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APPLICATION NUMBER:

200677Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	11/30/2012
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA #: 200677
Supplement#	
Applicant	Novartis
Date of Submission	2/17/2012
PDUFA Goal Date	12/17/2012
Proprietary Name / Established (USAN) names	Signifor (pasireotide)
Dosage forms / Strength	injection 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL in prefilled syringes for BID subcutaneous injection
Proposed Indication(s)	Medical treatment of Cushing's disease
Recommended:	Approval

1. Introduction

1.1 Signifor (pasireotide for injection) for the treatment of Cushing's disease

Pasireotide, the active ingredient in Signifor, is a new molecular entity. The Signifor application was submitted on February 17, 2012, under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the indication of medical therapy of Cushing's disease. Chemically, pasireotide is a cyclohexapeptide analogue of endogenous somatostatin.

Naturally occurring human somatostatin (SST) is a peptide hormone that circulates as two bioactive forms, SST-14 and SST-28, named after the number of amino acids that they contain. Human somatostatin producing cells are widespread throughout the body, but concentrated in the central and peripheral nervous system, and in the endocrine pancreas and gut. Somatostatin acts on a variety of targets including the pituitary (where it down-regulates secretion of human growth hormone), pancreas, gut, kidney, adrenal, etc., and has, in general, an inhibitory effect across multiple endocrine and exocrine systems. Somatostatin exerts its functions via binding to five structurally related somatostatin receptors (SSTRs). The different affinities of SST-14 and SST-28 for these receptors, along with their tissue-specific SSTR distribution, enhance the biological diversity of responses to somatostatin and the modulation of diverse target tissue functions.

Pasireotide is not the first somatostatin analogue to be brought to the market. Two somatostatin analogue products have already been approved by the Agency: Sandostatin (octreotide) and Somatuline (lanreotide). Octreotide was approved in 1988 and is currently marketed as a long-acting release product (Sandostatin LAR) for the treatment of 1) acromegaly, 2) severe diarrhea/flushing episodes associated with metastatic carcinoid tumors,

and 3) profuse watery diarrhea associated with vasoactive intestinal peptide (VIP) secreting tumors. Lanreotide has been approved as a depot formulation (Somatuline Depot) for the treatment of acromegaly. Information regarding the safety profile of the currently approved somatostatin analogues is likely to inform the pasireotide NDA, and includes inhibition of gallbladder contractility and decrease in bile secretion resulting in gallbladder sludge and cholelithiasis, dysglycemia due to blocking of the effects of counter-regulatory hormones (insulin, glucagon, growth hormone), suppression of thyroid stimulating hormone (with resulting hypothyroidism), bradycardic effect and prolongation of the QT interval.

Despite general similarities to octreotide and lanreotide, pasireotide exhibits a different pattern of receptor binding and, very importantly, different receptor affinities. Whereas lanreotide and octreotide bind primarily to SSTR2, pasireotide binds to a broader range of receptors (SSTR 1, SSTR2, SSTR3 and SSTR5) and has particular affinity for SSTR5, which has been shown to be expressed, albeit somewhat variably, on tumoral corticotrophs. In fact, pasireotide was specifically developed with the goal of enhanced binding to SSTR5. As illustrated in Table 2-1 from the applicant's Briefing Document for the Signifor Advisory Committee held on November 7, 2012, pasireotide has an affinity that is 31 times higher than octreotide, and 85 times higher than lanreotide for SSTR5 and a similar affinity (only two-fold difference) for the SSTR2 receptor.

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Bruns et al (2002), Eur J Endocrinol; 146:707-716, Gillespie et al (1998) J Pharmacol Exp Therap; 285:95-104

The consequence of pasireotide binding to the various SST receptors on the surface of pituitary tumors is a reduction in adrenocorticotropin (ACTH) secretion, with subsequent decline in adrenal cortisol production and the expectation of improvement of the biochemical and clinical signs of hypercortisolism.

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

Novartis is proposing the following indication for Signifor:

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

1.2 Cushing's disease, available therapies, and the role of pharmacological therapy in the treatment of Cushing's disease

Cushing's disease (CD) is an exceedingly rare disease. Incidence of CD has been estimated at 2.4-2.6 per million per year¹. The applicant proposes that the prevalence of Cushing's disease in the US is approximately 17,000 patients. Cushing's disease, almost exclusively an adult condition, is due primarily to an ACTH secreting tumor originating in the corticotroph cells of the pituitary or, less frequently, it is due to corticotroph hyperplasia or a corticotropin-releasing tumor (CRH). In most cases, the ACTH - secreting pituitary tumor is histologically a benign adenoma. The clinical manifestations of Cushing's disease are related to the local growth of the tumor and to systemic symptoms of hypercortisolism. Cushing's disease is the most common cause of endogenous Cushing's syndrome (CS), and accounts for approximately 70% of all cases of endogenous CS. In addition to the classical CS phenotype ("moon-shaped" face, cervical and abdominal fat accumulation, striae, easy bruising, hirsutism, abdominal obesity), hypercortisolism in Cushing's disease is associated with significant morbidity due to associated complications such as hypertension, impaired glucose tolerance/diabetes, dyslipidemia, osteoporosis, immune deficiency and subsequent increased risk for infections. Mortality in CS/CD is up to 5-fold higher than that of the general population² and is due primarily to cardiovascular complications³.

Initial treatment of CD is primarily surgical because the successful removal of the entire tumoral tissue responsible for the excess ACTH secretion is potentially curative. However, in practice, remission rates are below 65-90% for pituitary microadenomas, and less than 65% for macroadenomas. Moreover, even among patients who achieve remissions, recurrences can occur over time. Under such circumstances patients have limited options for the control of hypercortisolemia. They include repeat pituitary surgery, radiotherapy, medical therapy or, as a last resort, bilateral adrenalectomy. Medical therapy in Cushing's disease is reserved for patients who are not medically stable to undergo surgery, for patients who manifest recurrence or persistence of disease despite surgery (in such situations it is oftentimes used in conjunction with radiotherapy), or for patients with unresectable tumors.

Currently there are no drugs approved specifically for the treatment of Cushing's disease. Korlym (mifepristone) was approved on February 17, 2012 for the treatment of patients with endogenous Cushing's syndrome who have failed surgery or are not candidates for surgery and have concomitant manifestations of glucose intolerance or type 2 diabetes mellitus (of note, CD is included in the endogenous CS indication). Korlym is a glucocorticoid receptor antagonist and exerts its effect by blocking the effect of cortisol in target tissues.

¹ Arnardottir S and Sigurjonsdottir: The incidence and prevalence of Cushing's disease may be higher than previously thought: results from a retrospective study in Iceland 1955 through 2009. *Clinical Endocrinology*, 74,791-793, 2011.

Lindholm J et al: Incidence and late prognosis of Cushing's Syndrome: a population based study. *J Clin Endocrinol Metab* 86, 117-123, 2001.

² Nieman LK et al: The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 93: 1526-1540, 2008.

³ Arnaldi G et al: Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*, 88(12), 5593-5602, 2003.

2. Background

Pasireotide has been in clinical development since 2003 (b) (4). In the Division of Metabolism and Endocrinology Products (DMEP) pasireotide was evaluated for the treatment of Cushing's disease and acromegaly under INDs 68,635 (for an immediate-release product) and (b) (4). In the (b) (4) it was studied under (b) (4) an (b) (4).

DMEP met with representative from Novartis in an End-of-Phase 2 (EOP2) meeting on May 15, 2006, to discuss the Phase 3 program for Cushing's disease. The sponsor's intent at the time was to conduct a single-arm, 85-patient registration study that would evaluate the safety and efficacy of a single pasireotide dose of 600 mcg bid over a (b) (4). The proposed primary efficacy variable was urinary free cortisol measured over 24-hours, the most reliable quantitative measure of cortisol at the time; the primary efficacy analysis proposed to measure the percentage of subjects with cortisol reduction greater than 50% from baseline. The Division recommended to extend the duration of the study to 6 months and add a 6 months extension; questioned whether 600 mcg bid was indeed the optimal dose in absence of a dose ranging study in Cushing's disease; and recommended further dose-ranging exploration (including a lower dose of 300 mcg bid). The Division also recommended the implementation of stopping rules so that patients who do not respond to treatment should not be treated unnecessarily. The plan to conduct a single trial was found acceptable given the serious and life-threatening nature of the condition. Another issue that was discussed was the dose selection for a thorough QTc study.

The phase 3 study protocol was reviewed under a special protocol assessment. Although there was no formal agreement between the FDA and the sponsor at the end of the protocol review, many of the recommendations that the Division had made at the EOP2 meeting were accepted by the applicant including, among others, the addition of stopping criteria for non-responders, further dose escalation in patients with poor response, definition of the Intent-to-Treat population, imputation methods, definition of Month-6 responders, the minimum number of UFC measurements for each time point, and glucose monitoring. The Division maintained its recommendation that the pasireotide program determine the lowest effective dose, and asked the sponsor to consider studying a 300 mcg bid dose.

On July 24, 2009, pasireotide (SOM230) was granted orphan-drug designation for "the treatment of Cushing's disease" by the Office of Orphan Products Development (similarly, pasireotide was designated an orphan medicinal product on October 8, 2009 by the European Medicines Agency).

A Pre-NDA meeting was held with the sponsor on August 30, 2010. The meeting package included standard pre-NDA questions and requests for clarifications, but no controversial questions.

The pasireotide NDA was initially submitted on June 21, 2011. The drug product presentation consisted in pre-filled syringes containing 0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL of pasireotide. However, soon after the NDA submission, the applicant alerted the Agency that (b) (4) particulates were found in some syringes, and Novartis withdrew the NDA without prejudice on August 19, 2011. A root cause analysis was conducted, and Novartis arrived at the conclusion that the particulate matter originated in (b) (4). The NDA was re-submitted on February 17, 2012 with ampoules instead of pre-filled syringes at the same strengths as in the initial submission (0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL). Of note, the ampoule presentation was the presentation used in the Phase 3 clinical trial.

Of note, on January 19, 2012, the Committee for Medicinal Products for Human Use (CHMP) of EMA recommending the granting of a marketing authorization for Signifor, 0.3 mg, 0.6 mg, 0.9 mg solution for injection, for the following indication: " treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed." The marketing authorization included also a pharmacovigilance plan. The Phase 3 program submitted to the EMA contained the same clinical study that was submitted to the FDA.

3. CMC/Device

The CMC review (DARRTS, 10/16/12) recommends approval with the caveat that the recommendation from the Office of Compliance for GMP inspections was still pending at the time of the review. No Phase 4 recommendations are made.

The microbiology review (DARRTS, 7/3/12) recommends approval, and no Phase 4 studies are recommended.

The biopharmaceutics review (DARRTS/, 10/10/12) recommends granting a biowaiver for the 0.3 mg/mL dosage strength based on (b) (4) the clinically evaluated strengths of 0.6 and 0.9 mg/ml.

Pasireotide diaspartate is manufactured (b) (4). The CMC reviewer indicates that all likely impurities are accounted for in the drug substance, that impurity levels in the to-be-marketed product for batches manufactured on the equipment for commercial use are below the ICH Q3B qualification limits, and that residual solvent specifications comply with ICH Q3C. Applicant's justification of specifications was found to be adequate.

The excipients utilized for Signifor are well known and commonly used in parenteral products and they have been demonstrated to be compatible with pasireotide in stability studies.

The stability data supports a shelf -life of 24 months. The product requires light protection.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review (DARRTS 10/4/12) and the supervisory memorandum (DARRTS 11/08/12) recommend approval. There are no recommendations for additional Phase 4 studies.

The toxicities observed in toxicology studies are described as extensions of the pharmacologic activity of the drug and relatively consistent across species. Pasireotide was not found to be genotoxic. Carcinogenicity studies were negative for drug-related neoplasms.

With respect to hyperglycemia and hepatic adverse events (two safety concerns identified in humans during the pasireotide program) the supervisory memo indicates that the animal data provide only limited insight. The same observation that pasireotide inhibits insulin secretion was made in animals and in humans. Overt hepatic toxicity was not observed in healthy animals.

Since reproduction studies performed in rats and rabbits showed evidence of impaired fertility or harm to the fetus at therapeutic pasireotide exposures, the review recommends a pregnancy C category, indicating that pasireotide should be used during pregnancy only if clearly needed. Of note, patients with Cushing's disease, in general, have low fertility rates because of the effects of cortisol on the reproductive system and, for patients who undergo pituitary surgery, because of a higher likelihood of pituitary insufficiency.

Of note, pasireotide also had an inhibitory effect on GH/IGF-1 secretion in animals, which is the basis for being developed for the treatment of acromegaly.

Dr. Tsai-Turton's review concludes that, overall, there were no unexpected findings identified with pasireotide, and that the toxicity profile of pasireotide is consistent with that of other somatostatins.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review (DARRTS, 10/25/2012) finds the application "acceptable" and does not recommend any Phase 4 studies.

With a T_{max} of 0.25-0.5 hours, pasireotide appears to be promptly absorbed after subcutaneous administration. It shows linear pharmacokinetics in both healthy volunteers and Cushing's disease patients over the dose range studied, which include the proposed therapeutic doses. The effective half-life is approximately 12 hours. In plasma, it is 88% protein bound. Pasireotide is metabolically stable and is mainly eliminated via biliary system and only to a small extent via renal route. Relative to patients with intact hepatic function, patients with mild, moderate and severe hepatic impairment show an 8%, 60% and 79% increase in AUC,

and a 7%, 67% and 69% increase in C_{max} . Based on these data, the clinical pharmacology review recommends dose adjustment in patients with moderate hepatic impairment and contraindication of pasireotide use in patients with severe hepatic impairment.

The review indicates that based on *in vitro* studies pasireotide is not a substrate, inhibitor, or inducer for metabolic isozymes in the proposed dosing range, and therefore unlikely to be subject to drug-drug interactions.

Pasireotide was evaluated for potential QT prolongation in two thorough QT studies. Testing was conducted with one of the therapeutic doses (600 mcg) and with a supratherapeutic dose of 1950 μ g to simulate a possible “worst case scenario” such as administration to patients with hepatic impairment, for instance. In both studies an effect of pasireotide on the QTc interval was observed. The maximum placebo-subtracted mean change from baseline occurred at two-hour post dose. Pasireotide increased the double-corrected QTc interval by 13.19 ms (90%CI: 11.38; 15.01) and 16.12 ms (90%CI: 14.30; 17.95 ms) following 600 mcg BID and 1950 mcg BID, respectively. Of note, the QT studies have been reviewed by the Interdisciplinary Review Team (DARRTS, 8/29/12) who concluded that the studies were informative, and made specific labeling recommendations.

Finally, on the basis of efficacy and safety exposure-response analyses, the clinical review recommends a starting dose of 600 mcg bid. Several of these analyses will be presented in the efficacy and safety section of this memorandum where they will be integrated with the clinical data.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The main evidence of efficacy for pasireotide in patients with Cushing’s disease comes from the Phase 3 clinical trial B2305. Supportive evidence comes from the Phase 2 trial B2208.

Study B2208 was a multicenter, single-arm, study that evaluated a single pasireotide dose of 600 mcg bid administered subcutaneously to 39 adult patients with Cushing’s disease for 15 days (patients were allowed to participate in an extension phase at which time up- or down-titration of the pasireotide dose was allowed). This study has provided proof that the 600 mcg bid can normalize urinary free cortisol (UFC) after 2 weeks of therapy, an observation made in 5/29 (17%) of patients who contributed data. Dose-response analyses of the information obtained from this study indicated that patients who normalized their UFC had higher exposures to pasireotide than partial-responders or non-responders. This observation led to the exploration of a higher pasireotide dose (900 mcg bid) in the extension phase of the study, and to the addition of a 900 mcg bid dose regimen to the 600 mcg bid regimen already planned for the Phase 3 study. It was predicted that the mean pasireotide trough level for the 900 mcg bid

dose in the Phase 3 trial would be comparable to that observed in the 600 mcg bid subgroup of responders from Study B2208. Of note, some of these predictions were based on data from subgroups which were quite small (4-17 patients)⁴.

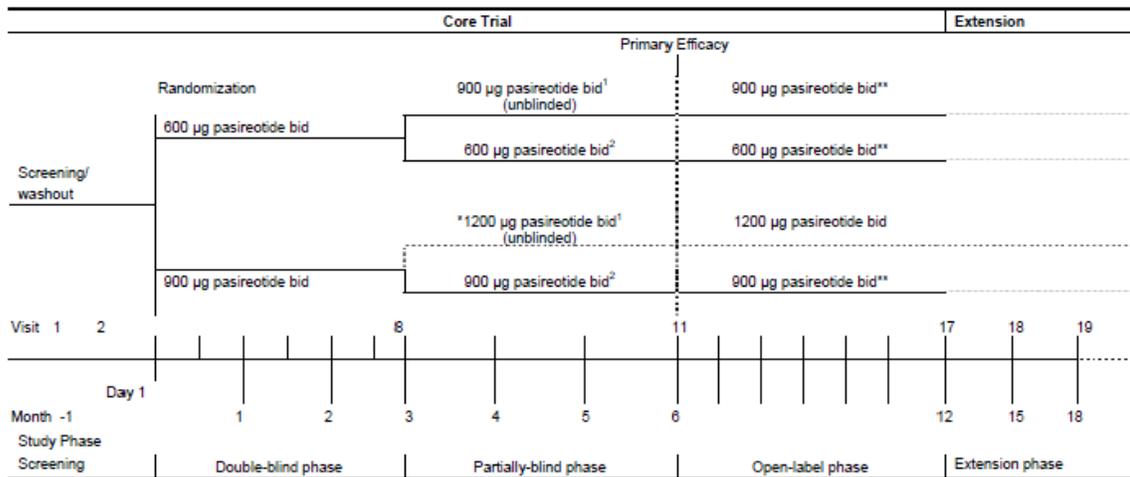
The pasireotide Phase 3 program included a single clinical trial, Study B2305. This was a 6-month, randomized, double-blind, two-arm, international study that was conducted in 162 patients with Cushing's disease enrolled at 68 sites in 18 countries. The study assessed the safety and efficacy of two pasireotide dose regimens: 600 mcg bid and 900 mcg. Consistent with the indication sought in this application (medical treatment of Cushing's disease) the study enrolled only CD patients that were candidates for medical therapy according to current medical practice, i.e. primarily patients with persistence or recurrence of hypercortisolism despite prior pituitary surgery, and some patients with *de novo* Cushing's disease who were poor surgical candidates or who refused surgery. The study had clear and rigorous inclusion criteria to confirm the diagnosis of Cushing's disease, confirm the presence of hypercortisolism at enrollment, and exclude conditions that may overlap clinically or biochemically with Cushing's disease. Any potential carry-over effect of previous medications was minimized by a washout of previous medical therapies which took into consideration the half-lives of specific drugs. Dr. Lowy's review of protocol violators did not identify any significant deviations in the way the inclusion/exclusion criteria were applied in the clinical trial. This is important since CD is not expected to improve spontaneously except in very rare situations.

The design of Study B2305 is displayed below, and is essential for understanding the efficacy analyses, in general, and the primary efficacy analysis in particular. Patients were randomized 1:1 to a regimen of either 600 mcg bid or 900 mcg bid of pasireotide; double blinding was planned for the "core" or initial 6-month phase of the trial (the post Month 6 phases were in essence open-label extensions). As previously indicated, the final design of the study took into considerations recommendations that were made by the FDA, including the definition of therapeutic success (i.e. normalization of UFC, which - it should be recognized - is a hard standard to meet). In addition, in agreement with FDA recommendations, the study protocol did not allow patients to continue pasireotide treatment at the randomized dose if they failed to show improvement after a reasonable period of time on treatment. As such, by month 3 of treatment, patients who did not reach an UFC level that was clearly trending toward normalization⁵ were unblinded and allowed to increase their dose by 300 mcg. Patients for whom the dose could not be escalated were discontinued from the trial. Regardless, all patients who were unblinded at Month 3 were considered treatment failure for the purpose of the primary efficacy analysis which defined a responder as any subject who normalized UFC at the Month 6 time point among the patients who maintained the blind. UFC was measured as an average of multiple urine collections to ensure better accuracy of measurements; therefore, it is referred as a mUFC (mean UFC) for each time point for each patient. Of note, mUFC is different from mean mUFC, which is the mean value of all individual mUFCs collected at any particular time point.

⁴ Table 6-3 of applicant's AC briefing document.

⁵ i.e. below twice the upper limit of normal AND below baseline (the latter to account for the patients who were enrolled with UFCs < 2xULN)

Design of Phase III study B2305 in patients with Cushing's disease



It should be noted that only approximately 66% of patients completed the first 6 months of the clinical trial; the 34% drop out rate was due to primarily to a combination of adverse events and unsatisfactory therapeutic response in some patients.

The primary efficacy analysis evaluated the efficacy of each pasireotide dose independently, rather than comparing the 600 mcg bid to the 900 mcg bid dose. The response rate of patients who normalized their mUFC at Month 6 was compared to a response rate of 15%. This threshold of presumed clinical benefit was agreed between the Division and the applicant in the early phases of drug development as a number that was necessary for hypothesis testing and powering the study (a dose “won” if the lower bound of the 95% CI for responders was > 15%). It was calculated that 73 patients in each group would provide 87% power to demonstrate statistical significance at 5% 2-sided level; the study enrolled around 80 patients per arm. The selection of the 15% threshold took into consideration that spontaneous improvement in Cushing’s disease is an exceedingly rare event. It followed advice from experts in the Cushing’s field whose opinion was sought given the paucity of prospective clinical trials of medical therapies in CD.

Primary efficacy analysis and related analyses

The primary efficacy analysis is reproduced below⁶ and indicates that only the 900 mcg bid dose reached statistical significance, in that it was the only dose whose lower bound of the 95 CI of 17% exceeded the prespecified 15% threshold. Additional sensitivity analyses conducted by the FDA statisticians confirmed the primary analysis. They include: 1) the use of a larger CI (97.5%) in order to control type 1 error, and 2) repeating the analysis after removal of 2 patients from the 900 mcg arm because of potentially incomplete urine collections which could have biased toward a favorable drug response. It should be acknowledged that a “statistical loss” in the primary efficacy analysis for the 600 mcg bid dose does not necessarily mean lack

⁶ Table 6 is from the Joint Clinical and Statistical Review for the FDA AC Briefing Document, which also served as the formal internal statistical review (DARRTS 11/5/2012).

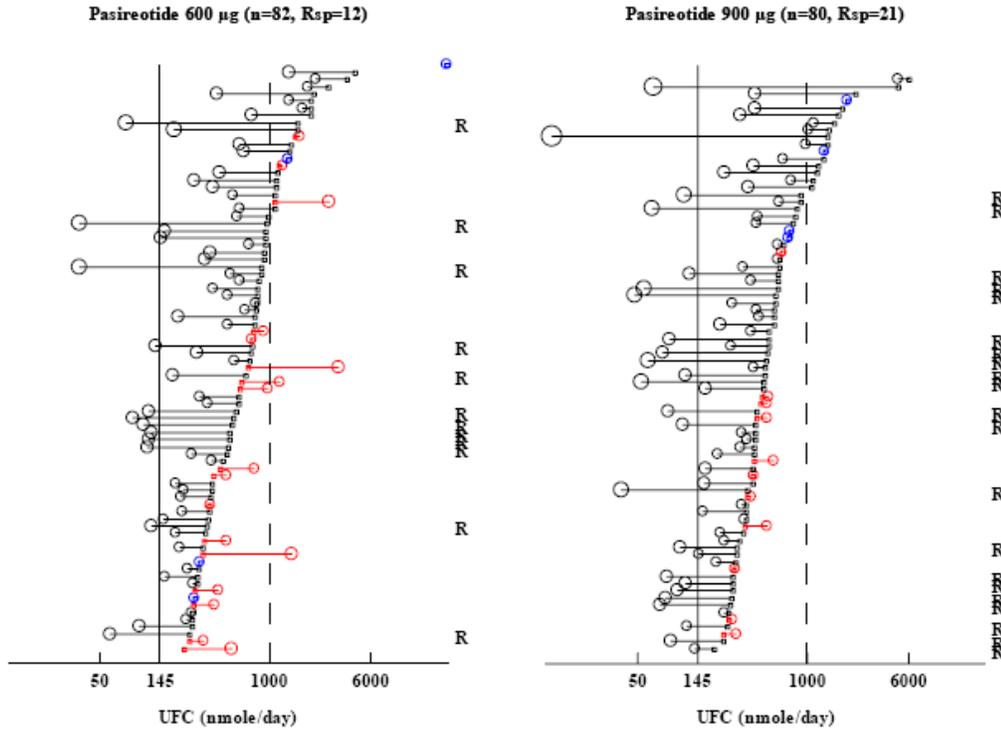
of efficacy since, from a clinical standpoint, each patient whose mUFC normalized likely represents a response to the dose and the drug, rather than a spontaneous improvement.

Table 6: Primary efficacy analysis (Month 6)

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

Additional evidence of efficacy for pasireotide came from a variety of other secondary and post hoc efficacy analyses. Specifically, the mean mUFC levels declined relative to baseline (the LSM change from baseline at Month 6 was 52% and 58% for the 600 and 900 mcg group, respectively), and were accompanied by reductions in serum ACTH and serum cortisol levels (although none of them normalized). The observed suppression in ACTH is consistent with the mechanism of action of pasireotide and corroborates the changes observed for urinary cortisol measurements. Although normalization of mUFC at Month 6 occurred only in a subgroup of patients, many others had reductions in mUFC. This is best illustrated in Figure 4 of the Clinical Review, reproduced below, which indicates that most patients in the 600 mcg and 900 mcg group had reductions in mUFC at Month 6 (in black) and only a minority had worsening (in red). In this graph, the endpoint mUFC value is represented by a circle. The graph includes the upper limit of normal of 145 mmol/24 hours; responders are identified with an "R" on the right side of each graph.

Figure 4 Individual UFC Changes from baseline to Month 6 (LOCF, FAS) in Study 2305



When a less restrictive definition of responder was used to account for the fact that some patients had very high baseline mUFC levels which could have declined substantially without resulting in mUFC normalization, a definition that included patients with an mUFC reduction either in the normal range or > 50 % relative to baseline, as many as 34% of subjects in the 600 mcg group and 41% in the 900 mcg group met this new criteria.

Changes in several other efficacy endpoints were reported, but they need to be interpreted cautiously in the context of an uncontrolled clinical trial. There were mean reductions in systolic and diastolic blood pressure⁷ (unfortunately in association with some increase in background blood pressure medication, see Section 6.1.5 of the Clinical Review, page 51-52 for details), reductions in waist circumference⁸, weight⁹, BMI¹⁰, and improvements in health-

⁷ Mean systolic reductions: -6.8 mm Hg for the 600 mcg dose and -11.4 for the 900 mcg dose. Mean diastolic reductions: -4.2 mm Hg for the 600 mcg dose and -5.0 for the 900 mcg dose.

⁸ -1.9 cm for the 600 mcg dose and -3.4 cm for the 900 mcg dose.

⁹ -3.1 kg for the 600 mcg dose and -5.7 for the 900 mcg dose

¹⁰ -1.2 kg/m² for the 600 mcg dose and -2.1 for the 900 mcg dose

related quality of life (these data were obtained with an instrument that, in the opinion of the SEALD reviewer, was not fully validated). There were no significant changes in tumor volume measurements (the number of the patients contributing data for this analysis is quite small and many did not have measurable adrenal adenomas to start with). Generally speaking, efficacy evaluations for the subgroup of patients who continued pasireotide through Month 12 were consistent with the Month 6 findings, and, due to the fact that patients who benefit most tend to stay in the trial, the effect was even more favorable, as was the case for weight, BMI and waist circumference.¹¹ Of particular interest is the fact that among patients who were hypertensive at baseline but did not receive antihypertensive medication(s) during the clinical trial, there was a decrease in both systolic and diastolic blood pressure at Month 12 (mean change of -13 mmHg and -7 mmHg respectively; see, below, Table 7-8 of applicant's AC Briefing Document).

Table 7-8 Change in BP to Month 12 by baseline hypertensive status (B2305)

	Change in SBP (mmHg) Mean (95% CI)	Change in DBP (mmHg) Mean (95% CI)
Overall, N=78	-6.1 (-9.8, -2.4)	-3.7 (-6.2, -1.2)
Hypertension at baseline	-8.0 (-12.4, -3.6)	-4.7 (-7.7, -1.7)
No antihypertensive medication use during study, n=16	-13.2 (-20.0, -6.4)	-7.3 (-12.9, -1.7)
Antihypertensive medication use during study, n=44	-6.1 (-11.5, -0.7)	-3.7 (-7.2, -0.2)
No hypertension at baseline	0.2 (-6.1, 6.4)	-0.4 (-4.6, 3.9)
No antihypertensive medication use during study, n=13	-0.3 (-8.2, 7.6)	-0.9 (-6.2, 4.5)
Antihypertensive medication use during study, n=5	1.5 (-9.1, 12.1)	1.0 (-6.0, 8.0)

SBP=systolic blood pressure; DBP=diastolic blood pressure

Efficacy evidence for dose selection

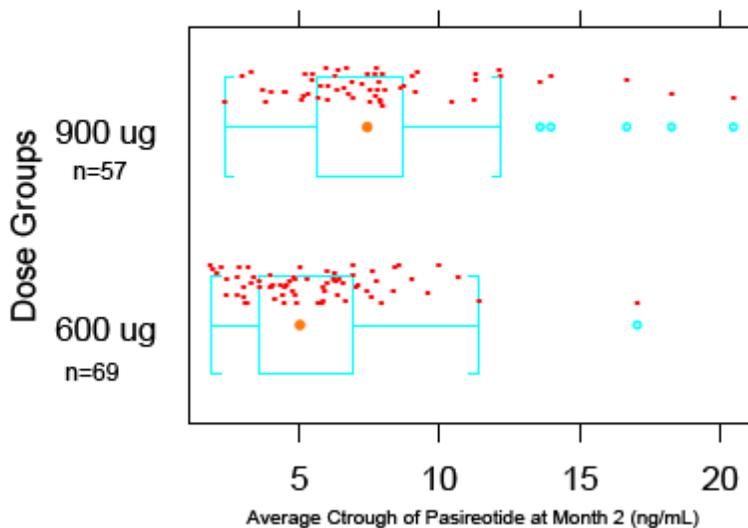
The issue of selecting a specific pasireotide dose is not a simple one. As previously mentioned, the 15% threshold was somewhat arbitrary and was selected because of the necessity to incorporate a statistical plan and power the study, but did not correlate with a specific outcome. In addition, normalization of mUFC was seen with both doses, although at different rates.

Taking into consideration the totality of the efficacy analyses, the 900 mcg bid dose seems to perform somewhat better than the 600 mcg bid dose (a larger percentage of patients normalized their mUFC or had mUFC reductions >50%), but the differences were not striking. This is recognized by the statistical review which concludes that although the 600 mcg bid dose did not formally meet the primary efficacy criterion, the overall results are not sufficient for declaring that the two doses are different statistically; that both doses were associated with consistent reductions from baseline in mUFC; and that relatively large proportions of patients in each dose group exhibited mUFC reductions. In other words, the 900 mcg bid regimen, although slightly better than the 600 mcg bid regimen in the primary and other efficacy

¹¹ At Month 12, the mean decrease from baseline in the 600 vs. 900 mcg bid groups was as follows: weight 5.8 kg vs. 7.7 kg, BMI 2.1 kg/m² vs. 2.8 kg/m², and waist circumference 4.4 cm vs. 5.6 cm.

analyses, had only a modest additional benefit. This could simply be a reflection of the fact that the two doses may not be very far away on the dose-response curve. This clinical and statistical conclusion is further supported by the data from Figure 3 of the clinical pharmacology review, which indicate that there is significant overlap in exposures between these two dose groups. Finally, to add further complexity to the decision of selecting a particular dose, one needs to also consider the fact that, due to tolerability issues, not all patients completed the double-blind phase of the trial at the randomized dose. In fact, some patients in the 600 mcg bid group of responders finished the trial with a dose of 300 mcg bid, and some patients in the 900 mcg bid group of responders finished the trial with a dose of 600 mcg bid. (add specific numbers, reference table).

Figure 3: Two dose groups have substantial overlap in exposure. The box plots depict the distribution of average trough concentration at month 2 in the two dose groups. Red dots are observed data for individual patients.



8. Safety

The safety data that are provided in this NDA encompasses information obtained from the phase 2 and 3 studies conducted in patients with Cushing's disease (including extensions up to 12 months and even beyond in a few patients), from several studies conducted in healthy volunteers, from safety studies that evaluated the pasireotide effect on QT interval prolongation and liver function, as well as from mechanistic studies designed to evaluate the effect of pasireotide on glucose metabolism in general, and insulin function, in particular. At the request of the FDA, the applicant has also provided analyses for some adverse events across all indications for which pasireotide is currently developed (including acromegaly, (b) (4)). The safety datasets include 726 subjects, 201 of which are Cushing's disease patients. The 162 patients enrolled in the pivotal study represent the largest group of patients with CD reviewed by the Division to date (by comparison the recently approved Korlym pivotal trial included 50 patients). Study B2305 is the largest prospectively conducted medical intervention study for this indication. The mean exposure was close to 11 months, and about 40% of the Phase 3 trial patients have been treated for ≥ 12 months. This Phase 3 study

included not only standard safety assessments, but also evaluations that focused on disease-specific safety concerns and adverse events of interest: e.g. glucose metabolism, biliary function, QT prolongation.

This memorandum will not attempt to re-summarize the safety data that have been extensively described in the safety section of the Clinical Review (DARRTS 11/1/2012) and in the Joint Clinical Statistical Review of the November 7, 2012, Advisory Committee.

Instead, my comments will address the major safety observations, such as those related to general adverse events and specific adverse events of particular relevance to Signifor such as hyperglycemia and liver enzyme/bilirubin elevations, and their implications for dose selection.

1. General adverse events

There were no patient deaths reported while on pasireotide treatment. Serious adverse events occurred in about ¼ of patients in the pivotal trial and about 5% also resulted in treatment discontinuation. Even in the absence of a comparator, some SAEs are likely to be pasireotide-related based on either the known mechanism of action of the drug (e.g. adrenal insufficiency), or based on the already characterized pattern of adverse reactions observed with other somatostatin analogues: gastrointestinal AEs (abdominal pain, constipation, increased lipase, food intolerance) including hepatobiliary disease (cholelithiasis, cholecystitis, acute cholecystitis), QT prolongation, and carbohydrate metabolism related (diabetes mellitus, hyperglycemia, hypoglycemia, type 2 diabetes). Trial discontinuations for adverse events were seen in 17.3% patients; the pattern of such adverse events was similar to that observed for SAEs and included gastrointestinal adverse events, QT prolongation, and diabetes /hyperglycemia.

Not surprisingly given the morbidity associated with CD in general, treatment-emergent adverse events were seen in almost all patients (98%). Most frequent were those in the gastrointestinal disorders system organ class (80.9%), followed by metabolism and nutrition disorders (74.7%), and general disorders and administration site conditions (54.3%). The most frequent individual adverse events were, in decreasing order, diarrhea (58%), nausea (52%), hyperglycemia (40%), cholelithiasis (30%), headache (28%), abdominal pain (24%), fatigue (19%) and diabetes mellitus (18%). Taking into consideration the severity of the TEAEs, the most frequent Grade 3/4 TEAEs across both treatment arms were hyperglycemia (13%), diabetes mellitus (7.4%), type 2 diabetes mellitus (4.3%), increased gamma-glutamyltransferase (3.7%) and diarrhea (3.1%).

A total of 20 adverse events of special interest were analyzed in the pivotal study. They were intended to capture events that characterized Cushing's disease manifestations, or adverse events that have been associated with somatostatin analogues, as well as safety signals observed in pre-clinical studies. They are reviewed in detail by Dr. Lowy in Section 7.3.5 of the clinical review and are summarized as follows:

- Gastrointestinal events included 58% of subjects who reported diarrhea and 52% who had nausea.

- Cholelithiasis was reported for nearly one-third of subjects.
- Bradycardia was occasionally identified, but it remained generally asymptomatic.
- QT prolongation was reported in approximately 6% of subjects and no events of torsade de pointes were diagnosed (as described in Section 5 of this memorandum QT prolongation was confirmed in two thorough QT trials).
- Hypocortisolism was seen in 8.0% subjects but only about one quarter required exogenous steroid treatment and only for a short duration.
- PTT and PT/INR elevations were minimal and of no clinical relevance.
- Hemoglobin decreases were not clinically relevant.

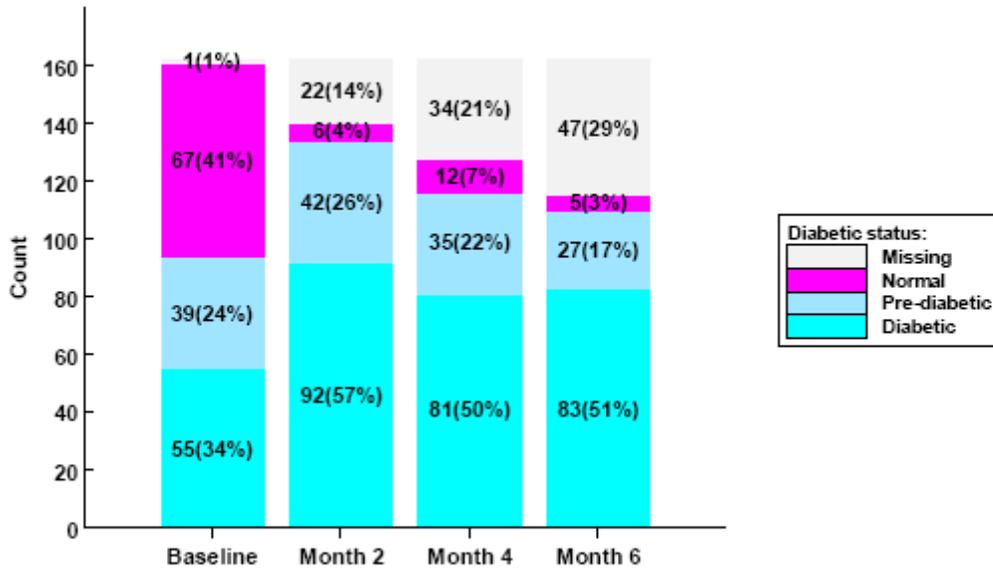
While all these adverse events should not be taken likely, as they may associated with quite significant morbidity and even mortality (e.g. QT prolongation), I believe that they can be communicated through labeling, and some of them (QT prolongation, bradycardia, hypocortisolemia, cholelithiasis) should be described in the Warnings and Precautions section. Not only they will inform of the potential risk but by making practitioners aware of their existence and magnitude, but they will help them in making decisions regarding patient selection and use of concomitant medications.

2. Hyperglycemia

Pasireotide treatment was associated with a remarkable degree of hyperglycemia, an issue of particular concern given that patients with Cushing's disease already have insulin resistance as a manifestation of the underlying hypercortisolism. In the pivotal study B2305 marked increases in fasting plasma glucose were observed as early as 2 weeks after pasireotide treatment initiation, and a mean HbA1c increase from baseline of 1.5% was seen in both dose groups by Month 2. In addition, an increase in the use of antihyperglycemic medications was observed during the trial (see Section 3.7 of the Joint Clinical and Statistical AC Review and Section 7.3.5 of the Clinical Review for details).

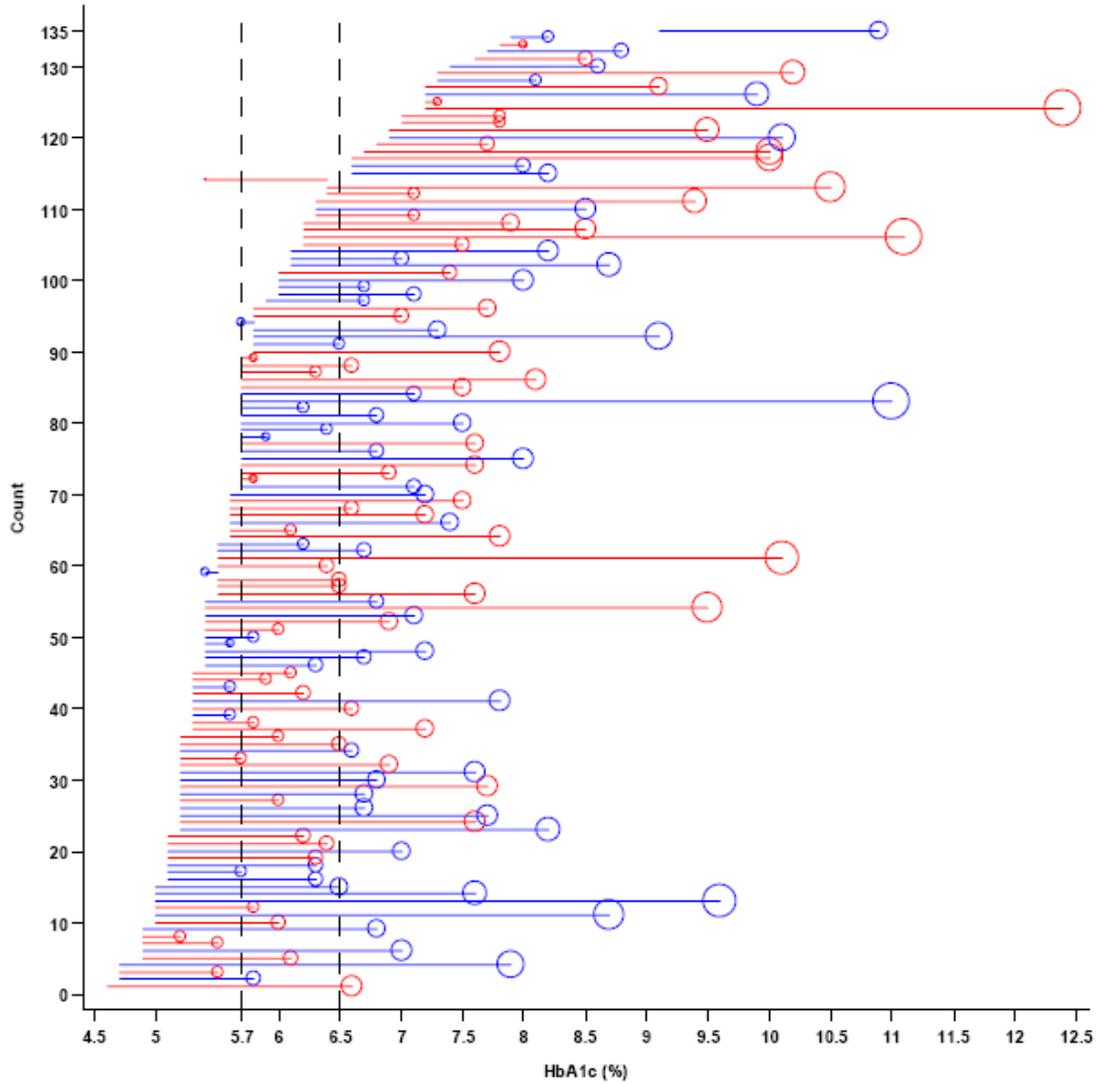
Mean fasting plasma glucose values increased similarly for the 600 mcg and 900 mcg groups from high normal values to pre-diabetic or even diabetic values. Similarly, mean HbA1c started with values slightly above the limit of normal (5.8%) and ended in a diabetic range (7.2%). Most telling of the changes in glucose metabolism status are the findings presented in Figure 12 of the Statistical Review, reproduced below, which indicates that the percentage of patients with diabetes increased from 34% at baseline to above 50% at all subsequent time points in the trial. At the other end, the percentage of patients with normal glucose status decreased from 41% at baseline to 3-7% (but a large percentage of patients did not contribute postbaseline data). The percentage of patients who were in the pre-diabetes category at baseline (24%) did not change much during the trial. A likely explanation is that some patients moved in the diabetes category while other patients shifted from the normal to the pre-diabetic category and masked the change.

Figure 12: Changes in pre-diabetes and diabetes status



A figure that complements Figure 12, in that it includes all patients (including those missing in Figure 12) is Figure 11 of the same review. It contains several important observations. First of all, it shows that most patients had elevations of HbA1c relative to baseline, regardless of the pasireotide dose. Second, that some patients had remarkable elevations in HbA1c, notwithstanding whether they were diabetic or not at baseline. Third, it indicates that there were patients with normal HbA1c at baseline that had upward but less dramatic shifts. The graph does not identify patients who discontinued treatment early in the trial and, therefore, it may overestimate the number of patients with milder HbA1c elevations.

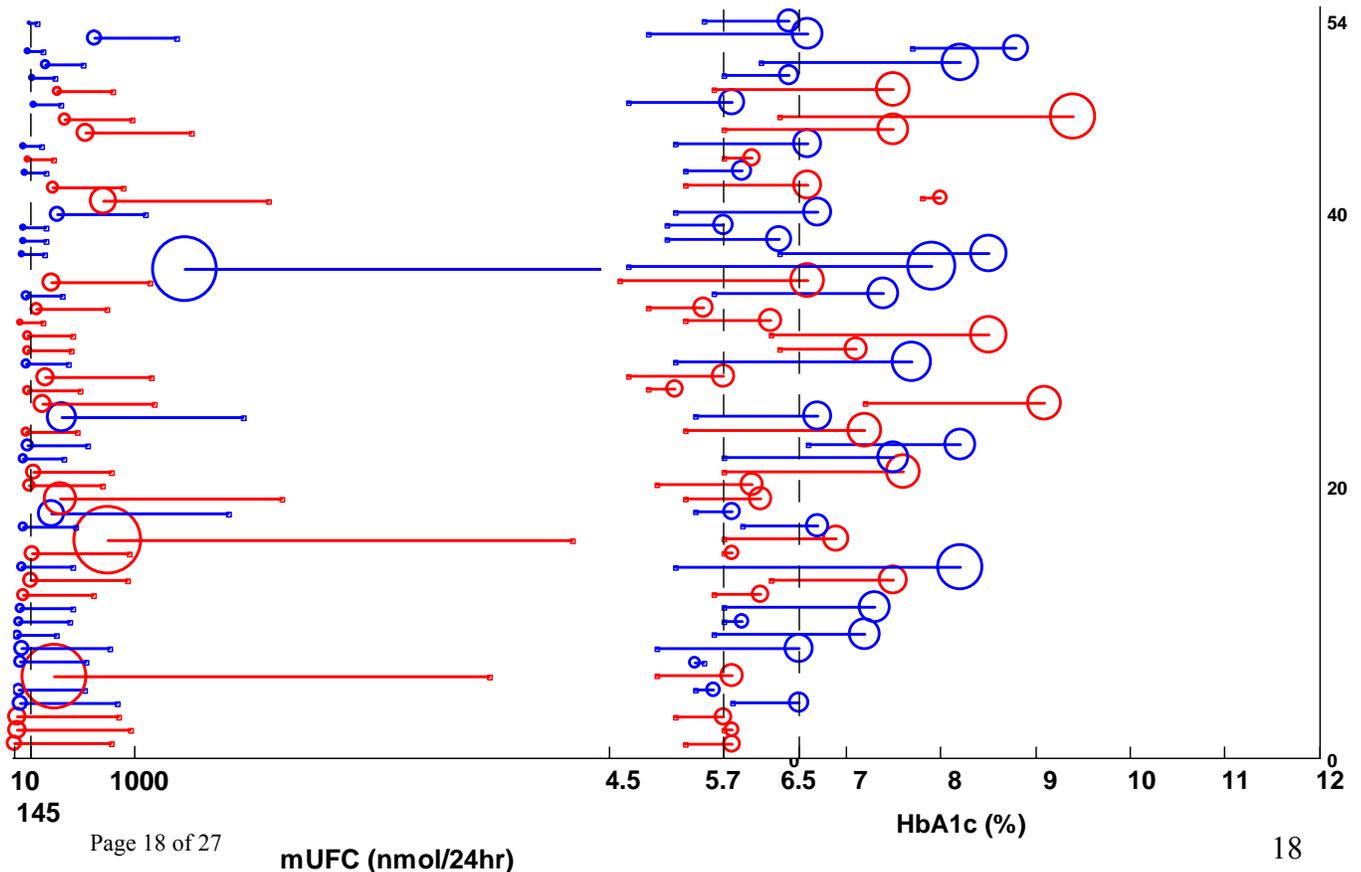
Figure 11: Individual changes in HbA1c from baseline to Month 6



Sorting is by start value
(smallest sort value at bottom)
Treatment at start:
■ Pasireotide 900µg bid
■ Pasireotide 600µg bid
○ End (sized to value of HbA1c change)

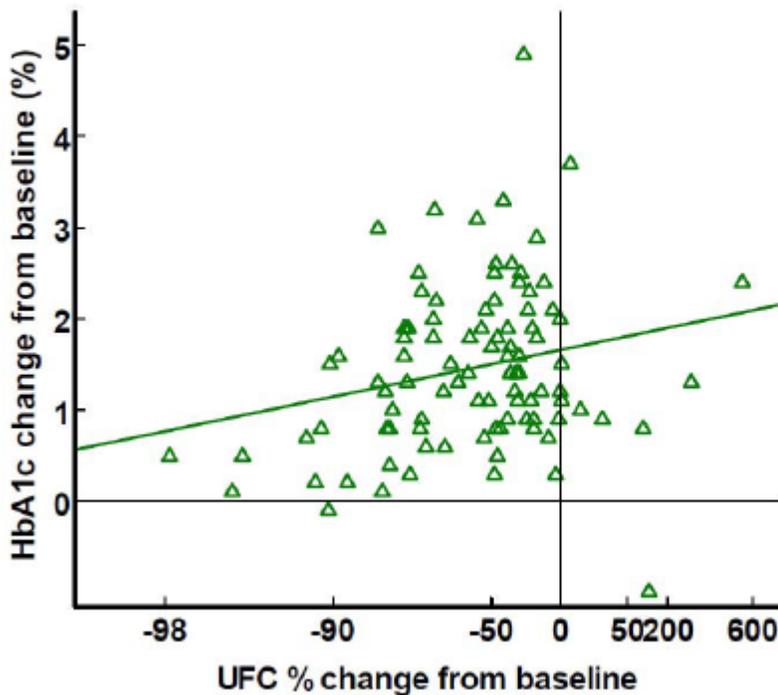
Finally another way to look at the significance of HbA1c elevations is by evaluating the HbA1c changes among the patients who get the most benefit in mUFC reduction, such as those who either normalized or had at least a 50% reduction in mUFC. The figure, below, provided by Dr. Lee Pian includes side by side the mUFC response and the HbA1c change for this subgroup of patients. Of note, as in a previous figure, the circle represents end-of-treatment values. As in previous graphs blue color represents patients in the 900 mcg dose group and in red those in the 600 mcg group; the X-axis for the left-sided graph includes the upper limit of normal of 145 mmol/24 hours for UFC, and for the right-sided graph the values for HbA1c are presented along with two important thresholds that are used for the diagnosis of pre-diabetes (5.7%) and diabetes (6.5%). Although, it is clear that all the responders included in this analysis had increases in HbA1c, it should be noted that a large proportion did not reach the diabetes range (i.e. did not have absolute HbA1c values >6.5%). Patients whose HbA1c remained below 6.5% may represent a group that has the smallest risk of hyperglycemia-related AEs and complications, while still benefiting from mUFC reductions. The totality of this information suggests that monitoring HbA1c and mUFC together can identify a patient population with maximum therapeutic benefit and the lowest risk of hyperglycemia. It should also be noted that according to Table 34 (Page 76) and Figure 14 (page 81) of the Clinical Review, mean HbA1c elevations occurred early during treatment and did not increase over time, therefore the data presented below are not part of a worsening trend.

Individual mUFC and Hb A1c changes among responders (responders are defined as having either a normalized or ≥50% reduction relative to baseline); LOCF (at or after Month 3) to Month 6.



The following analysis (Figure 15 taken from FDA’s Clinical Review), confirms that there is a subgroup of patients whose HbA1c elevations were less dramatic (e.g. <1%) and that within this subgroup some patients had substantial mUFC reductions (e.g. >90%). Overall, there was a weak positive correlation ($r=0.23$, $r^2=0.05$, $p=0.02$) between the HbA1c and mUFC change from baseline.

Figure 15 Change in HbA1c as UFC changes from baseline (Completers at Month 6)



Of note, the mechanism of pasireotide-induced hyperglycemia has been well characterized by the applicant in several mechanistic studies, and is consistent with the somatostatin receptor binding profile of pasireotide. In humans, somatostatin-related inhibition of insulin secretion is almost entirely mediated by the SSTR2 and SSTR5, and pasireotide has high affinity for both these receptors (this is in contrast with the binding profile of the other currently marketed somatostatin receptors, lanreotide and octreotide, who have lower SSTR 5 affinities and have shown less glucose elevations in clinical trials). This fact not only explains the observations made in the pasireotide clinical program, but also can be the basis for a rational approach to treating pasireotide-associated hyperglycemia with either insulin or even insulin-secretagogues (the latter that may or may not be able to override the pasireotide-induced insulin reduction).

3. Liver function

Liver enzyme elevations have been seen previously in association with somatostatin analogues, and have been also seen in the pasireotide phase 3 clinical program. Although mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values remained in the normal range for the duration of Study B2305, categorical analyses of liver enzyme elevations indicated that 5.1% patients had elevations of ALT or AST >3x upper limit of normal (ULN), and only one subject was found to have an ALT elevations >6 x ULN. These observations are consistent with our current knowledge of somatostatin analogues as reflected in the octreotide and lanreotide labels, or in the general medical literature. The general experience is that liver enzyme elevations associated with somatostatin analogues are mostly benign, transient and/or reversible.

However, several individual patient observations made during the pasireotide clinical trial raised the possibility that pasireotide may have a different safety profile. I am referring to four patients (once with Cushing's disease treated in a compassionate program and 3 healthy volunteers) who developed biochemical findings suggestive of Hy's law (ALT or AST > 3xULN and bilirubin > 2xULN)¹². All patients recovered without sequelae and, of note, the healthy volunteers were only identified retrospectively following the report of the "index case" in the compassionate use program. No other cases suggestive of Hy's law were identified in applicant's entire database, which also included studies conducted for other indications. For a detailed analysis of liver enzyme and bilirubin elevation across the whole pasireotide clinical program refer to the Clinical Review section 7.3.5.

Unfortunately the applicant did not conduct any detailed hepatological evaluations to help identify a specific cause for the changes observed in the four above mentioned patients; as previously mentioned, the three volunteers, being asymptomatic, were identified only after the respective trials were completed and were not rechallenged. Only the index case had additional information, including a work-up which indicated occasional elevation of liver enzymes prior to receiving pasireotide and a possible diagnosis of obstructive jaundice.

DMEP sought additional expertise on the interpretation of these findings and consulted Dr. John Senior, an FDA expert in drug-induced liver injury (DILI). In his consult (DARRTS 7/11/2012) Dr. Senior comments that the bilirubin elevations seen in these patients occurred either before or concomitant with the elevations in liver enzymes, that this finding is not consistent with hepatocellular injury, and that it may be "the result of some other effect of pasireotide". This was also the understanding of the Division since, as discussed in the 2009 FDA Guidance for Industry (Drug-Induced Liver Injury: Premarketing Clinical Evaluation) and in the medical literature, bilirubin elevation in DILI follows hepatocellular injury (in many cases with a delay of several weeks after the onset of liver injury) because significant hepatocellular injury has to occur before bilirubin excretion can be impaired and result in elevations of serum bilirubin.

Finally, one needs to also keep in mind that Hy's law is not a diagnosis of DILI, but rather a signal that one needs to evaluate a patient for the possibility of DILI. In the face of a missing

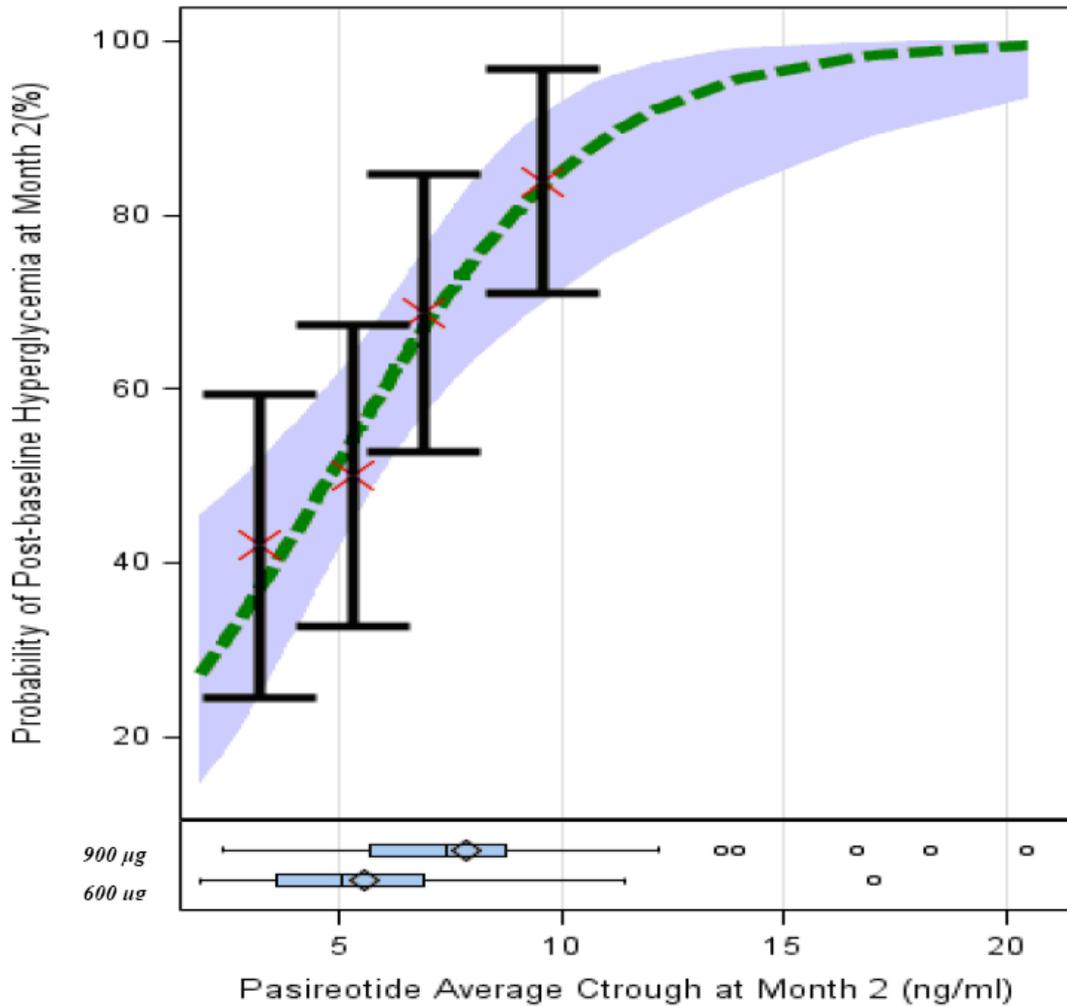
¹² It is not known if these bilirubin elevations were due to the direct or indirect fraction (or both).

comprehensive evaluation for other causes, one has to rely on indirect observations (such as the observation made by Dr. Senior regarding the timing of bilirubin increase). Of note, the issue of liver toxicity was raised as one of the issues of concern for the FDA at the November 7 Advisory Committee Meeting. The liver expert on the panel also concluded that the cases presented (and discussed in this memorandum) are not consistent with DILI.

4. Safety and dose selection

The safety profile of the two different doses evaluated in the pivotal trial was not very different. Comparisons of incidence and severity across different categories of adverse events identified only discrete differences. For instance, “drug-related SAEs” were more frequent in the 900 mcg b.i.d. group (15.0%) vs. the 600 mcg b.i.d. group (8.5%), while trial discontinuations were only slightly higher in the 900 mcg bid group (18.8% for 900 mcg b.i.d vs. 15.9% for 600 mcg b.i.d). Some of the frequencies of adverse events related to glucose metabolism were also slightly higher for the 900 mcg bid: hyperglycemia (42.5% vs. 37.8% for the 600 mcg group; diabetes mellitus 20% vs. 15.9% for the 600 mcg group). A possible explanation may be the fact that, as discussed in the efficacy section, of this memo, trough pasireotide levels were not very different between the two doses. It is worth noting that despite the absence of distinct differences in the incidence of hyperglycemia in the pivotal clinical trial between the two randomized groups, exposure-response analyses evaluating the risk of hyperglycemia suggest that higher exposure to pasireotide is associated with increased risk (see Figure 7 of the Clinical Pharmacology review reproduced below). It should be noted, however, that this graph should not be necessarily interpreted that the 900 mcg dose is expected to be associated with a higher risk of HbA1c elevations than the 600 mcg dose, but rather that patients treated with either 600 mcg bid or 900 mcg bid who have high serum levels of pasireotide are expected to have higher Hb A1c than patients with lower serum levels.

Figure 7: Increase in Probability of Developing Post-baseline Hyperglycemia (>1% HbA1c increase from baseline) at Month 2 with the Increase of Exposure in all Patients after adjusting for baseline HbA1c. Logistic regression model includes the probability of post-baseline hyperglycemia at month 2 as a function of average pasireotide concentration at month 2 after controlling for baseline mUFC (Ctough P value=0.0004; Baseline HbA1c P value=0.045). The mean and 95% CI of the observed response rate versus the mean observed baseline mUFC is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of probability of post-baseline hyperglycemia. The box plots at the bottom represent the distribution of trough concentration in each dose group.



9. Advisory Committee Meeting

An Advisory Committee meeting was held on November 7, 2012. The Division asked the AC members to comment on the following:

- The clinical relevance of efficacy analyses that looked at reductions > 50% in mUFC relative to baseline.
- The relevance of several secondary efficacy analyses that measured ACTH levels, quality of life assessments, and blood pressure reductions.
- Hepatic safety, particularly whether routine liver enzyme monitoring is necessary during pasireotide treatment, and whether any additional data or studies would be necessary to investigate the hepatic risk.
- The impact of pasireotide-induced hyperglycemia on the management of Cushing's disease: whether baseline glycemic profile should influence the decision to use pasireotide in general, influence pasireotide dose or duration of use, and how dysglycemia should be best monitored during treatment.
- Whether the favorable biochemical changes seen with pasireotide (specifically mUFC reduction) were also accompanied by meaningful changes in clinical signs and symptoms of Cushing's disease.

Since none of the above issues were voting questions but rather requests for comments, an in-depth understanding of the opinions voiced by each committee member on such a diversity of questions requires a review of the transcript. With this caveat, I would summarize the general discussion as follows:

- There seemed to be agreement that substantial reductions in mUFC, even if not associated with mUFC normalization, are clinically relevant.
- While most members recognized the limitations of the secondary efficacy analyses, in their totality, secondary analyses helped in understanding the efficacy of pasireotide and provided efficacy information beyond that of the mUFC reduction.
- The changes in blood pressure and the question of whether increases in background blood pressure medication may have driven the favorable response in blood pressure, received a lot of attention. Some members felt that the BP reductions were, at least in part, pasireotide-related.
- Panel members recommended routine liver monitoring in patients receiving pasireotide.
- There was general agreement that the increase in liver enzymes associated with concomitant bilirubin elevations that were observed in 3 healthy volunteers and in one CD patient in the compassionate program were not consistent with DILI.
- Hyperglycemia received a lot of attention and was discussed extensively in the context of risk-benefit. In final analysis many panel members commented that, as undesirable as hyperglycemia may be, there are drugs available to control it, and individualized decisions will need to be made by health care providers in an effort to minimize hyperglycemia risks. The need for monitoring for hyperglycemia was stressed.
- There were no strong recommendations that diabetes should be considered a contraindication although consideration to the glucose status at baseline should be given in deciding whether to proceed with pasireotide in such patients. Panelists

seemed to accept that hyperglycemia is as a safety issue that can to be dealt with and treated.

- Many panel members stressed the need to conduct a study that identifies an antihyperglycemic treatment that is able to lower or normalize serum glucose, and indicated that insulin is the likely treatment for pasireotide-induced hyperglycemia and needs to be evaluated.
- A postmarketing study, general pharmacovigilance, or a registry (opinions were very diverse) were felt to be necessary in order to further characterize some of the adverse events observed in the program, including hyperglycemia, and other complications such as osteoporosis and cardiovascular events.
- Panel members recognized the challenges imposed by the rarity of the disease in the ability to collect extensive pre- and postmarketing data.
- Some panelists indicated that before beginning the treatment with pasireotide patients should be informed and educated of the risk of hyperglycemia and of the kind of monitoring and potential treatment(s) that may be required.

In the end the AC panel voted 10 to 0 in favor of approval and indicated that the severity of Cushing's disease and the paucity of approved medical therapies (Korlym being the only drug approved to date) weighed heavily in favor of providing a favorable recommendation.

10. Pediatrics

Since pasireotide received orphan designation for the treatment of Cushing's disease on July 24, 2009 from the Office of Orphan Products Development, it is exempted from PREA requirements.

11. Other Relevant Regulatory Issues

Several consults have already been discussed in the context of the review (i.e. the hepatic safety consult of Dr. John Senior and the IRT consult), and will only be acknowledged here.

Financial disclosure forms were reviewed by Dr. Lowy who mentions that payments were made to a handful of investigators as educational grants, but they were unlikely to bias the result of the trial since these investigators contributed very few patients to the clinical studies.

A conditionally acceptable recommendation was issued by the Division of Medication Error Prevention Analysis for the proprietary name Signifor (DARRTS 5/16/12). A follow-up review (DARRTS, 11/28/12) conforms that the proposed name, Signifor, is acceptable.

A Patient Reported Outcome Consultation was provided by the Study Endpoint and Labeling Development group (DARRTS, 8/23/12). The review concludes that the evidence submitted by the applicant did not demonstrate a clear measurable benefit in health-related quality of life measurements. No dossier for the Cushing QoL was submitted, and this raises concerns about

the content validity of the questionnaire, which cannot be fully assessed and confirmed. (b) (4)

A DSI consult (DARRTS, 10/15/12) reports the results of inspections conducted at three sites, one in China (15 patients), one in Italy (14 patients) and one in Belgium (5 patients). At the Chinese site the inspection investigated an unusual pattern of blood pressure (BP) results that seem to lack variability in 10 of the 15 patients who were enrolled at this site (of note, similar observations were made at four other sites, but such sites enrolled only 1-2 patients). In its assessment of data integrity OSI notes that blood pressure assessments from the Chinese site should not be considered reliable, and suggests that they be excluded from secondary efficacy analyses. The rest of the data from this site appeared to be reliable. The data from the other two sites that were inspected were judged reliable as well.

The issue of lack of variability of blood pressure measurements was discussed with Novartis who indicated that at some sites BP measurements were rounded off to the nearest multiple of 5 mmHg, and this practice was identified by some study monitors and corrected. This does not appear to be the case with the Chinese site. An FDA analysis conducted by Dr. Lee Pian indicates that the mean change from baseline in systolic blood pressure excluding 16 patients from sites with low BP variability was -8.5 mm Hg, and not very different from the overall mean of - 9.1 mm Hg. Similar results were noted for the mean diastolic BP (-3.7 mm Hg excluding sites and -4.6 mm HG including all sites).

...

12. Labeling

I am in agreement with the labeling recommendations made by the other review disciplines. At the time of this review, labeling negotiations are ongoing.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I am in agreement with Dr. Lowy's recommendation for approval of Signifor as a medical treatment of Cushing's disease, assuming a favorable recommendation from the Office of Compliance regarding the GMP inspection.

- Risk Benefit Assessment

In making the above recommendation I rely on the following observations:

- Pasireotide demonstrated that it can normalize urinary free cortisol (a widely recognized and generally accepted biochemical standard of therapeutic response in hypercortisolism) in 20% of patients across doses.
- Even in patients who did not normalize biochemically, pasireotide resulted in distinct reductions of urinary free cortisol and additional biochemical changes fully consistent with these changes: serum ACTH reductions and serum cortisol reductions.
- In addition to biochemical control or improvement, pasireotide treatment was associated with evidence of clinical benefit: weight/BMI reduction, waist circumference reduction, and possibly BP reductions as suggested by a reduction in BP in a subgroup of patients who did not receive antihypertensive medications.
- Additional analyses of efficacy such as signs of Cushing's syndrome and subjective evaluations of quality of life, although not methodologically persuasive, moved in the same direction as the biochemical changes and the other clinical changes of greater reliability.
- The potential risks and adverse events associated with pasireotide treatment in patients with CD have been relatively well characterized in the pasireotide clinical program, particularly in the Phase 3 clinical trial, and most of them can be handled efficiently through labeling and appropriate patient selection.
- Clinical reviewers, experts within the FDA and outside the FDA (i.e. the AC panel) are in agreement that the concomitant liver enzyme and bilirubin elevations seen in 4 patients are not consistent with biochemical manifestations of drug induced liver injury (although no satisfactory mechanistic explanation is available to date).
- The isolated elevations in liver enzymes not associated bilirubin increases could be monitored in clinical practice.
- Hyperglycemia, which emerged as the major safety concern, can be identified early in the course of treatment, appears to be reversible upon treatment discontinuation, and as such health care providers can make a clinical decision whether continuing pasireotide treatment is in the best interest of a particular patient based on the interplay of the clinical picture for Cushing's disease, the benefit of pasireotide treatment, and the degree of pasireotide-induced hyperglycemia.
- Currently there are multiple antihyperglycemic products that can be used for the treatment of hyperglycemia if the patient and his/her physician so choose.

In making the above recommendation I am also acknowledging, in agreement with the comments made by the AC panel, that patients with Cushing's syndrome have extremely limited therapeutic choices in terms of medical treatment, and that there is a clear unmet medical need for pharmacological interventions for the treatment of hypercortisolism.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A medication Guide should be issued. The regulatory basis for this is that Signifor 1) is a "drug product [...] for which patient labeling could help prevent serious adverse effects," and 2) it has "serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use,

the product”. The medication guide should contain information regarding the adverse events that are to be expected with pasireotide treatment (gastrointestinal AEs in general, biliary AEs, QT prolongation, liver enzyme elevations, hyperglycemia and the likelihood of a need for an antihyperglycemic treatment). It should also contain specific information about glucose monitoring during pasireotide treatment, and how such information is to be communicated to health care providers in order that appropriate antihyperglycemic intervention be initiated.

- Recommendation for other Postmarketing Requirements and Commitments

The following post marketing studies are being discussed by the pasireotide review team and OSE with the applicant:

1. A clinical trial to assess hyperglycemia management in patients with Cushing’s disease treated with pasireotide.
2. A long-term prospective observational cohort study (registry) of patients with Cushing’s disease treated with pasireotide. The registry will continue for (b) (4) years from the date of last patient enrollment (b) (4) serious (treatment in Emergency Department, hospitalization) cases of hyperglycemia, liver-related adverse events (b) (4) events related to QT prolongation, (b) (4) atypical infections, and (b) (4) adrenal insufficiency.
3. Enhanced pharmacovigilance program for reports of serious (b) (4) (hospitalization, or death) hyperglycemia, acute liver injury, and adrenal insufficiency in patients with Cushing’s disease treated with pasireotide for a period of (b) (4) years from the date of approval to collect data that will be analyzed to better define these risks. (b) (4)

- Recommended Comments to Applicant

None. The finally agreed label and list of postmarketing studies should be communicated in the Action Letter.

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/s/

DRAGOS G ROMAN
11/30/2012

MARY H PARKS
12/03/2012