination of metformin and sulfonylureas was also prescribed frequently with 13 patients using this therapy at Month 12.

As mentioned at the beginning of this section, it is believed that impaired beta-cell function leading to reduced insulin secretion is the mechanism responsible for hyperglycemia associated with pasireotide. It is possible that anti-diabetic treatment that increases insulin availability is an ideal choice for treatment in patients taking pasireotide. While metformin is not likely to be highly effective in treating pasireotide induced hyperglycemia, it is an appropriate choice in the treatment of the insulin resistance that accompanies acromegaly. What the most effective anti-diabetic treatment is for acromegaly patients treated with pasireotide is yet to be determined.

After crossover phase

Approximately 68% of patients who crossed over to pasireotide LAR experienced a hyperglycemia related AE versus 21.1% of patients who crossed to octreotide LAR. As expected, those that crossed to octreotide entered the extension phase of the study with higher baseline glucose levels than those patients that crossed to pasireotide LAR. In contrast, after three months in the extension phase, patients who crossed to octreotide LAR saw an improvement in FPG values while those that crossed to pasireotide LAR saw deterioration of FPG values, Figure 14.

Figure 14. Fasting plasma glucose by visit and treatment, after crossover, CAS, C2305



The numbers shown between the x-axis tick marks and the numerals for the month represent the numbers of patients in pasireotide/octreotide treatment group with data available.
Source: Figure 12-2, Clinical Study Report C2305

Summary of Glycemic Changes, C2305:

The results for the ITT (SAS) population in the CORE phase accurately reflect the average change in mean FPG and HbA1c when comparing it to the groups by diabetic status. The maximum rise in mean FPG and HbA1c occurred between months 1 and 4 with the most significant rise in values and time to onset, from baseline, seen in the diabetes group followed by pre-diabetes and normal glucose tolerance groups.

In all groups, mean FPG and HbA1c plateaued between months six and 12. Mean FPG levels came down a few points, which might be due to the loss of the patients with the most severe increases in FPG.

Review of the discontinuation data shows that five subjects discontinued (3 AE, and 2 SAE) for reasons related to glucose metabolism in the CORE phase. However, this does not account for missing patient data. In the AE group, one patient had a history of normal glucose tolerance and two had diabetes mellitus at baseline. In the SAE group, one had a history of diabetes mellitus and the other pre-diabetes at baseline.

Comparison of FPG, HbA1c and medication usage results during the CORE phase between the ITT and completer populations show similar results.

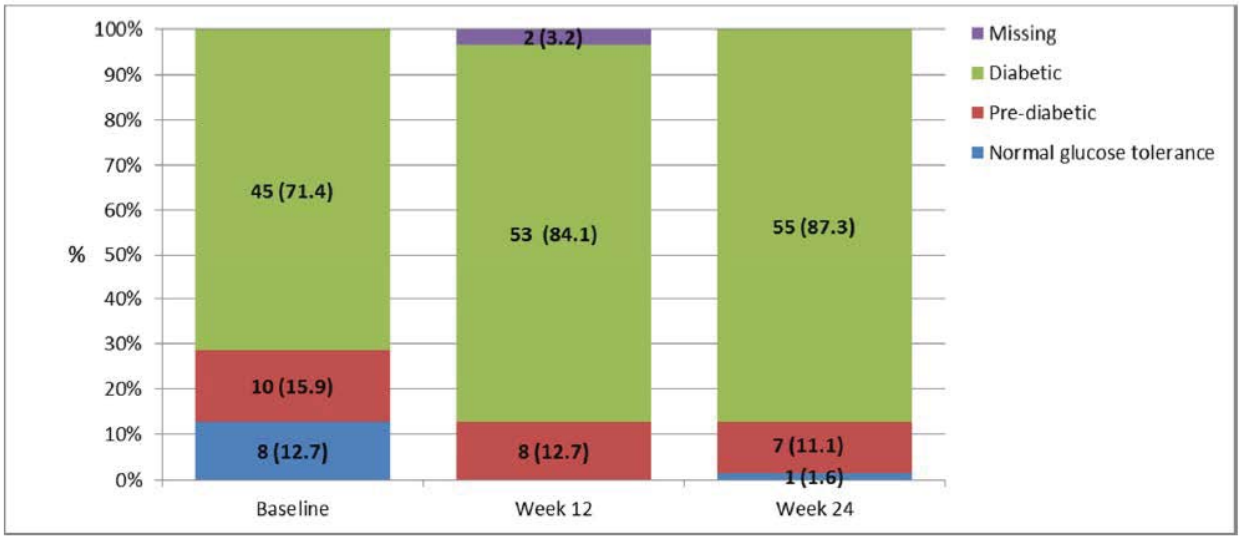
In the ITT pasireotide LAR group, mean FPG and HbA1c values at month 12 remain similar to the values observed in the up to crossover phase. However the number of subjects included in the calculations drops off precipitously to n=64 at month 19 to n=5 in month 43, the last month for which data is available. Further evaluation of the up to crossover phase mean FPG and HbA1c values in subgroups by diabetes category did not reveal new or notable findings.

In the octreotide LAR group ITT population, mean FPG and HbA1c values remained stable throughout the CORE phase of the study in those with normal glucose tolerance, pre-diabetes and diabetes.

Glycemic Control in C2402

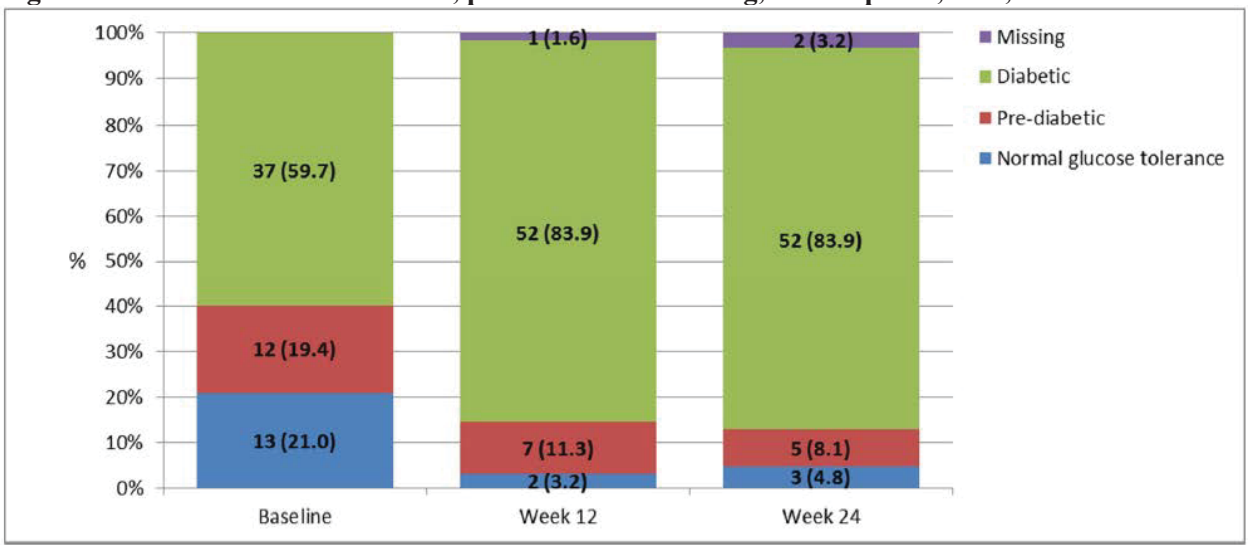
Changes in FPG and HbA1c in the inadequately controlled population of C2402 parallel the changes observed in the medically naïve patient population of C2305 as seen in Figures 9 and 10. However, the baseline rate of diabetes in C2402 is much higher and pre-diabetes is much lower than the respective rates seen in C2305. Also, the figures show that there is a 16% increase in prevalence of diabetes at 24 weeks in the pasireotide LAR 40 mg group versus a 24% increase in the 60 mg group. The possibility of dose dependence is discussed in section 7.5.1.

Figure 15. Diabetic status over time, pasireotide LAR 40 mg, CORE phase, SAS, C2402



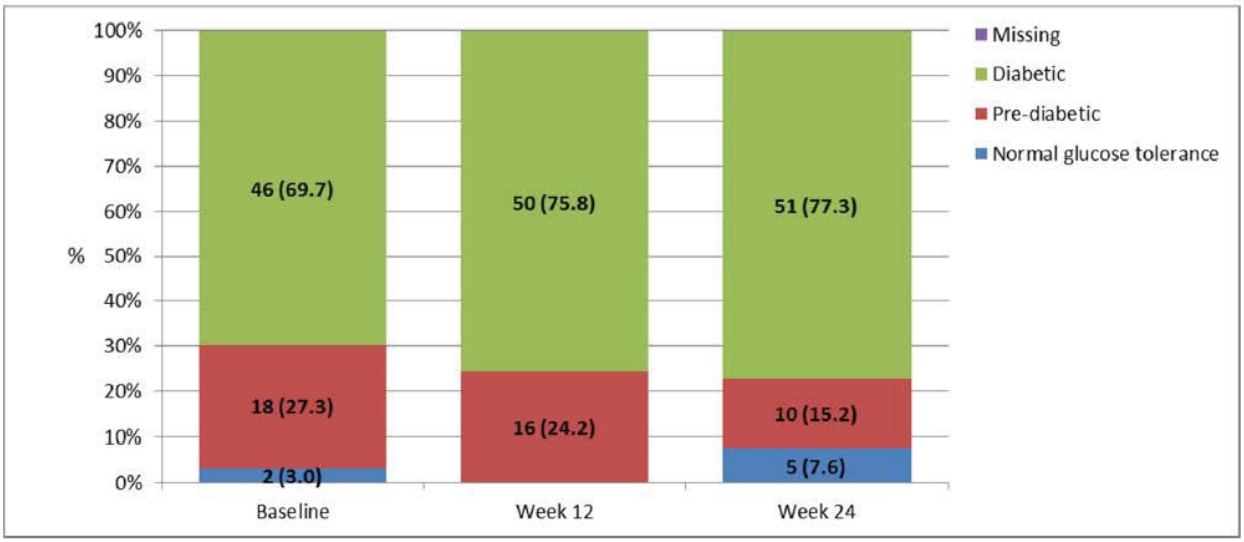
Source: Figure 2-7, Response to information request received by FDA May 9, 2014

Figure 16. Diabetic status over time, pasireotide LAR 60 mg, CORE phase, SAS, C2402



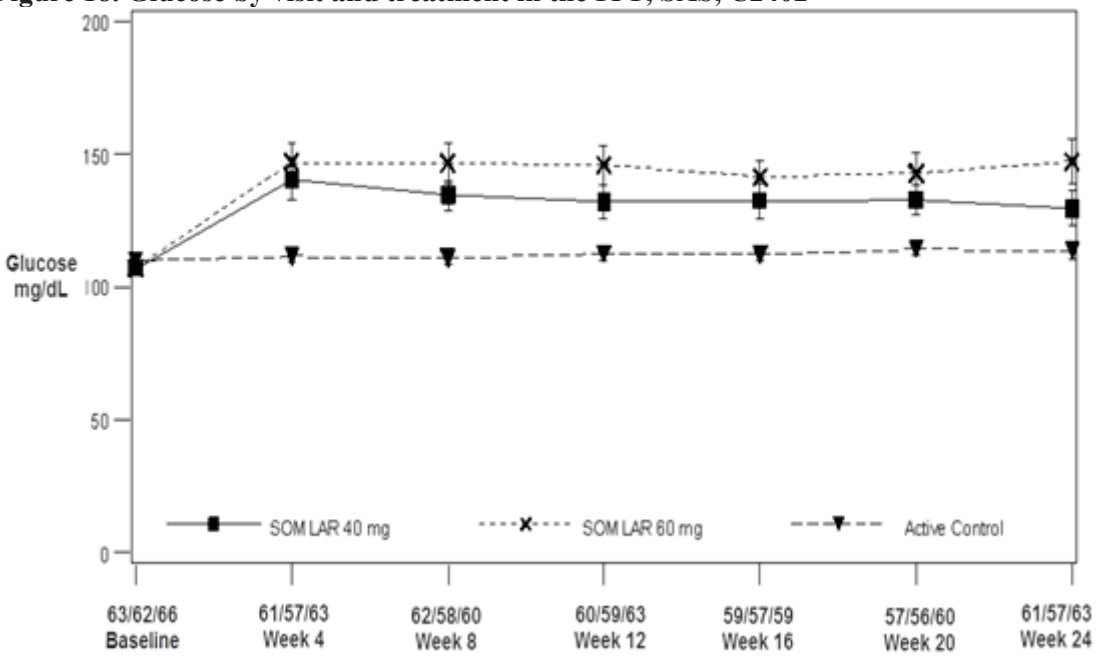
Source: Figure 2-8, Response to clinical information request received by FDA May 9, 2014

Figure 17. Diabetic status over time, active control, CORE phase, SAS, C2402



Source: Figure 2-3, Response to clinical information request received by FDA May 9, 2014

Figure 18. Glucose by visit and treatment in the ITT, SAS, C2402



Source: Figure 12-1, Clinical Study Report C2402

Som LAR =Signifor LAR

Changes in glycemia parameters in the **ITT population in C2402**: (from Tables 14.3-2.36 and 14.3-2.37 in CSR 2402)

Pasireotide LAR 40 mg:

- Mean FPG peak was 140.6 mg/dL representing a **29% increase** from baseline in the occurring by study month 1.
- Mean baseline HbA1c rose from 6.0 ± 0.6% to 6.8 ± 1.7% at Month 6 representing a **12.2 ±20.8%** increase over the study period.

Pasireotide LAR 60 mg:

- Mean FPG peak was 147.1 mg/dL representing a **36% increase** from baseline occurring by study month 1.
- Mean baseline HbA1c rose from 6.0 ± 0.8 to 7.0 ±1.8 at Month 6 representing a 17.5 ± 20.3% increase over the study period.
- Between months 2 and 6, mean FPG values drop slightly and plateau in the 40 mg group, whereas in the 60 mg group, the values remain at the peak level throughout the study.

Active control:

- The rise in mean FPG over the study period was minimal between baseline, 110.1 ± 19.0 mg /dL and Month 6, 113.7 ± 23.0 mg/dL, representing a 3.5 ± 20.7% increase.

- HbA1c remained essentially the same throughout the study period with values of 6.0 ± 0.5% at baseline compared to 6.0 ± 0.6% at Month 6.

Changes in glycemia parameters in the **completer population in C2402**: (from response to FDA clinical FDA information request, received April 11, 2014)

These values are similar to what was seen for the ITT population just described.

Pasireotide LAR 40 mg:

- Mean baseline FPG of 106.8 ± 19.0 rose to a mean peak FPG of 136.7 ± 52.6 mg/dl by month 1 representing a **26.5% increase**. Mean FPG at month 6 was 129.9 ± 50.4 mg/dl (22.5% increase from baseline)
- Mean baseline HbA1c of 6.0 ± 0.6 % rose to 6.7 ± 1.4% by month 3 and 6.8% by month 6 representing a **12 ± 13.9% increase**.

Pasireotide LAR 60 mg:

- Mean baseline FPG of 106.3 ± 18.3 mg/dl rose to a mean peak FPG of 144.7 ± 59.4 mg/dl by month 6, however by month one, mean FPG had risen to 142.8 ± 54.7 mg/dl representing a **34% increase**.
- Mean baseline HbA1c of 6.0 ± 0.8% rose to a mean peak HbA1c of 7.0 ± 1.8% at month 3 and remained at approximately that level at month 6 representing a **17% increase**.

Active control:

- Mean baseline FPG of 110.3 ± 19.1 rose to a mean peak FPG of 114.3 ± 20.6 mg/dl at month 5 representing **a 4.3 ± 20.3% increase**.
- Mean baseline HbA1c of 6.0 ± 0.5% remained approximately the same throughout the study.

Medication usage for glucose control, C2402

Anti-diabetic medication usage in the pasireotide LAR 40 (N=63 total; diabetes N=45, pre-diabetes N=10, normal glucose tolerance N =8) **and** 60 mg (N=62 total; diabetes N=37, pre-diabetes N=12, normal glucose tolerance N=13) groups (data is combined) is presented below.

Table 37. Anti-diabetic medication usage, CORE phase, SAS, C2402

# meds at baseline	Diabetic Status (N)	Baseline N (%)	Started or Increased Usage by Week 24
No Med	Diabetes (82)	46 (56)	19 (23)
	NGT (21)	21 (100)	1 (5)
	Pre-Diab (22)	22 (100)	1 (5)
One Med	Diabetes	17 (21)	11 (13)
	NGT	0	0
	Pre-Diab	0	0

Two Meds	Diabetes NGT Pre-Diab	14 (17) 0 0	8 (10) 0 0
3+ Meds	Diabetes NGT Pre-Diab	5 (6) 0 0	No change 0 0

Source: Response to clinical information request received by FDA April 11, 2014; Table 14.3-2.31, Clinical Study Report C2402

Of 125 patients in the pasireotide LAR 40 and 60 mg groups, 89 (71%) were not using anti-diabetic medications at baseline. By week 24, 40 (32%) had started or increased dosage of anti-diabetic medications.

Table 38. Summary of anti-diabetic medication by visit and treatment, CORE phase, SAS, C2402

	Pasireotide LAR 40 mg N = 63 n (%)		**Pasireotide LAR 60 mg N = 62 n (%)**		**Active Control N = 66 n (%)**	
ATC class	**Baseline**	**Week 24**	**Baseline**	**Week 24**	**Baseline**	**Week 24**
Insulin alone	1 (1.6)	1 (1.6)	2 (3.2)	3 (4.8)	1 (1.5)	0
Biguanides Alone	**8 (12.7)**	**7 (11.1)**	**4 (6.5)**	**7 (11.3)**	**13 (9.7)**	**12 (18.2)**
Sulfonylurea Alone	0	1 (1.6)	1 (1.6)	1 (1.6)	0	0
DPP4 Inhibitor Alone	1 (1.6)	1 (1.6)	1 (1.6)	0	0	0
Combination therapy	**9 (14.3)**	**16 (25.4)**	**9 (14.5)**	**14 (22.6)**	**5 (7.6)**	**4 (6.1)**

Source: Table 2-2, Response to clinical information request received by FDA May 16, 2014

As in C2305, the use of biguanides alone, but, more so combination therapy was most commonly prescribed. The combination of biguanides and DPP4 inhibitors, biguanides and sulfonlyureas and insulin+biguanide+sulfonlyurea were the three top combination therapies used with three patients (4.8%) in each group.

II. Hepatic Safety

The issue of hepatic safety related to pasireotide use arose in 2010 with the identification of elevated liver enzymes and bilirubin in a patient receiving pasireotide for compassionate use. Novartis then conducted an Advisory Board with hepatologists to gain further insight on the hepatic data in the pasireotide clinical development program. A comprehensive review of the program-wide dataset for LFT categorical outliers was completed and reported in an Investigator Notification (IN) released on October 31, 2011 to health authorities worldwide where studies with pasireotide were being conducted. Three healthy volunteers and one patient in a

compassionate use study had concomitant ALT and total bilirubin elevations, which resolved with discontinuation of pasireotide. The data did not suggest a mechanism of drug-induced liver injury; however, warnings were incorporated into the label. Novartis submitted a dedicated "Hepatic Report" with NDA 200,677 (pasireotide; Signifor®) which has been reviewed in detail by Dr. Naomi Lowy.

Novartis recently submitted a hepatic genetic report (B2128). The report describes a genetic testing study investigating individual predisposition to hyperbilirubinemia or drug-induced liver injury (DILI) in healthy volunteers previously dosed with pasireotide s.c. in studies B2124 and B2125. To be eligible for the study the patients had met at least one of the following:

1. Met the biochemical criteria for Hy's law
2. Developed elevations in ALT > 3x upper limit normal (ULN)
3. Developed an SAE of jaundice with an increase in bilirubin of CTC Grade 3

Of 12 eligible patients, 11 participated in the study. Gene analysis of the *1/*28 allele of the UGT1A1 gene (SNP [single nucleotide polymorphism]: rs5719145insTA) was performed in the three individuals who met the biochemical criteria for Hy's Law. Genotyping of known variants in bilirubin and bile acid transporter genes, i.e., SLCO1B1/SLCO1B3, ABCC2 and ABCB11, was performed in all 11 subjects entered into this study.

Results showed that three of the 11 patients might have a genetic predisposition to drug-induced liver elevations of bilirubin and/or ALT.

However, the results do not support implementation of pharmacogenetic testing for patients being prescribed pasireotide.

Hepatic, gallbladder and biliary related events for C2305 and C2402 are described below. There were no cases of Hy's law and the abnormalities seen in liver function did not further raise concern above what was raised in the Signifor® NDA review.

A. Study C2305

The tables below provide a summary of hepatic, gallbladder and biliary events occurring in the CORE phase. Please note that Table 39 represents adverse events while Table 40 represents all abnormal laboratory values, which may or may not have been designated an adverse event.

Table 39. Incidence of patients with hepatic, gallbladder and biliary adverse events occurring in the CORE phase, SAS, C2305 (percentages provided if > 5%)

PT_TXT	Octreotide LAR (N=180)	Pasireotide LAR (N=178)

	n (%)	**n (%)**
ALT increased	8 (4.4)	14 (7.8)
AST increased	7 (3.8)	10 (5.6)
Bile duct stone	0	1
Bile output decreased	1	0
Biliary dilatation	6	2
Bilirubin conjugated increased	0	1
Blood alkaline phosphatase increased	4	3
Blood bilirubin increased	5	7
Blood cholesterol increased	0	3
Cholecystitis	1	1
Cholelithiasis	64 (35.6)	46 (25.8)
Cholesterosis	0	1
Deficiency of bile secretion	0	1
Dilatation intrahepatic duct acquired	3	0
Gallbladder disorder	0	1
Gallbladder enlargement	2	1
Gallbladder polyp	1	3
Hepatic adenoma	0	1
Hepatic cyst	3	2
Hepatic steatosis	7	6
Hepatomegaly	0	2
Hydrocholecystis	1	0
Hyperbilirubinaemia	1	1
Mixed hepatocellular cholangiocarcinoma	0	1
Transaminases increased	2	1

Source: AAEV dataset JMP analysis 2305 using search terms: hepa, bile, bili, gall, chole, alkaline, alanine, aspartate and transaminase, CORE phase.

Table 40. Categorical liver function tests abnormalities, up to crossover, SAS, C2305

Categorical LFT outliers	Pasireotide LAR N=178 n (%)	Octreotide LAR N=180 n (%)
ULN < ALT ≤ 3xULN	43 (24.2)	57 (31.7)
ULN < AST ≤ 3xULN	33 (18.5)	47 (26.1)
ULN < AST and ALT ≤ 3xULN	19 (10.7)	34 (18.9)
ALT > 3xULN	8 (4.5)	6 (3.3)
AST > 3xULN	6 (3.4)	1 (0.6)
ALT and AST > 3xULN	5 (2.8)	1 (0.6)
ALT > 5xULN	1 (0.6)	1 (0.6)
AST > 5xULN	0	1 (0.6)
ALT and AST > 5xULN	0	1 (0.6)
ALT > 10xULN	1 (0.6)	0
AST > 10xULN	0	0
ALT and AST > 10xULN	0	0
TB > ULN and < 2xULN	33 (18.5)	40 (22.2)
TB ≥ 2xULN	4 (2.2)	5 (2.8)

Worst normalized post-baseline value was used to assign patients to different categories.

ULN, upper limit normal
Source: Response to clinical information request received by FDA May 16, 2014

Review of the after crossover and C2402 hepatic, gallbladder and biliary related adverse events did not reveal a different pattern of abnormalities than what is shown in the above table.

In appendix 4 of the summary of clinical safety C2305, Novartis provides narratives of patients with any of the following elevations: blood bilirubin increased (≥ 2xULN), alanine aminotransferase increased (ALT > 5x ULN) and/or aspartate aminotransferase increased (AST > 5x ULN) as these levels of elevation were judged clinically important. These narratives are summarized below.

Pasireotide LAR

In the pasireotide LAR group five patients met the aforementioned criteria; however, these did not meet criteria for Hy's law (aminotransferases > 3x ULN, total bilirubin ≥ 2x ULN, and Alk phos < 2x ULN).

Three of the five patients had elevations in bilirubin without concomitant aminotransferase elevation. These patients all had mild elevations in bilirubin prior to starting pasireotide LAR therapy.

C2305-0176-00006: Maximum increase in bilirubin 2.38x ULN at Day 29; completed core phase; cholelithiasis diagnosed in extension on Day 339 at which time bilirubin was 1.88x ULN. Day 1142, bilirubin was 1.21x ULN.

C2305-0251-00008: Maximum increase in bilirubin 2.45x ULN at Day 194; completed core phase; 70 days after last dose of pasireotide LAR, bilirubin 1.85x ULN.

C2305-0711-00003: Maximum increase in bilirubin 2.5x ULN at Day 169; on same day diagnosed with cholelithiasis and started treatment with ursodeoxycholic acid; completed core phase; 29 and 57 days after the last dose of pasireotide LAR bilirubin levels were 1.1x and 1.6x ULN, respectively.

Hyperbilirubinemia of equal or lesser severity persisted in these three patients upon discontinuation of pasireotide LAR. None of these patients had an SAE as a result of LFT abnormalities nor did they require interruption, dose adjustment or discontinuation of pasireotide LAR.

The fourth of five patients **(C2305-0731-00005)** had a history of hepatic steatosis and cholelithiasis, both diagnosed at Day -32 of the study. Medications included aspirin (Day-3 to Day 1) and allopurinol for hyperuricemia (Day 1-Day 25). The table below describes liver function test results over time.

Pasireotide LAR, liver function tests, C2305-0731-00005

CSOM 2305-0731-00005	Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	Alk Phos (U/L)	GGT (U/L)
Day 1	0.99	24	24	71	16
Day 15	4.76 (2.98x ULN)	81 (1.5x ULN)	68 (1.39x ULN)	84	54
Day 31	6.22 (3.89x ULN)	116 (2.15x ULN)	72 (1.47x ULN)	122	74
Day 51	3.55 (2.22x ULN)	69 (1.28x ULN)	52 (1.06x ULN)	129	60
Day 58	n/a	wnl	wnl		
Day 79	1.37	n/a	n/a	n/a	n/a
Day 115	1.7 (1.06x ULN)	27	24	79	13
Patient discontinued pasireotide LAR after first injection (Day 1) but participated in liver function monitoring until clinical concern was mitigated.					

Source: Appendix 4, Summary clinical safety, page 92
Note: if no parenthetical data presented, value is within normal limits (wnl); n/a, not available

The fifth of five patients **(C2305 0802-00001)** had a history of obstructive cholelithiasis and cholecystectomy in 1999. Concomitant medications of interest include atorvastatin and metformin. Despite experiencing very high ALT elevations, bilirubin levels remained normal.

The hepatic withdrawal criteria had not been implemented yet, thus, this patient remained in the study.

Pasireotide LAR, liver function tests, C2305-0802-00001

C2305-0802-00001	Bilirubin (µmol/L)	ALT (U/L)	AST (U/L)	Alk Phos (U/L)	GGT (U/L)
Day 1	9	18	20	94	26
Day 15	13	405 (13x ULN)	76 (2.45x ULN)	248 (2.07x ULN)	532 (15.2x ULN)
Day 85	12	413 (13.32x ULN)	88 (2.83x ULN)	206 (1.71x ULN)	475 (13.57x ULN)
Day 197	8	**533 (17.19x ULN)**	118 (3.8x ULN)	126 (1.05x ULN)	219 (6.25x ULN)
Day 338	10	155 (5.00x ULN)	26	105	169 (4.8x ULN)
Day 365	10	70 (2.26x ULN)	27	108	184 (5.25x ULN)
Patient completed core phase and did not continue in extension phase; pituitary surgery planned.					

Source: Appendix 4, Summary Clinical Safety, page 108
Note: if no parenthetical data presented, value is within normal limits (wnl); n/a, not available

In the pasireotide LAR group, two patients developed hepatobiliary related SAEs related to cholelithiasis resulting in cholecystectomy (core, n=1; extension, n=1). Neither patient had a dose adjustment, study drug interruption or discontinuation of pasireotide LAR due to these events. Two patients discontinued pasireotide LAR due to hepatobiliary related adverse events. The first, C2305-0731-00005, is described above. The second patient, C2305-0714-00004, discontinued in the extension phase of the trial after 18 injections of pasireotide LAR. Day 1 liver function tests were within normal limits. On Day 506, AST increased to 138 UI/L and IGF-1 decreased to 78µg/L. Pasireotide LAR was discontinued due to both of these events. Fifty-six days after the last dose of pasireotide LAR, AST decreased to 68 UI/L (grade 1).

Octreotide LAR

Six patients met criteria set forth as clinically important by Novartis: blood bilirubin increased (≥ 2xULN), alanine aminotransferase increased (ALT > 5x ULN) and/or aspartate aminotransferase increased (AST > 5x ULN). One patient (C2305-0161-00006) had values suspicious for Hy's law but the bilirubin and alkaline phosphatase values made it unlikely (see below).

Three of the six patients had elevations in total bilirubin without concomitant increases in aminotransferase levels. All three had mild elevations in bilirubin prior to starting octreotide LAR.

C2305-0175-00007: Maximum bilirubin 1.8x ULN at Day 14; cholelithiasis diagnosed at Day 86; treated with ursodeoxycholic acid; bilirubin 1.48x ULN at Day 170; completed the core

phase and participated in extension, no further bilirubin levels reported and cholelithiasis was ongoing at time of last available report. Event occurred in the CORE phase.

C2305-0206-00004: Maximum bilirubin 3x ULN at Day 30; diagnosed with one episode of biliary dilation and one episode of cholelithiasis on Days 256 and 337, respectively. Crossed over to pasireotide LAR and experienced two subsequent episodes of biliary dilation (Days 701 and 1037) and one more episode of cholelithiasis (Day 1121). Bilirubin levels were 1.17, 1.33 and 1.08x ULN, respectively. Cholelithiasis resolved and biliary dilation ongoing at time of last available report. Event occurred in the CORE phase.

C2305-0711-00001: Maximum bilirubin on octreotide LAR 2.4x ULN at Day 14 and again at Days 197 and 253; cholelithiais diagnosed on Day 256. Patient crossed over to pasireotide LAR and maximum bilirubin 2.5x ULN at Day 423. Pasireotide LAR discontinued on day 507 due to unsatisfactory therapeutic effect. Fifty-six days after the last dose of pasireotide LAR, bilirubin 1.3x ULN. Event occurred in the CORE phase.

Hyperbilirubinemia of equal or lesser severity persisted in these three patients upon discontinuation of octreotide LAR. None of these patients had an SAE because of LFT abnormalities nor did they require interruption, dose adjustment or discontinuation of octreotide LAR.

The three remaining patients had bilirubin and aminotransferase elevations as described below.

C2305-0161-00006 was diagnosed with cholelithiasis (grade 1) on Day 254, which resolved by Day 354. Patient completed core phase and continued on octreotide LAR in the extension phase. Cholestasis was diagnosed on Day 367 and resolved by Day 373 on which day a second diagnosis of cholelithiasis was made. By Day 404, patient developed cholecystitis (grade 3) and worsened cholelithiasis (grade 3). Patient underwent laparoscopic cholecystectomy. No action was taken with octreotide LAR, however, upon discharge from the hospital, patient no longer wanted to participate in the study. The last dose of octreotide LAR was received on Day 394. Approximately one month later, patient reported to be recovering well at home. Liver function test abnormalities persisted at time of last available report. Liver function test abnormalities and SAE occurred in the extension phase.

Octreotide LAR, liver function test results, C2305-0161-00006.

C2305-0161-00006	Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	Alk Phos (U/L)	GGT (U/L)
Day 1	0.3	10	16	89	18
Day 254	0.9	11	22	70	18
Day 367	2.34 (1.8x ULN)	380 (7.31x ULN)	229 (6.36x ULN)	586 (4.65x ULN)	410 (9.53x ULN)
Day 394	0.66	154 (2.96x	46	728	524

		ULN)	(1.28x ULN)	(5.77x ULN)	(12.19x ULN)
***SAE of cholelithiasis-two episodes and cholecystitis in extension phase**					

Source: Appendix 4, Summary Clinical Safety pg 35
Note: if no parenthetical data presented, value is within normal limits; uln, upper limit of normal

C2305-0278-00009 developed liver function test abnormalities by Day 28. On Day 169, a diagnosis of cholelithiasis (grade 1) was made. Patient completed the core phase of the study and participated in the extension completing this phase on Day 702. Cholelithiasis was ongoing at the time of the last available report. Liver function test abnormalities occurred in the CORE phase.

Octreotide LAR, liver function test results, CSOM 2305-0278-00009

C2305-0278-00009	Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	Alk Phos (U/L)	GGT (U/L)
Day 1	0.81	28	18	73	27
Day 28	2.13 (1.94x ULN)	52 (1.3x ULN)	31	89	47
Day 58	0.45	28	21	74	68 (1.36x ULN)
Day 113	2.21 (2.01x ULN)	85 (2.12x ULN)	76 (1.9x ULN)	60	62
Day 142	0.53	27	22	53	45
Day 197	1.17 (1.06x ULN)	41 (1.02x ULN)	19	57	62 (1.24x ULN)
Day 253	1.27 (1.15x ULN)	29	25	47	31
Day 422	1.17 (1.06x ULN)	14	18	38	39

Source: Appendix 4, Summary Clinical Safety, pg 74
Note: if no parenthetical data presented, value is within normal limits; uln, upper limit of normal

C2305 0771-00007 had increased ALT at Day 225, which resolved by Day 253 without any adjustment, interruption or discontinuation of octreotide LAR. At the same time of ALT increase the patient's lipase increased slightly to 1.07x ULN. This also resolved by Day 253. Pt. crossed over to pasireotide LAR in the extension and had no further liver function test abnormalities. Liver function test abnormalities occurred in the CORE Phase.

Octreotide LAR, liver function tests, CSOM 2305-0771-00007

C2305-0771-00007	Bilirubin (µmol/L)	ALT (U/L)	AST (U/L)	Alk Phos (U/L)	GGT (U/L)
Day 1	99.3 (4.47x ULN)	13	19	75	16
Day 225	13.8	47 (1.18x ULN)	40 (1.08x ULN)	69	44

Day 253	13.9	13	20	58	25

Source: Appendix 4, Summary Clinical Safety, pg 96
Note: if no parenthetical data presented, value is within normal limits; uln, upper limit of normal

In the octreotide LAR group, four patients had hepatobiliary related SAEs, 1 in the CORE and 3 in the extension phases. **Patient C2305-0161-00006** is described above.

Patient C2305-0512-00004 diagnosed with cholelithiasis (grade not given) at Day 172, which persisted on all future ultrasounds. Patient crossed over to pasireotide LAR in the extension. Fifty-three days after the last dose of pasireotide LAR, the patient developed symptomatic cholelithiasis and underwent laparoscopic cholecystectomy. SAE occurred in the **extension** phase.

Patient C2305-0519-00002 diagnosed with cholelithiasis (grade 1) on Day 87 and treated with ursodeoxycholic acid. Patient decreased dose of octreotide LAR from 30 mg to 20 mg due to hypoglycemia. On Day 424, patient was diagnosed with acute cholecystitis and underwent laparoscopic cholecystectomy. Patient recovered from this event and completed the extension phase of the study. SAE occurred in the **extension** phase.

Patient C2305-0842-00003 diagnosed with cholelithiasis (grade 2) on Day 167. On Day 237, patient underwent cholecystectomy without report of symptoms or cholecystitis to prompt the procedure. Patient recovered from the procedure and continued into the extension phase of the protocol. SAE occurred in the **CORE** phase.

No patients in the octreotide LAR arm were required to discontinue the drug due to hepatobiliary events.

C2402

Four patients in the pasireotide LAR groups in study C2402 met the criteria for clinically significant liver function abnormalities (as defined for C2305 above). Three of these patients had bilirubin elevations (highest of all values 3.76x ULN) without concomitant aminotransferase elevations. Two had a history of Gilbert's syndrome. The fourth patient had a history of asymptomatic cholelithiasis. On study day 84, the fourth patient experienced an AST elevation 3.1x ULN and ALT 5.7x ULN. Pasireotide LAR was temporarily stopped. By study day 110, aminotransferase levels returned to normal, pasireotide LAR was re-started and the patient completed the study without further complication.

In the active control group, three narratives were submitted in the hepatic safety section. All three patients had serum bilirubin elevations, none greater than 2x ULN. No actions were taken with octreotide LAR or lanreotide ATG and all patients completed the study.

Summary Hepatic Safety

The rate and severity of hepatobiliary events is similar in the pasireotide LAR and octreotide LAR groups in the CORE phase of both pivotal trials. Again, one must take into consideration that the C2402 population had been on previous somatostatin analogue therapy. Thus, those with significant adverse effects may have been inadvertently screened out.

Table 41. Summary of hepatic safety in C2305 and C2402, CORE phase

Pivotal Trial	Hy's Law Cases	SAE	Discontinuations
C2305 Pasireotide LAR	0	1 (cholelithiasis/cholecystitis)	1 (liver enzyme elevation)*
Octreotide LAR	0	1** (cholelithiasis)	0
C2402 Pasireotide LAR (40 and 60 mg)	0	0	1 (temporary) (liver enzyme elevation)
Active Control	0	0	0

*discontinuation due to liver enzyme elevation is patient C2305-0731-00005 described on page 101
**SAE of cholelithiasis occurred in patient C2305-0842-00003 described on page 105

III. Hypocortisolism

In the pasireotide LAR group, seven patients experienced eight instances of decreased cortisol/adrenal insufficiency in study C2305. In C2402, one patient experienced this adverse event. In C2305, two patients had a history of adrenal insufficiency prior to enrolling in study C2305. Of the remaining five, four cases occurred in the CORE phase (2.2%) and one in the extension.

There were five cases of decreased cortisol/adrenal insufficiency reported in the octreotide LAR group, one of which is reported as an SAE (C2305-0912-00012) in the after crossover data.

All instances of decreased cortisol/adrenal insufficiency were reported as adverse events of special interest. Narratives were provided for all of the cases and each was reviewed. While plasma ACTH levels and serum cortisol levels were checked throughout the study, there is no mention of how Novartis or the study investigators defined adrenal insufficiency. The use of

ACTH stimulation testing to confirm the diagnosis of adrenal insufficiency was not done, therefore, the diagnosis of adrenal insufficiency in any of the aforementioned patients is questionable. Evaluation of these cases does not imply that there is a direct cause and effect relationship between pasireotide LAR and the development of adrenal insufficiency. However, given that the pasireotide is known to lower ACTH levels, the risk of adrenal insufficiency is ever present and must be adequately labeled. Better designed studies to assess the incidence of adrenal insufficiency in acromegaly patients taking pasireotide LAR are needed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

By SOC, AEs in gastrointestinal disorders were the most frequent in the pasireotide and octreotide groups in all phases of the study. The largest difference between the two drug groups was seen in metabolism and nutrition disorders due to the increased number of glucose metabolism events in the pasireotide group.

Most subjects reported an adverse event. In the CORE phase adverse events of hyperglycemia, diabetes mellitus, blood glucose increased, type 2 diabetes mellitus were more frequent in the pasireotide LAR vs. octreotide LAR group (at least 5% difference). Diarrhea, cholelithiasis, nausea, constipation and headache were more common in the octreotide LAR group. After crossover, preferred terms that were reported with higher frequency (at least 5% difference) were mostly related to glucose metabolism. However, diarrhea, headache, cholelithiasis, muscle spasms, arthralgia and urinary tract infection were more frequent in those subjects who crossed over to pasireotide LAR than those who crossed to octreotide LAR.

Glucose metabolism related events account for the increased number of grade 3 and 4 AEs seen in the pasireotide LAR group across all phases.

A display of the adverse events emerging in the CORE phase is shown below.

Table 42. Frequent adverse events (>5% in pasireotide LAR group), by treatment group in the CORE phase, SAS C2305

	Pasireotide LAR (N=178)	Octreotide LAR (N=180)
Preferred Term	**All grades n (%)**	**All grades n (%)**
Diarrhea	**70 (39.3)**	**81 (45)***
Hyperglycemia	**51 (28.7)***	**15 (8.3)**
Cholelithiasis	**46 (25.8)**	**64 (35.6)***
Diabetes mellitus	**34 (19.1)***	**7 (3.9)**

Headache	**33 (18.5)**	**46 (25.6)***
Abdominal pain	32 (18)	40 (22.2)
Alopecia	32 (18)	35 (19.4)
Nasopharyngitis	28 (15.7)	28 (15.6)
Nausea	**24 (13.5)**	**39 (21.7)***
Blood creatine phosphokinase increased	23 (12.9)	21 (11.7)
Abdominal distension	21 (11.8)	21 (11.7)
Fatigue	17 (9.6)	18 (10)
Arthralgia	17 (9.6)	22 (12.2)
Dizziness	17 (9.6)	19 (10.6)
Vomiting	15 (8.4)	13 (7.2)
Influenza	15 (8.4)	7 (3.9)
Blood glucose increased	**15 (8.4)***	**4 (2.2)**
ALT increased	14 (7.9)	8 (4.4)
Back pain	14 (7.9)	20 (11.1)
Hypertension	14 (7.9)	13 (7.2)
Sinus bradycardia	12 (6.7)	9 (5.0)
Injection site pain	12 (6.7)	8 (4.4)
URI	12 (6.7)	6 (3.3)
Type 2 diabetes mellitus	**12 (6.7)***	**0**
Pain in extremity	12 (6.7)	8 (4.4)
Anemia	10 (5.6)	10 (5.6)
Abdominal pain upper	10 (5.6)	15 (8.3)
AST increased	10 (5.6)	7 (3.9)
HbA1c increased	**10 (5.6)**	**4 (2.2)**
Weight decreased	9 (5.1)	8 (4.4)
Hypoglycemia	9 (5.1)	13 (7.2)
Cough	9 (5.1)	14 (7.8)

Adapted and modified from Table 12-7, page 189, Clinical Study Report CSOM 2305;
Orange highlight indicates glucose related AE; *, indicates >5% difference between study drugs and which one has greater frequency; URI, upper respiratory tract infection, ALT, alanine aminotransferase, AST, aspartate aminotransferase, HbA1c, glycosylated hemoglobin

C2402

Table 43 shows the common adverse events that occurred in C2402. GI disorders are slightly lower in incidence in this study falling behind metabolism and nutrition disorders. Again, this is a selected patient population so whether the lower incidence of GI events is of significance is not known. Otherwise, the pattern of adverse events in C2402 is not significantly different from that of C2305 by visual inspection. There is a high incidence of nervous system disorders, mostly due

to headache, in the pasireotide 40 mg group, however, the etiology of this is not known and significance unclear.

Table 43. Adverse events (≥ 5%) by primary system organ class (SOC) and treatment group, CORE phase, SAS, C2402

SOC	Pasi 40 mg N = 63 Any grade: n (%)	Pasi 60 mg N = 62 Any grade: n (%)	Active Control N = 66 Any grade: n (%)
Metabolism and nutrition disorders	40 (63.5)	39 (62.9)	22 (33.3)
GI disorders	21 (33.3)	17 (27.4)	12 (18.2)
Infections and Infestations	12 (19.0)	15 (24.2)	11 (16.7)
Nervous system disorders	13 (20.6)	6 (9.7)	7 (10.6)
Hepatobiliary disorders	9 (14.3)	9 (14.5)	15 (22.7)
Musculoskeletal and connective tissue disorders	7 (11.1)	9 (14.5)	9 (13.6)
General disorders and administration site conditions	5 (7.9)	8 (12.9)	8 (12.1)
Cardiac disorders	5 (7.9)	3 (4.8)	0
Vascular disorders	5 (7.9)	3 (4.8)	4 (6.1)

Source: Table 12-3, Clinical Study Report C2402

Gallbladder

Approximately one-third of patients had a new or worsened finding on gallbladder ultrasound in the up to crossover data for C2305 in both treatment arms. In C2402, the percentage of patients with a new or worsened finding on gallbladder ultrasound was 14.8%, 15.4% and 19.3% for pasireotide LAR 40 mg, 60 mg and active control.

Urinalysis

Review of the shift data for urinary protein did not reveal any findings of clinical concern at this time.

7.4.2 Laboratory Findings

Hematological Parameters:

C2305

Review of the newly occurring or worsening CTC hematological abnormalities in **up to crossover data** of C2305 shows worsening hemoglobin in 50.7% (worst value Grade 2) versus 42.0% (worst value Grade 3) of patients in the pasireotide LAR and octreotide LAR groups, respectively (Table 12-25, Clinical Study Report C2305). A Grade 1 abnormality implies that the hemoglobin value is less than the lower limit of normal but > 10.0 mg/dL. A Grade 2 abnormality puts the hemoglobin between 8-10 mg/dL. In both study drug groups, the majority of patients had a baseline value of Grade 0, which progressed to Grade 1. There were no grade 3 or 4 abnormalities in the pasireotide LAR group compared to two grade 3 abnormalities in the octreotide LAR group.

The rates of anemia were 5.6% in both pasireotide LAR and octreotide LAR groups in the **CORE** phase as seen in Table 42 above. These rates seem lower than what is mentioned in the paragraph above; however, the rates of anemia are in the CORE and not up to crossover phase, which is what the hemoglobin shift data represent. Also, all shifts in hemoglobin might not have translated to an adverse event of anemia.

The percentage of hemoglobin values below the lower limit of normal increased from baseline to Month 12, 20.8% versus 29.2%. However, mean (SD) hemoglobin values did not show significant change from baseline to Month 12. The overall significance of these changes in hemoglobin is not clear at this time. Of note, Novartis reported that they did not have a specific definition for anemia and left the definition to the discretion of the investigators. Novartis states that the lower hemoglobin values might be related to higher IGF-1 suppression and binding of pasireotide to receptors in precursor cells.

Differences in other hematological parameters between pasireotide LAR and octreotide LAR were < 3% except in absolute neutrophils grade 0 -> grade 2 (4.8%) and WBC grade 0 -> grade 1 (4.7%). Review of the mean values, percent above and below the limits of normal

for these two parameters and corresponding AE data during the CORE phase does not reveal a significant safety signal.

Prothrombin time values were reported as prothrombin time international normalized ratio (PT-INR) in Clinical Study Report 2305 as this parameter is CTCAEv3.0 gradable. Fifty-five patients had PT-INR available for analysis. The remaining patients had either prothrombin time (PT; n=100) or prothrombin time index (PT index; n=15). Nine patients did not have any of these parameters reported at baseline. Review of Table 12-25 (Appendix 3) provided in the Clinical Study Report as well as Novartis' response to an information request (response to FDA clinical information request received16-May-2014) regarding shifts to extreme values for PT and PT-index did not show clinically relevant differences between pasireotide LAR and octreotide LAR.

C2402

Review of the C2402 hematology shift tables also shows low hemoglobin as the most frequently occurring abnormality both at baseline and post-baseline in all three treatment groups (23.8%, pasireotide LAR 40 mg, 22.6 %, pasireotide LAR 60 mg, 33.3% active control. All were grade 1 or 2 abnormalities and the corresponding rates of anemia were 6.3%, 3.2%, and 3.0%. No other concerning hematologic pattern was recognized.

Biochemistry

C2305 and C2402

Generally, review of the biochemical data did not reveal strong safety signals for abnormalities due to pasireotide LAR. However, we inquired about abnormalities in creatinine, calcium and sodium where a significant difference between pasireotide LAR and octreotide LAR, favoring octreotide LAR, was noted, Table 44. An inquiry was also made regarding an extreme elevation in lipase.

Table 44. Newly occurring or worsening CTC biochemistry abnormalities by treatment for electrolytes of concern, up to crossover, SAS, C2305

Test	Worsening From Baseline to	Pasireotide LAR N=178			Octreotide LAR N=180		
		Total	n	%	Total	n	%
Creatinine	Grade 1	175	14	**8.0**	180	8	**4.4**
	Grade 2	177	0	0	180	1	0.6
	Grade 3	178	0	0	180	0	0
	Grade 4	178	0	0	180	0	0
Calcium (hyper)	Grade 1	171	24	**14**	173	14	**8.1**
	Grade 2	176	0	0	178	1	0.6
	Grade 3	176	0	0	178	0	0
	Grade 4	176	0	0	178	0	0
Sodium (hypo)	Grade 1	176	25	**14.2**	178	12	**6.7**
	Grade 2	-	-	-	-	-	-
	Grade 3	177	2	1.1	179	2	1.1

	Grade 4	177	1	0.6	179	0	0

There is no CTC grade 2 for hyponatremia, therefore these cells are blank
Source: Tables 12-26 and 12-27, Clinical Study Report C2305

For each of the lab values in question the mean (SD), % of upper limit normal (ULN) and lower limit normal (LLN), and range of values for each month in the CORE phase of C2305 and at weeks 12 and 24 for C2402 were reviewed (response to information request received May 30, 2014).

Creatinine: In C2305, a slightly higher number of patients (n = 3 to 6 versus n = 0 to 1) with values above the ULN from baseline to month 12 in the pasireotide LAR vs octreotide LAR group was observed. However, mean creatinine levels appear stable over time without increases in the maximum creatinine values. The adverse event profile reviewed above also does not show recurring instances of renal insufficiency or kidney disorders. Review of creatinine results in C2402 does not show a signal for worsening creatinine over time.

Hypercalcemia and Hyponatremia: Three patients had an AE of hypercalcemia with values of 10.9, 10.3, and 10.5 mg/dL (upper limit normal 10.2 mg/dL) in the pasireotide LAR group of C2305. There were no hypercalcemia related AEs reported in the octreotide LAR group.

The main difference seen in hyponatremia between the two study drug groups arose during Month 3 of the CORE phase when six patients (3.6%) versus one patient (0.6%) had sodium values below the lower limit of normal. The sodium level at Month 3 in the pasireotide LAR group ranged from 133-135 mmol/L and was 129 mmol/L in the octreotide LAR patient. Overall, in C2305 and C2402, calcium and sodium values did not worsen over time nor was there a significant difference in the percent above or below the limits of normal between pasireotide LAR and octreotide LAR over time.

Lipase: Patient C2305-0506-00006 experienced a Grade 3 elevation in lipase correlating to a value of 1320 U/L, normal range: 50-360 U/L). The patient had no history of pancreatitis, hypertriglyceridemia, gallbladder disease, or alcohol abuse. At no point in the study was the patient prescribed a dose reduction or recommended to discontinue the study.

The patient did not have symptoms associated with this increase in lipase. Amylase levels were not concomitantly elevated; however, the patient's high triglyceride levels may have masked elevations in amylase. At baseline, an ultrasound of the gallbladder did not show evidence of gallstones or sludge, however, by Visit 10, ultrasound of the gallbladder showed sludge. As seen in the table below, it is also at Visit 10 when the lipase reached peak level. The patient's AST and ALT were mildly elevated at baseline, but, they along with the GGT level increased and remained elevated throughout the study. The patient's triglycerides and fasting glucose rose significantly as well.

Visit name	Date of sample	Alkaline phosphatase (serum) U/L (25 – 150)*	Bilirubin (total) µmol/L (1.7-20.5)*	GGT U/L (0–65)*	Lipase (Blood) U/L (50–360)*	Alpha amylase (Serum) U/L (28–100)*	AST U/L (0–50)*	ALT U/L (0–55)*	Triglycerides mmol/L (0-1.69)*	Fasting glucose mg/dL (60-99)*
SCREENING	06NOV2008	53	8.6	56	330	68.0	28	46	1.69	103 H G1
BASELINE	20NOV2008	61	5.1	56	336	59.0	71 H G1	93 H G1	3.07 H G1	119 H G1
VISIT 3	05DEC2008	65	18.8	82 H G1	224	58.0	39	54	4.15 H G1	135 H G1
VISIT 4	18DEC2008	64	10.3	74 H G1	233	52.0	87 H G1	119 H G1	3.30 H G1	170 H G2
VISIT 5	15JAN2009	77	6.8	221 H G2	631 H G2	83.0	43	95 H G1	3.08 H G1	176 H G2
VISIT 7	12FEB2009	78	10.3	845 H G3	327	133.0 H G1	96 H G1	123 H G1	15.15 H G3	319 H G3
VISIT 8	12MAR2009	83	6.8	297 H G2	458 H G1	54.0	20	14	6.45 H G2	362 H G3
VISIT 9	09APR2009	84	8.6	161 H G1	281	37.0	104 H G1	111 H G1	3.64 H G1	345 H G3
VISIT 10	07MAY2009	118	17.1	672 H G3	1320 H G3	108.0 H G1	179 H G2	168 H G2	1.74 H G1	295 H G3
VISIT 11	08JUN2009	79	12.0	380 H G3	456 H G1	54.0	132 H G2	147 H G2	5.68 H G2	281 H G3
VISIT 12	06JUL2009	122	20.5	761 H G3	391 H G1	54.0	247 H G2	230 H G2	2.51 H G1	266 H G3
VISIT 13	05AUG2009	124	22.2 H G1	907 H G3	211	54.0	147 H G2	138 H G2	3.09 H G1	255 H G3
VISIT 14	27AUG2009	112	13.7	1165 H G3	565 H G2	58.0	199 H G2	158 H G2	5.42 H G2	321 H G3
VISIT 15	24SEP2009	80	13.7	579 H G3	304	68.0	94 H G1	97 H G1	3.08 H G1	271 H G3
END OF TREATMENT -C	22OCT2009	154 H G1	17.1	1117 H G3	340	43.0	168 H G2	138 H G2	4.03 H G1	348 H G3

* Normal range
L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Gx denotes a value meeting corresponding toxicity grading criteria

Laboratory values post treatment were not provided. Lipase increases were reported in 7 (3.9%) of pasireotide LAR patients and 10 (5.6%) of octreotide LAR patients. There was only one other patient who had persistently waxing and waning lipase values (Grade 1-3) during the CORE phase, which appeared to be related to new onset of gallbladder and stones and sludge. This patient did not have concomitant transaminase or GGT elevation, but did have a report of grade 1 pancreatic disorder.

It is likely that the lipase abnormalities described above are related to cholelithiasis.

According to the withdrawal criteria for C2305, the patient should have been discontinued from the study. When asked about this (information request received August 4, 2014), Novartis responded that some diabetes care was at the discretion of the investigator. In this case, the investigator specifically recommended that the patient remain in the study. In addition, Novartis conducted a review of cases in C2305 and C2402) where patients had persistently elevated FPG or HbA1c with and without anti-diabetic treatment: They did not find cases where subject disposition did not change (i.e. withdrew consent, discontinued due to AE, etc).

7.4.3 Vital Signs

There were no significant differences in the rates of high and low blood systolic or diastolic blood pressure between pasireotide LAR and octreotide LAR in the CORE phase of C2305 or C2402. The most common abnormality in vital signs was decreased weight followed by low pulse rate.

Body weight decrease of > or = 10% (as defined by Novartis) occurred the most frequently in the pasireotide LAR group at a rate of 22.5% vs. 8.9% in the octreotide LAR group in the up to crossover dataset. This might be expected as the rates of partial and full response to

pasireotide LAR were greater than octreotide LAR. As part of the improvement in symptoms, one could hypothesize that reduction in soft tissue swelling and water weight could contribute to weight loss.

The definition of low pulse rate and/or bradycardia in relationship to what is reported as an adverse event is not straightforward. Low pulse rate is defined as < 50 bpm and a decrease > or = 15 bpm in Table 14.3-3.1.1 entitled "Notably abnormal vital signs by treatment – up to crossover". This table represents abnormal vital signs detected during the physical exam per Novartis. However, not all of the notably abnormal vital signs in Table 14.3-3.1.1 are necessarily reported as adverse events. Thirty (16.9%) patients on pasireotide LAR experienced a low pulse rate meeting the aforementioned criteria. However, only 10/30 had an adverse event classified as bradycardia related event.

The rates of bradycardia related events in the CORE phase were similar in the pasireotide LAR versus octreotide LAR groups (Table 45).

Table 45. Bradycardia related AEs in the CORE phase, SAS, C2305

Bradycardia related adverse events	Pasireotide LAR N=178 n (%)	Octreotide LAR N=180 n (%)
Total	27 (15.2)	24 (13.3)
Sinus bradycardia	12 (6.7)	9 (5.0)
Bradycardia	5 (2.8)	3 (1.7)
ECG QT prolonged	8 (4.5)	9 (5.0)
AV block first degree	4 (2.2)	2 (1.1)
Conduction disorder	1 (0.6)	1 (0.6)

Source: Table 14.3.1-5.1.3, Clinical Study Report C2305

The majority of events were of CTC Grades 1 or 2. One patient in the octreotide LAR group experienced a grade 3 ECG QT prolonged adverse event.

Bradycardia as an ECG finding (not an AE) occurred in 35% of pasireotide LAR and 38% of octreotide LAR patients.

There were no serious adverse events related to bradycardia or QT prolongation in the pasireotide LAR group. There were six cases of syncope recorded in the up to crossover data classified as "QT related events". Novartis reports three of these to be drug related although narratives are not provided. There were no reported discontinuations because of bradycardia related events or vital sign abnormalities in the pasireotide LAR group.

In C2402, there were no significant differences in vital sign abnormalities or other related abnormalities of mention.

Per discussion with the QT-IRT team, the bradycardia effect is approximately 8 bpm at the 40 mg dose for pasireotide LAR and similar for octreotide LAR. Bradycardia should be in the label but does not require any monitoring at this time.

7.4.4 Electrocardiograms (ECGs)

Please refer to the detailed review by the Interdisciplinary Review Team for QT studies consultation.

Two TQT studies, B2113 and B2125, were performed on the s.c. formulation and were reviewed by QT-IRT. A significant QTc prolongation effect of pasireotide was detected with a maximum mean (2-sided 90% CI upper bounds) ΔΔQTcI of 12.7 (14.7) ms and 16.6 (18.6) ms for s.c. doses of 0.6 mg and 1.95 (supra-therapeutic) mg bid, respectively. However, as there is a lag time between the peak pasireotide concentration and the peak in QT effect, pasireotide may not have a direct interaction with cardiac ion channels. In addition, the QT-IRT evaluation suggests that pasireotide-associated QT prolongation may not be associated with increased arrhythmogenic potential.

The QT-IRT determined that no new cardiac signals emerged in the studies in patients with acromegaly.

7.4.5 Special Safety Studies/Clinical Trials

No new special safety studies/clinical trials were submitted with this NDA. Please refer to the clinical review for NDA 200, 677 (Signifor®) in which Dr. Naomi Lowy reviewed in detail special safety studies/clinical trials related to pasireotide.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The proposed dosage administration is 40 mg IM every 28 days with titration up to 60 mg or down to 20 mg based on biochemical response and tolerability. C2305 was not designed to compare safety issues between the doses. However, Novartis did analyze patient groups according to average dose received over the CORE phase. Evaluation of occurrence of AEs of special interest by dose category of pasireotide LAR was inconclusive for the first six months of the trial as the majority of patients were on their randomized dose. In the 6-12

month period, the average dose of pasireotide was < 30 mg for four patients, 30-50 mg for 72 patients, and >50 mg for 81 patients. Comparisons between the 30-50 mg and >50 mg dose groups revealed comparable incidence rates of AEs of special interest. However, the incidence of hyperglycemia related AEs was higher in the > 50 mg (22%) vs. 30-50 mg (14%) group, respectively. Likewise, the severity of the AE was more severe in the higher average dose group (7% grade 3/4 AEs vs. 1%) than in the 30-50 mg dose group. In contrast, gallbladder and biliary related AEs were more frequent in the 30-50 mg group (24%) vs. the 50 mg group (14%).

For those on octreotide LAR, occurrence and severity of AEs of special interest was comparable in most categories including hyperglycemia (17% in 15-25 mg group vs. 20% in > 25 mg group). Gallbladder and biliary related AEs were slightly more frequent in the higher vs. lower dose group (28% vs. 24%).

In C2402, pasireotide LAR 40 mg and 60 mg were evaluated separately. With the exception of down titration in case of tolerability issues, during the CORE phase upward dose titration was not prescribed. The C2402 population included patients with inadequately controlled acromegaly after several months of treatment with approved somatostatin analogues. Therefore, patients with significant adverse events due to class effect may have been inadvertently screened out of this study and resulted in a limited adverse event profile. This noted, with the exception of hyperglycemia, comparison of the percentage and types of serious adverse events, adverse events of special interest and common adverse events did not reveal a pattern suggesting an increased number of events in the pasireotide LAR 60 mg versus 40 mg group.

Novartis reports that the odds of being in a higher ADA category (most extreme or last category post baseline) increased with increasing pasireotide LAR C_{trough} concentrations. A repeated measures generalized linear model suggested a 36% increase in the odds of hyperglycemia for a 1.5-fold increase in pasireotide LAR trough concentration (corresponding to a dose increase from 40 to 60 mg), adjusted for mean of log-transformed baseline fasting glucose. This finding is confirmed by the FDA clinical pharmacology team. Please see their report for further details.

7.5.2 Time Dependency for Adverse Events

Table 46 shows the frequency of AEs of special interest by time exposed to study drug. Hyperglycemia related AEs occurred with higher frequency in the pasireotide LAR group and the incidence was highest in the first 3 months of being on drug. In contrast, the incidence of gallbladder and biliary related AEs increased with time exposed to octreotide LAR whereas for patients on pasireotide LAR the incidence over time was relatively stable. The increased frequency of AEs seen in the > 12 month interval is likely due to the study design allowing more patients to receive pasireotide LAR after 12 months. The incidence of

diarrhea and nausea related AEs (not shown) was highest in the first three months with a steady decline over time for both drugs. The incidence of other AEs of special interest was generally low and relatively constant over time.

Table 46. Frequency of AEs of special interest (%) by time interval up to crossover, SAS, C2305

	0-3 mos Pasi Octreo	>3-6 mos Pasi Octreo	>6 -12 mos Pasi Octreo	> 12 mos Pasi Octreo
Overall	75 64	47 48	55 53	51 32
Hyperglycemia related AEs	48 13	20 8	19 11	24 10
Gallbladder and biliary related AEs	17 13	15 20	17 24	22 12

Pasi, pasireotide LAR; Octreo, octreotide LAR
Source: Text, page 210-211, CSOM 2305 Clinical Study Report

7.5.3 Drug-Demographic Interactions

Demographics for the patient populations in C2305 and C2402 are presented in section 6.1.2 of this review. Comparison of AEs by gender and race are shown in Tables 46 and 47. Only results for C2305 are shown as C2402 represents a selected population. In a population mixed-effect model, gender was found to be a significant covariate for steady state concentrations of pasireotide LAR. Females have approximately 30% higher pasireotide concentrations than males after adjusting for bodyweight and GGT level. It is not known if this translates into a higher safety risk. The 30% difference in concentrations lies within inter- and intra-patient PK variability. There are some notable differences; however, the trial was not powered to identify signals by demographic data. Thus, these results are purely observational.

Table 47. Adverse events by treatment and gender, AEs with difference ≥ 10% shown, SAS, C2305

	Pasireotide LAR		Octreotide LAR	
Primary SOC	**All grades N (%)**		**All grades N (%)**	
	Male (N=86)	Female (N=92)	Male (N=86)	Female (N=94)
Infections and infestations	31 (36.0)	46 (50.0)	34 (39.5)	44 (46.8)
Metabolism and nutrition disorders	43 (50.0)	61 (66.3)	22 (25.6)	31 (33.0)
Skin and subcutaneous tissue disorders	22 (25.6)	30 (32.6)	19 (22.1)	31 (33.0)

Source: Response to clinical information request received by FDA Aug 4, 2014

With regards to race, notable differences are that Asians had a slightly higher incidence of AEs compared with Causasians (97.4 vs. 92.5%). The largest difference (Caucasian vs. Asian) was seen for general disorders and administration site conditions (22.4% vs. 38.5%), nervous system disorders (26.2% vs. 53.8%) and skin and subcutaneous disorders (23.4% vs. 43.6%).

Novartis performed a logistic regression analysis to identify risk factors associated with increased risk for developing hyperglycemia. Baseline age and HbA1c as well as history of diabetes and/or hypertension were associated with increased risk, Table 48.

Table 48. Logistic regression analysis of possible risk factors for developing hyperglycemia, CORE phase, C2305

Baseline age (years)			
per unit increase	1.02	(1.01 , 1.04)	0.012
Baseline age (years)			
≥ 65 vs <65	0.89	(0.36 , 2.24)	0.810
BMI (kg/m^2)			
25-<30 vs <25	1.91	(0.99 , 3.69)	0.053
≥ 30 vs <25	2.16	(1.09 , 4.27)	0.027
≥ 30 vs 25-<30	1.13	(0.69 , 1.85)	0.626
Years with disease			
per unit increase	0.99	(0.93 , 1.06)	0.844
Baseline FBG (mg/dL)			
per unit increase	1.00	(0.99 , 1.01)	0.722
Baseline FBG (mg/dL)			
100-<126 vs <100	1.15	(0.70 , 1.87)	0.586
≥ 126 vs <100	1.32	(0.55 , 3.16)	0.535
≥ 126 vs <100-<126	1.15	(0.46 , 2.88)	0.766
Baseline HbA1c (%)			
per unit increase	1.99	(1.31 , 3.02)	0.001
Baseline HbA1c (%)			
≥ 5.7-<6.5% vs <5.7%	2.19	(1.30 , 3.68)	0.003
≥ 6.5%-<8% vs <5.7%	2.75	(1.23 , 6.12)	0.013
≥ 8% vs <5.7%	4.52	(0.24 , 84.95)	0.314
≥ 6.5%-<8% vs >=5.7-<6.5%	1.25	(0.62 , 2.55)	0.531
≥ 8% vs >=5.7-<6.5%	2.06	(0.11 , 37.53)	0.625
≥ 8% vs >=6.5%-<8%	1.64	(0.09 , 30.26)	0.738
History of diabetes mellitus			
Yes vs No	3.24	(1.90 , 5.53)	<0.0005
History of hypertension			
Yes vs No	2.89	(1.81 , 4.62)	<0.0005
History of dyslipidemia	1.18	(0.71 , 1.94)	0.523
Mean baseline GH			
per unit increase	1.00	(0.99 , 1.01)	0.609
Baseline IGF-1 (Acromegaly)			

per unit increase	1.00	(1.00 , 1.00)	0.628

Source: Novartis response to FDA information request received April 1, 2014

7.5.4 Drug-Disease Interactions

Pasireotide has been studied in Cushing's disease (NDA 200,677) and metastatic carcinoid. Safety data for comparison are not available for metastatic carcinoid. The most common (>15% of subjects) adverse events NDA 200,677 identified with pasireotide s.c. (Signifor®) use were diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus. The most commonly reported adverse events for pasireotide LAR in C2305 and C2402 as seen in Tables 42 and 43 of this review are similar. Many of the common adverse events reported for both Signifor® and pasireotide LAR are inherent to the underlying disease processes being studied making it difficult draw conclusions about AEs without placebo controlled data.

7.5.5 Drug-Drug Interactions

For an in-depth review of this information, please refer to the clinical pharmacology section of this NDA review. Because pasireotide is the same active entity in both the s.c. and LAR formulations, it was agreed at pre-submission meetings with the FDA to bridge drug-drug interaction studies. Overall, there is no significant drug-drug interaction potential to or from pasireotide LAR. However, prescribers should be aware of the following as noted in the Signifor® label:

- Co-administration of drugs that prolong the QT interval with pasireotide LAR may have additive effects on the prolongation of the QT interval.
- Cyclosporine given in conjunction with pasireotide LAR may decrease the relative bioavailability of cyclosporine, therefore, dose adjustment may be necessary.
- Co-administration of somatostatin analogues with bromocriptine may increase the blood levels of bromocriptine, therefore, dose reduction may be necessary.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The non-clinical program did not identify evidence of carcinogenicity due to pasireotide LAR. For further details, please refer to Dr. Miyun Tsai-Turton's (nonclinical reviewer) review.

Studies C2305 and C2402 were not of sufficient duration to assess for long-term carcinogenicity. No unusual neoplasms were reported during the clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

Hypogonadism is a frequent consequence of acromegaly.[5] While the data on pregnancy outcomes in acromegaly is limited, there are reports of increased rates of spontaneous abortion in this population believed to be intrinsic to the disease process.

No pregnancies were reported in the CORE phases of C2305 or C2402. Three pregnancies were reported in the **120 day clinical safety update for C2402** in subjects taking pasireotide LAR:

- C2402-0220-00006, Pasireotide LAR: Received first dose of study medication on July 10, 2012. Last menstrual period was December 22, 2012. No specific pregnancy tests reported. Started open label extension on unspecified date. Last dose of study medication was January 24, 2013. On February 25, 2013, subject experienced a spontaneous abortion.

- C2402-0440-00008, Pasireotide LAR: Completed CORE phase of the study and entered the extension. Patient received last dose of pasireotide LAR 60 mg on July 22, 2013. Last menstrual period was June 24, 2013. Pregnancy was confirmed on August 22, 2013. Pregnancy outcome is unknown.

- C2402-0601-00001, Pasireotide LAR: Received first dose of study medication on September 26, 2011, completed the CORE phase and entered the extension (unspecified date). Last menstrual period on March 31, 2013. On May 14, prenatal ultrasound showed 5 week pregnancy. Planned abortion of May 23, 2013. Action taken with pasireotide LAR not reported.

Reproductive studies were all conducted under the Signifor® NDA (200,677). Most adverse effects seen in the fetus were associated with maternal toxicity. The nonclinical program did not identify teratogenic effects of pasireotide LAR at non-exaggerated doses.

[5] Unuane D et al. Endocrine disorders & female infertility. Best Pract Res Clin Endocrinol Metab, 2011

7.6.3 Pediatrics and Assessment of Effects on Growth

Pasireotide LAR is an orphan drug. The applicant was exempted from pediatric assessment and has provided the appropriate documentation.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no specific reports of overdose or abuse with pasireotide LAR nor is there expected abuse potential for this drug. No signs of dependency have been observed in clinical trials.

7.7 Additional Submissions / Safety Issues

Novartis submitted a 120 day clinical safety update, which provides additional safety data up to June 3, 2013.

- C2305: Original submission provides data for 12 month CORE phase and extension phase in which all patients completed 26 months of treatment or had withdrawn from the study (cut-off date December 29, 2011).
- C2402: Original submission provides data for six month CORE phase in which all patients completed the CORE phase or had withdrawn from the study (cut-off date was patient specific; last patient completed CORE phase January 2013).

Novartis ARGUS (i.e. Novartis safety database) listings up to February 2014 are also provided for C2305 and C2402 as well as B2201, B2201E and C2110. Any notable updates for C2305 and C2402 are incorporated into the discussion below.

In the phase 1 trials, B2201, B2201E and C2110, there were no deaths reported. There was one notable SAE in B2201E of a female patient diagnosed with mucoepidermoid carcinoma of low grade malignancy in the palate.

Table 49. Patient disposition, C2305

	Pasireotide LAR (N=176) N(%) Up to Crossover		Pasireotide LAR (N=176) N(%) After Crossover	
Disposition	Original NDA	Safety Update	Original NDA	Safety Update
Extension + continued Pasi treatment past Month 26	51 (100)	51 (100)	50 (100)	50 (100)
Ongoing at cut-off date	45 (88.2)	38 (74.5)	39 (78.0)	30 (60.0)

Discontinued after Month 26:	6 (11.8)	13 (74.5)	11 (22.0)	20 (40.0)
-withdrew consent	5 (9.8)	5 (9.8)	4 (8.0)	8 (16.0)
-no longer required study drug	0	4 (7.8)	-	-
-administrative problem	1 (2.0)	3 (5.9)	1 (2.0)	1 (2.0)
-abnormal lab value	0	1 (2.0)	1 (2.0)	2 (4.0)
-adverse event	-	-	2 (4.0)	4 (8.0)
-death	-	-	1 (2.0)	1 (2.0)
-unsatisfactory therapeutic effect	-	-	2 (4.0)	4 (8.0)

Source: 120 day clinical safety update Tables 1-9, 1-10.

C2305 clinical safety update summary:
In C2305, mean exposure to pasireotide LAR increased by approximately four months in the up to crossover group. In the after crossover group mean exposure to pasireotide LAR increased by approximately seven months (212 days). Median and mean exposure were similar.
There were no deaths during the extension study. The percentage of subjects with an SAE or AE was similar to the data presented in the initial application. Compared to the incidence of adverse events in the CORE phase presented in section 7.4.1, the majority of adverse events increased in incidence by < 3%. Adverse events that had rate increases, between the CORE phase and safety update, of 4-5% were:

Table 50. Rate increases in adverse events, C2305

	Pasireotide LAR (N = 178)		
PT	**CORE n (%)**	**Up to Crossover n (%)**	**Safety Update n (%)**
Cholelithiasis	46 (25.8)	58 (32.6)	60 (33.7)
Headache	33 (18.5)	41 (23.0)	41 (23.0)
Back pain	14 (7.9)	22 (12.4)	24 (13.5)

Source: Table 12-7, Clinical Study Report C2305 and Table 2-3 120 day Clinical Safety Update.

Notable updates include two patients with SAEs due to abnormal liver function tests:

02305-0363-00001, SAE: 20 y Caucasian female on octreotide 20 mg LAR and pasireotide LAR in the extension developed increased AST 1078 IU/L (33.7x ULN) and ALT 410 (13.2x ULN) with normal alkaline phosphatase and normal total bilirubin on Day 1381. Transaminase levels returned to normal by Day 1465 without any interruption of study drug.

02305-0664-00004, SAE: 57 y Caucasian male on pasireotide LAR 40 mg throughout the study. On Day 869 AST was elevated at 69 IU/L (1.72x ULN) and ALT 86 IU/L (1.56x ULN) and GGT 130 IU/L (2.0 x ULN) with normal alkaline phosphatase and total bilirubin. On Day 925,

transaminases increased to grade 2 (no laboratory values provided) and pasireotide LAR dosing was delayed. By Day 981, transaminases increased to grade 3 (no laboratory values provided) and pasireotide LAR continued to be delayed. By Day 1014, transaminases decreased to grade 1 levels and the patient received the next dose of pasireotide. On Day 1037, transaminase levels returned to normal. Of note, the patient was taking multiple herbal supplements around the time of the transaminase elevation.

C2305-0206-00004: 55 y Caucasian female on octreotide LAR during the CORE and pasireotide LAR during the extension phase. Throughout the study patient experienced biliary dilation and cholelithiasis. On Day 421, the patient was diagnosed with type 2 diabetes mellitus. By Day 1205, the HbA1c had risen to 7% from a baseline of 5.9% and pasireotide LAR was discontinued.

C2402 clinical safety update summary:

In C2402, the mean increase in exposure to pasireotide LAR was 10-11 months in patients originally randomized to 40 or 60 mg of the study drug. In those that crossed over to pasireotide LAR from the active control arm, exposure increased by approximately 11 months.

Table 51. Patient disposition, C2402

Disposition Reason	Pasireotide 40 mg N=65 n (%)	Pasireotide 60 mg N=65 n (%)	Active control* N=68 n (%)
Completed core period	**59 (90.8)**	**57 (87.7)**	**65 (95.6)**
Entered extension period	**57 (87.7)**	**54 (83.1)**	**63 (92.6)****
Discontinued during bridging period	**3 (4.6)**	**2 (3.1)**	**1 (1.5)**
Adverse event	2 (3.1)	0	0
Unsatisfactory therapeutic effect	1 (1.5)	1 (1.5)	0
Subject withdrew consent	0	1 (1.5)	1 (1.5)**
Discontinued during extension period (after Month 7)*	**17 (26.2)**	**13 (20.0)**	**12 (17.6)**
Adverse event	1 (1.5)	3 (4.6)	3 (4.4)
Unsatisfactory therapeutic effect	9 (13.8)	2 (3.1)	6 (8.8)
Subject withdrew consent	4 (6.2)	5 (7.7)	3 (4.4)
Lost to follow-up	0	1 (1.5)	0
Administrative problem	0	1 (1.5)	0
Death	1 (1.5)	0	0
Protocol deviation	2 (3.1)	1 (1.5)	0

*Patients in the active control arm crossed-over to pasireotide LAR 40 mg in the extension period.
**One patient randomized to active control at study entry entered the extension period but withdrew consent during the bridging period and therefore was not dosed with pasireotide LAR.

Source: 120 day clinical safety update, Table 1-11

One death and 9/18 SAEs occurred in the pasireotide LAR 40 and 60 mg groups in C2402. The death is unlikely related to pasireotide LAR use and review of the SAEs and AEs do not reveal a new or unexpected safety signal. Notable cases are presented below.

Deaths

- **C2402-0273-00002**: One death occurred in the extension arm of C2402. A 26 y male with a five year history of known acromegaly, mental retardation, hypopituitarism, diabetes insipidus and impaired glucose tolerance experienced sudden death on day 410. Autopsy results were reviewed and per Novartis are consistent with sudden death. No history regarding cardiopulmonary disease or recent related symptoms were noted in the

narrative provided by Novartis. Review of vital signs, hematologic, chemistry and liver function results from screening to week 24 show normal values throughout.

SAEs

C2402-0104-00001: 67 y Caucasian male developed pneumonia and anemia in the extension phase. However, in the last line of the narrative, Novartis states that the patient also underwent resection of squamous cell carcinoma of the penis.

C2402-0223-00005: 28 y Caucasian male randomized to pasireotide LAR 60 mg with no reported history of psychiatric disease experienced mood alterations starting Day 211. Patient was started on topiramate around Day 350. On Day 372, patient attempted suicide. Patient was hospitalized and recovered; however, withdrew consent for study participation. The investigator felt that the change in behavior was related to the study drug. Mood alterations ongoing time of last available report.

C2402-0223-00014: 46 y male randomized to pasireotide LAR 60 mg experienced tachycardia, ventricular extrasystoles, and ST segment changes on Day 486 requiring hospitalization. Study medication was discontinued with last dose being on Day 485. Event resolved.

Notable Updates:

C2402-0151-00026: 49 y Caucasian female randomized to pasireotide LAR 40 mg experienced first episode of deep vein thrombosis during the CORE phase of C2402 (Day 112). Pasireotide LAR dose was increased to 60 mg on Day 203. On Day 240, patient diagnosed with second episode of deep vein thrombosis. Pasireotide LAR was permanently discontinued. Event resolved.

C2402-0502-00003: 51 y Caucasian female randomized to pasireotide LAR 60 mg experienced SAE of hyperglycemia, abdominal abscess, atrial flutter and back pain during CORE phase. Patient further experienced metabolic encephalopathy, acute respiratory failure, acute renal failure and a staphylococcal infection in the extension phase. After discharge from the hospital, patient withdrew consent.

Common adverse events

C2402: While no new treatment emergent adverse events were identified, several adverse events increased in frequency by 5% or more from the CORE phase in those randomized to pasireotide LAR 40 and 60 mg at study entry listed below. (If only one percentage is provided, it is approximately representative of both the 40 and 60 mg dose.)

- hyperglycemia 5%
- diarrhea 6%
- cholelithiasis 11%
- anemia 3% in 40 mg group, 9% in 60 mg group
- back pain 6% in the 40 mg group only; no change in rate in the 60 mg group.
- headache 5%

Review of the adverse event profile in those that crossed to pasireotide LAR from the active control group in C2305, did not reveal new treatment emergent adverse events. However, the increase in cholelithiasis > 10 % in C2402, implies that increased duration of pasireotide exposure puts one at risk for this adverse event even with previous SSA exposure. In the C2305 CORE phase, Novartis reported that GB and biliary events present early and remain stable in incidence throughout the 12 month trial. Therefore the increased incidence of cholelithiasis during the extension (6-12 months) of C2402 seems unusual if the incidence were, in fact, to remain stable. The C2402 patients had already been on SSA, including pasireotide LAR, therapy for at least one year.

The increased frequency of $\geq$ 5% in the events listed above could be attributable to the increased duration of exposure to pasireotide LAR; however, the etiology of the increased event rates is unclear at this time.

8 Postmarket Experience

Pasireotide LAR is not approved in the United States or in any other country.

9 Appendices

9.1 Literature Review/References

The literature is cited in the body of the review.

9.2 Labeling Recommendations

The label will be reviewed separately.

9.3 Advisory Committee Meeting

There is no advisory committee meeting set for pasireotide LAR.

Appendix 1. Visit Schedules

Figure 19. Visit schedule, CSOM 2305, incorporates amendment 4

	Screening 28 to-1	Baseline									EOS Core/V1 Extension	Follow-up Core
Visit	**V1**	**V2**	**V3**	**V4,5**	**V6**	**V7**	**V8,9**	**V10**	**V11,12**	**V13**	**V14,15**	**EOS Core**	**FU Core**
Study Day	**-28 to -1**	**1**	**15**	**29/57**	**78**	**85**	**113/141**	**169**	**197/225**	**253**	**281/309**	**337**	**365**
Month (1 month = 28 days)		**0**	**0.5**	**1,2**		**3**	**4,5**	**6**	**7,8**	**9**	**10,11**	**12**	**13**
LAR Injection		**1**		**2, 3**		**4**	**5, 6**	**7**	**8, 9**	**10**	**11, 12**		
Informed Consent	X												
Inclusion/Exclusion criteria	X	X											
Medical history	X	X											
Archival Tumor Sample		X											
Demography	X												
Physical Examination	X	X	X	X		X	X	X	X	X	X	X	X
Vital signs	X	X	X	X		X	X	X	X	X	X	X	X
Height	X												
Weight	X	X	X	X		X	X	X	X	X	X	X	X
MRI	X							X				X	
ECG	X	X		X		X	X	X	X	X	X	X	X
Gallbladder ultrasound	X					X		X		X		X	
Pregnancy test	X	X		X		X	X	X	X	X	X	X	X
Hematology	X	X	X	X		X	X	X	X	X	X	X	X
Coagulation Parameters (PT and APTT)	X	X	X	X		X	X	X	X	X	X	X	X
HbA1c	X	X				X		X		X		X	X
Biochemistry	X	X	X	X		X	X	X	X	X	X	X	X
Fasting blood glucose	X	X	X	X		X	X	X	X	X	X	X	X

		Screening 28 to-1	Baseline										EOS Core/V1 Extension	Follow-up Core
Visit		**V1**	**V2**	**V3**	**V4,5**	**V6**	**V7**	**V8,9**	**V10**	**V11,12**	**V13**	**V14,15**	**EOS Core**	**FU Core**
Study Day		**-28 to -1**	**1**	**15**	**29/57**	**78**	**85**	**113/141**	**169**	**197/225**	**253**	**281/309**	**337**	**365**
Month (1 month = 28 days)			**0**	**0.5**	**1,2**		**3**	**4,5**	**6**	**7,8**	**9**	**10,11**	**12**	**13**
LAR Injection			**1**		**2, 3**		**4**	**5, 6**	**7**	**8, 9**	**10**	**11, 12**		
Fasting serum cortisol			X				X		X		X		X	X
Plasma ACTH			X				X		X		X		X	X
Urinalysis		X	X		X		X	X	X	X	X	X	X	X
Acromegaly QoL and Symptoms of Acromegaly			X		X		X	X	X	X	X	X	X	
PK blood collection			X		X	X	X	X	X	X	X	X	X	
Efficacy assessments	GH profile	X	X			X	X		X		X		X	
	PRL	X	X				X		X		X		X	
	GH suppression post OGTT	X	X				X		X		X		X	
	Total IGF-1	X	X			X	X		X		X		X	
Free T4, TSH		X	X				X		X		X		X	X
IVRS Call		X	X										X	
Randomization			X											
Study drug administration (blinded)			X		X		X	X	X	X	X	X	X[1]	
Study completion data													X	
Adverse events		CONTINUOUS												
Concomitant med		CONTINUOUS												
Comments		CONTINUOUS												

Source: Table 7-1, Protocol version 7, C2305

Figure 20. Visit Schedule, C2402

Visit[A]	Screening	Baseline									Study Completion	Safety Follow-up period[11]
	V1	V2	V3[E]	V4	V401[E]	V5	V6	V7[E]	V8	V9	V10[B]	Last dose of study treatment + 8 weeks
Day[C]	- 28	0	20	28	48	56	84	104	112	140	168	
Week[C]	- 4	0	3	4	7	8	12	15	16	20	24	
Informed Consent[1] (S)	X											
Inclusion / Exclusion Criteria[13] (S)	X											
Relevant medical history / current condition (D)	X	X										
Demography (D)	X											
History of Acromegaly (D)	X											
Physical Examination (S)	X	X		X		X	X		X	X	X	
Vital signs (body temperature, blood pressure[2], heart rate[2]) (D)	X	X	X	X	X	X	X	X	X	X	X	
Height, body weight (D)	X										X	
Previous treatment with octreotide LAR 30 mg or lanreotide ATG 120 mg (D)	X											
Administration of octreotide LAR 30 mg or lanreotide ATG 120 mg or double-blind pasireotide LAR (D)		X		X		X	X		X	X		
ECG[3] (D)	X	X	X	X		X	X	X	X	X	X	
MRI (D)	X[12]										X	
Gallbladder ultrasound (D)	X						X				X	
Serum pregnancy test (D)	X	X					X				X	
Hematology (D)	X	X					X				X	

Visit[A]	Screening	Baseline									Study Completion	Safety Follow-up period[11]
	V1	V2	V3[E]	V4	V401[E]	V5	V6	V7[E]	V8	V9	V10[B]	Last dose of study treatment + 8 weeks
Day[C]	- 28	0	20	28	48	56	84	104	112	140	168	
Week[C]	- 4	0	3	4	7	8	12	15	16	20	24	
Biochemistry (except for LFTs) (D)	X	X					X				X	
LFTs (ALT, AST, total bilirubin, albumin, ALP, γ-GT) (D)	X	X	X[14]	X[14]	X[14]	X[14]	X				X	
Hbs-Ag and anit-HCV (D)	X											
Urinalysis (D)	X	X					X				X	
Coagulation parameter APTT (D)	X	X					X				X	
Coagulation parameter PT (D)	X	X	X[14]	X[14]	X[14]	X[14]	X				X	
HbA1c (D)	X						X				X	
Fasting blood glucose (D)	X	X		X		X	X		X	X	X	
Fasting serum cortisol[4] (D)		X									X	
Plasma ACTH (D)		X					X				X	
Free T4, TSH (D)	X	X					X				X	
oGTT[5] (D)	X										X	
5-point GH profile[6] (D)	X	X					X				X	
IGF-1 assessment[6] (D)	X	X					X				X	
Archival tumor sample[7] (D)		X										
Optional pharmacogenetics blood sample[8] (D)		X										
Biomarker plasma sample (D)	X	X		X			X				X	
Biomarker serum sample (D)	X	X		X			X				X	
PK[9] (D) - ONLY FOR PATIENTS RANDOMIZED TO PASIREOTIDE LAR!		X	X	X		X	X	X	X	X	X	
Symptoms of acromegaly (D)	X	X		X		X	X		X	X	X	

Visit schedule, C2402, continued…

Visit[A]	Screening	Baseline									Study Completion	Safety Follow-up period[11]
	V1	V2	V3[E]	V4	V401[E]	V5	V6	V7[E]	V8	V9	V10[B]	Last dose of study treatment + 8 weeks
Day[C]	**- 28**	**0**	**20**	**28**	**48**	**56**	**84**	**104**	**112**	**140**	**168**	
Week[C]	**- 4**	**0**	**3**	**4**	**7**	**8**	**12**	**15**	**16**	**20**	**24**	
QoL (AcroQoL) (D)		X		X		X	X		X	X	X	
Prior/concomitant medications (D)	X	X	X	X	X	X	X	X	X	X	X	
Contact IVRS/IWRS[10]	X	X	X	X		X	X	X	X	X	X	
Adverse Events (D)	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event follow-up[11] (S)												X

A All visits can take place up to 2 days before or after the specified study week (total window of 4 days) except for visits 3 and 7 which can take place up to 1 day before or after the specified study week. Unless indicated otherwise, blood samples/assessments and urine are to be taken after an overnight fast and before medication administration.

B To be completed if the patient discontinues prematurely or at study completion.

C 4 weeks represent a 28-day period between two visits. Screening visit is expected to coincide with a regular visit with either octreotide LAR 30 mg or lanreotide ATG 120 mg administration.

D Data/assessments to be entered into the database

E V3, V401 and V7 are extra visits only required for patients randomized to the double-blind pasireotide LAR treatment arm

S Data/assessments that remain in source documents only, not to be recorded on CRF.

1 To be completed prior to any study specific assessments.

2 Blood pressure and heart rate to be measured after the patient has been in a supine position for 3 minutes.

3 ECG to be performed according to guidelines of the central reader facility. **Please also refer to Section 7.5.2.2.**

4 One single sample taken prior to study drug/active control administration.

5 oGTT is mandatory for all patients except for diabetic patients

6 5-point GH profile to be done within a 2-hour time period after one hour at rest at the hospital.
Scheduled time points for blood sampling at visit 2 and visit 6 (no oGTT required) must be done pre-dose at 0, 30, 60, 90, and 120 minutes. Study drug/active control is administered after the GH profile.
Scheduled time points for blood sampling at visit 1 and visit 10 (oGTT required) must be done pre-dose at 0, 30, 60, 90, and 120 minutes. Glucose is administered after the GH profile. Study drug/active control is administered at the end of the oGTT i.e., at earliest 120 minutes after the end of the GH profile.
IGF-1 samples are taken prior to the administration of both study drug/active control and glucose, when applicable. This sample must be taken together with the first sample of the GH profile.

Source: Table 7-1 Protocol version 5, C2402

Appendix 2.

Table 52. Summary of anti-diabetic medication by visit and treatment – CORE phase, SAS, C2305

	Pasireotide LAR N = 178 n (%)			Octreotide LAR N = 180 n (%)		
ATC class	**Baseline**	**Month 6**	**Month 12**	**Baseline**	**Month 6**	**Month 12**
Insulin alone	1 (0.6)	1 (0.6)	3 (1.7)	3 (1.7)	3 (1.7)	2 (1.1)
Biguanides alone	**11 (6.2)**	**24 (13.5)**	**19 (10.7)**	**15 (8.3)**	**15 (8.3)**	**16 (8.9)**
Alpha glucosidase inhibitor alone	0	0	0	1 (0.6)	0	0
Glinides	1 (0.6)	1 (0.6)	0	0	0	0
Combination drugs	**6 (3.4)**	**29 (6.3)**	**34 (19.1)**	**19 (10.6)**	**18 (10.0)**	**18 (10.0)**
-Bg+ Bg/DPP4	0	0	1 (0.6)	0	0	0
-Bg/DPP4	0	1 (0.6)	1 (0.6)	0	0	0
-Bg + SU	0	1 (0.6)	1 (0.6)	0	0	0
-SU + Bg/DPP4	0	1 (0.6)	1 (0.6)	0	0	0
-Bg + DPP4	1 (0.6)	2 (1.1)	4 (2.2)	1 (0.6)	1 (0.6)	1 (0.6)
-Bg + glinides	0	1 (0.6)	1 (0.6)	0	0	0
-Bg + SU	4 (2.2)	11 (6.2)	13 (7.3)	3 (1.7)	5 (2.8)	6 (3.3)
-Bg + SU + TZD	0	1 (0.6)	0	3 (1.7)	2 (1.1)	2 (1.1)
Bg + SU + TZD + DPP4	0	0	1 (0.6)	0	0	0
Bg + TZD	0	0	0	1 (0.6)	2 (1.1)	1 (0.6)
Insulin + AGI	0	1 (0.6)	0	1 (0.6)	2 (1.1)	1 (0.6)
Insulin + Bg	0	2(1.1)	1 (0.6)	6 (3.3)	5 (2.8)	6 (3.3)
Insulin + Bg + AGI	1 (0.6)	1 (0.6)	1 (0.6)	0	0	0
Insulin + Bg + SU	0	4 (2.2)	3 (1.7)	1 (0.6)	1 (0.6)	1 (0.6)
Insulin + Bg + SU + TZD	0	1 (0.6)	1 (0.6)	1 (0.6)	0	0
Insulin + Bg + TZD	0	0	0	1 (0.6)	0	0
Insulin + glinides	0	1 (0.6)	1 (0.6)	0	0	0
Insulin + SU	0	1 (0.6)	4 (2.2)	0	0	0

Bg, biguanide; DPP4, DPP 4 inhibitor; Bg/DPP4, marketed combination of biguanide and DPP4 inhibitor; SU, sulfonylurea; TZD, thiazoledinedione.
Source: Table 2-1, Response to information request received May 16, 2014.

Appendix 3.

Table 53. Newly occurring or worsening CTC hematological abnormalities by treatment – data up to crossover, SAS, C2305

Hematological test	Worsening from baseline to:	Pasireotide LAR N=178			Octreotide LAR N=180		
		Total	n	%	Total	n	%
Absolute Lymphocytes	Grade 1	163	28	17.2	166	28	16.9
	Grade 2	176	8	4.5	177	11	6.2
	Grade 3	177	2	1.1	179	3	1.7
	Grade 4	177	0	0	179	0	0
Absolute Neutrophils (Seg. + Bands)	Grade 1	155	30	19.4	153	31	20.3
	Grade 2	173	15	8.7	178	7	3.9
	Grade 3	177	2	1.1	179	1	0.6
	Grade 4	177	1	0.6	179	0	0
Activated partial thromboplastin time	Grade 1	146	21	14.4	142	22	15.5
	Grade 2	154	1	0.6	153	1	0.7
	Grade 3	154	1	0.6	153	0	0
Haemoglobin	Grade 1	141	66	46.8	134	48	35.8
	Grade 2	178	7	3.9	178	9	5.1
	Grade 3	178	0	0	180	2	1.1
	Grade 4	178	0	0	180	0	0
Platelet count (direct)	Grade 1	172	19	11.0	178	15	8.4
	Grade 2	177	0	0	180	0	0
	Grade 3	178	2	1.1	180	0	0
	Grade 4	178	0	0	180	0	0
Prothrombin time (INR)	Grade 1	55	4	7.3	48	3	6.3
	Grade 2	55	0	0	50	0	0
	Grade 3	55	0	0	50	0	0
WBC (total)	Grade 1	154	31	20.1	162	25	15.4
	Grade 2	178	8	4.5	177	3	1.7
	Grade 3	178	0	0	180	0	0
	Grade 4	178	0	0	180	0	0

n = number of subjects who had less than grade x at baseline, and worsened to grade x post-baseline.
Missing baseline values were excluded.
Subjects are counted only for the worst grade observed post-baseline.
Source: Table14.3-2.1.1

Source: Table 12-25, Clinical Study Report C2305.

Appendix 4.

Table 54. Clinical studies in other indications

Trial	Description	# of patients	Status
Cushing's disease			
B2208 (proof-of-concept)	Phase 2, 15 day, open label, single-arm, non-randomized, multicenter study to assess the safety, efficacy and PK of 600 µg pasireotide administered s.c. bid in patients with Cushing's disease	39	Completed
B2208E1 (extension to proof-of concept)	Open-label extension to B2208 that assessed long-term safety, efficacy and PK	19	Extension ongoing
B2305 (pivotal study for Signifor®)	12 month Phase 3, double-blind, randomized, multi-center study of 2 dose levels in Cushing's disease patients to assess efficacy, safety, QoL, PK, and PK/PD relationships. Primary efficacy analysis done at Month 6	162	Extension ongoing
Carcinoid syndrome			
B2202	Open-label, non-randomized study in inadequately controlled carcinoid patients to assess safety, efficacy, QoL and PK	45	Completed

Source: Tabular listing of clinical studies, CTD Module 5.2

Five Phase 1, healthy volunteer studies with pasireotide LAR have also been conducted in support of the pasireotide LAR for acromegaly indication. These are phase 1 studies evaluating pasireotide s.c. and LAR formulations in different ethnic groups. The results of these studies have not been reviewed for support of this application.

C2110 Brief Summary (wording slightly modified from Sponsor's study synopsis):

Title: A phase 1, multicenter, open-label, randomized study assessing the pharmacokinetics, safety and tolerability of monthly doses of SOM230 i.m. LAR injection in patients with acromegaly and patients with carcinoid disease.

Objectives:

The primary objectives were to:

1. Determine the pharmacokinetic profile of single and monthly doses of pasireotide LAR intramuscular (i.m.; 20, 40 and 60 mg) injection in patients with acromegaly and in patients with carcinoid disease.
2. Investigate the safety/tolerability profile of single and monthly doses of pasireotide LAR i.m. (20, 40 and 60 mg) injection in patients with acromegaly and in patients with carcinoid disease.

The secondary objective was to explore the pharmacodynamic profile of single and monthly doses of pasireotide LAR i.m. (20, 40 and 60 mg) injection in patients with acromegaly and in patients with carcinoid disease.

Methods:

Patients aged between 18 and 80 years with active acromegaly due to a pituitary adenoma who provided written informed consent could be enrolled in the study for the acromegaly indication.

Thirty-five patients with acromegaly were enrolled. Ten were randomized to the 20 mg dose, 12 to the 40 mg dose and 13 to the 60 mg dose. For patients with carcinoid disease 12 of the 42 patients were randomized to the 20 mg dose, 14 to the 40 mg dose and 16 to the 60 mg dose. All the 35 randomized patients with acromegaly were included in the PK, second PK, PD and safety analysis populations.

For patients not previously treated with pasireotide s.c., a 300 µg dose was to be injected subcutaneously into the abdominal wall at Visit 2 by the study center personnel after completion of all visit assessments. The first pasireotide LAR i.m. was to be administered at least five days after the pasireotide s.c. injection.

Eligible patients were randomized on a 1:1:1 basis to receive one of three pasireotide LAR i.m. doses: 20 mg, 40 mg, or 60 mg. Pasireotide LAR was to be given as an i.m. depot intragluteal injection at about 8:00 am for the first dose (i.e. defined as time zero or t0) and as close as possible to that time of the day for the following doses. Pasireotide LAR was administered as an intramuscular injection once every 28 days for three months.

Safety summary:

There were no deaths in this study. Two patients experienced SAEs, one of diabetes mellitus (related to study drug) and the other renal colic (unrelated to study drug).

In the acromegaly population, almost 70% of patients experienced an AE. Gastrointestinal, metabolism and nutrition, infections and infestations and investigations (blood glucose) were the

AE categories with the most frequent events. One patient discontinued the drug to diabetes mellitus and two others had dose interruptions or adjustments, one due to diabetes mellitus and the other because of over-suppressed IGF-1 levels. Mean fasting serum glucose levels increased and mean fasting serum insulin levels decreased in the population.

In the carcinoid population, there were two deaths determined not to be study drug related. Three patients experienced the following SAEs: 1) small bowel obstruction 2) hyponatremia and liver metastases 3) type 2 diabetes mellitus, hyperglycemia, thirst, nocturia, hyperglycemic hyperosmolar nonketotic syndrome and polydipsia.

Approximately 80% of carcinoid patients experienced AEs with the following SOC categories being most common: GI, general disorders and administration, metabolism and nutrition, and musculoskeletal and connective tissue disorders.

PK/PD summary:

1. A steady state of pasireotide concentration appeared to be achieved following three monthly i.m. injections of pasireotide LAR in patients with acromegaly or carcinoid disease. PK exposures were approximately dose proportional in patients with acromegaly and appeared to be over dose proportional in patients with carcinoid disease. The drug accumulation after repeated dosing was minimal.

2. Patients with acromegaly had similar exposures as healthy volunteers, while patients with carcinoid had approximately 2-fold PK exposures of those in healthy volunteers.

3. Reduction effect of pasireotide LAR on levels of GH, IGF-1 and free IGF-1 were well maintained over three-month treatment period for all three dose groups.

4. The inhibitory effect of pasireotide on GH and IGF-1 levels (i.e. exposure-response relationship) in patients with acromegaly was well characterized by a direct inhibitory effect sigmoid Emax model, for most patients however, due to the large variability in the data, concentration-dependent efficacy could not be demonstrated.

5. The parameter estimates derived from the Emax model for GH following pasireotide LAR doses were similar to those estimates following pasireotide s.c. doses, indicating a similar pharmacological potency of pasireotide on GH between pasireotide LAR and s.c. formulations in patients with acromegaly.

6. The data from PK and PK/PD analysis support that monthly i.m. injection is an appropriate dosing regimen for pasireotide LAR in patients with acromegaly and in patients with carcinoid disease.

7. Overall pasireotide LAR treatment was well tolerated at the three doses tested: 20, 40 and 60 mg in both, patients with acromegaly and patients with carcinoid disease.

Appendix 5

Evaluation of the proportion of patients reaching a GH level < 1.0 µg/L alone or as part of the primary endpoint was not an objective in C2305; however, these were secondary objectives in C2402.

Similarly, evaluation of GH levels after a 75 g OGTT was also not an objective of C2305 or C2402, although, at the End of Phase 2 meeting held on October 15, 2007, FDA proposed that it be an additional efficacy endpoint. These "endpoints" will be briefly discussed here.

GH level < 1.0 µg/L

C2305

As part of the primary combined endpoint or by itself, the proportion of patients reaching GH < 1.0 µg/L is much lower compared to those reaching GH < 2.5 µg/L in both treatment groups. The clinical significance of reaching a GH < 1.0 µg/L is not known at this time.

Table 55. GH levels and GH levels with normalized IGF-1, by treatment group, FAS, C2305

	Pasireotide LAR		Octreotide LAR		
GH level	**n/N (%)**	**95% CI**	**n/N (%)**	**95% CI**	**Odds ratio (95% CI)**
< 1.0 µg/L	40/176 (22.7)	(16.8, 29.6)	39/182 (21.4)	(15.7, 28.1)	1.1 (0.66, 1.78)
< 2.5 µg/L	76/176 (43.2)	(35.8, 50.8)	86/182 (47.3)	(39.8, 54.8)	0.85 (0.56, 1.3)
GH level with normalized IGF-1					
< 1.0 µg/L	27/176 (15.3)	(10.4, 21.5)	17/182 (9.3)	(5.5, 14.5)	1.77 (0.93, 3.36)
< 2.5 µg/L	51/176 (29.0)	(22.4, 36.3)	32/182 (17.6)	(12.3, 23.9)	1.94 (1.17, 3.21)

Values presented to not represent analysis with LOCF as presented for primary efficacy results
Source: Tables 11-11, 11-12 Clinical Study Report C2305 and Table 2-5 and 2-6 Response to information request received July 28, 2014

In C2402, the proportion of patients with a reduction of GH to < 1 µg/L was highest in the pasireotide LAR 60 mg arm (18.5%) followed by pasireotide LAR 40 mg arm (12.3%) and the active control group (2.9%). In both C2305 and C2402, the percentage of patients reaching GH < 1.0 is lower than the percentage reaching a GH < 2.5 µg/L.

GH levels post OGTT

In the U.S., conducting an OGTT with GH levels was part of the protocol, whereas, it was optional outside of the U.S. The majority of non-diabetic patients (37/41) in the U.S. had a baseline OGTT compared to less than half (137/317) outside of the U.S. A GH < 1.0 µg/L during an OGTT represents biochemical control of acromegaly. By Month 12, the number of patients with OGTT data are much less (see table below). A comparison of GH + IGF-1

response, IGF-1 response and GH nadir post OGTT shows that there are discrepancies among the different response categories; although, all three criteria have been described in various academic publications as defining control.

Table 56. Summary of GH+IGF-1 response, IGF-1 response, and GH nadir at Month 12 for patients with OGTT, FAS, C2305

	Pasireotide LAR N = 28		Octreotide LAR N = 44	
Response at Month 12	GH nadir after OGTT at Month 12		GH nadir after OGTT at Month 12	
	< 1 µg/L N = 15	> 1 µg/L N = 13	< 1 µg/L N = 19	> 1 µg/L N = 25
GH+IGF-1 (LOCF)				
Responder	11 (73.3)	7 (53.8)	9 (47.4)	2 (8.0)
Non-responder	4 (26.7)	6 (46.2)	10 (52.6)	23 (92.0)
IGF-1 (LOCF)				
Responder	12 (80.0)	9 (69.2)	9 (47.4)	2 (8.0)
Non-responder	3 (20.0)	4 (30.8)	10 (52.6)	23 (92.0)

Source: Response to clinical information request received by FDA July 28, 2014

OGTT with GH levels was not performed in C2402.

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

/s/

SMITA B ABRAHAM
08/29/2014

DRAGOS G ROMAN
08/29/2014

JEAN-MARC P GUETTIER
09/02/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203255 **Applicant: Novartis Pharmaceuticals Corp.** **Stamp Date: November 15, 2013**

Drug Name: Signifor LAR (pasireotide) **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)1
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: B2201 and C2110 Study Title: B2201: " A multicenter, randomized, crossover, open label, dose finding study to compare the safety, efficacy, and PK/PD relationship of multiple doses of SOM230 (200 µg, 400 µg and 600 µg b.i.d.) and doses of open-label Sandostatin® (100 µg t.i.d.) in acromegalic patients." N = 53 Location in submission: Module 5 Study Title: C2110: " Phase 1, open-label, randomized	X			B2201: All patients had 28 d treatment period with octreotide 100 µg s.c. t.i.d. After this, patients randomized to one of six treatment sequence groups to receive treatment with s.c. injections of 200, 400 or 600 µg b.i.d. of pasireotide for 28 days.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	study assessing PK, safety, and tolerability profiles of 3 doses of pasireotide im in patients with acromegaly or carcinoid disease." Sample Size: 35 acromegaly, 42 carcinoid Arms: Single arm Location in submission: Module 5				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1**: "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly." **Pivotal Study #2**: "A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly."	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				Most centers are located in the U.S.A. We believe that the medical characteristics of patients enrolled outside of the U.S.A are similar to those enrolled within the U.S.A.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Dedicated QT studies are cross-referenced from NDA 200677 (pasireotide s.c.). Safety data on QT intervals is provided in the pivotal trial clinical study reports.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Orphan drug. The applicant was exempted from pediatric assessment and has provided the appropriate documentation.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Comments to the Novartis:

1. Please clarify why the day range limit for considering a GH or IGF-1 value missing was changed from 15 days to 35 days? In addition, please justify why a 35 day limit is acceptable given that the Signifor LAR injections were given every 28 days. The day range limit applies to both CSOM 2305 and 2402 however, protocol CSOM 2402, Amendment 1 is referenced.

Smita Abraham, M.D. 01/06/2014
Reviewing Medical Officer Date

Dragos Roman, M.D. 01/06/2014
Clinical Team Leader Date

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

/s/

SMITA B ABRAHAM
01/03/2014

DRAGOS G ROMAN
01/03/2014