CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200677Orig1s000

SUMMARY REVIEW

Division Director's Memo

Date	December 13, 2012
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	200677
Applicant Name	Novartis Pharmaceuticals Corp
Date of Submission	February 17, 2012
PDUFA Goal Date	December 17, 2012
Proprietary Name / **Established (USAN) Name**	Signifor® (pasireotide)
Dosage Forms / Strength	300, 600 and 900 ug
Proposed Indication(s)	Cushing's Disease
Action/Recommended Action for NME:	Approval

1. Introduction

Cushing's disease is a state of endogenous hypercortisolism resulting from over-secretion of ACTH from a pituitary adenoma. The chronic exposure to elevated cortisol levels results in classic clinical Cushingoid features of moon facies, buffalo hump, increased supraclavicular fullness, hirsutism, bruising, and violaceous straie and co-morbidities such as diabetes/glucose intolerance, hypertension, muscle weakness, depression and osteoporosis.

The diagnosis of Cushing's disease requires a multitude of laboratory and radiologic tests whose discussion extends beyond the scope of this memo. The objective of the laboratory tests is to demonstrate inappropriate and sustained hypercortisolism to distinguish these patients from conditions such as pseudo-Cushings, severe depression, or cyclical Cushing's. In addition, establishing that the excess cortisol production is an ACTH-dependent process as opposed to ACTH-independent (e.g., adrenal adenoma) and then to establish that the source is pituitary, not an ectopic ACTH source, is critical for directing treatment.

The first-line therapy for Cushing's disease is surgical resection of the adenoma. Complete resection is curative but this is highly dependent upon surgical experience and even then, recurrence has occurred wherein repeat surgery has a lower success rate. Pharmacologic therapy is often considered second-line therapy along with radiation therapy. Bilateral adrenalectomy is a consideration after other therapies have been exhausted.

Current medical therapies employed to treat Cushing's disease target a reduction in adrenal steroid production or blocking glucocorticoid receptor activity. There is no drug specifically approved for the treatment of Cushing's disease; several are used off label; and only Korlym (mifepristone) is approved for a subset of patients who have Cushing's syndrome and diabetes/glucose intolerance requiring glycemic control.

Pasireotide is a somatostatin analogue targeting the pituitary adenoma through inhibition of the somatostatin receptor (SSTR) 5 which is over-expressed in these tumor cells. It is this novel mechanism of action that sets pasireotide apart from other approved somatostatin analogues, both in terms of efficacy and safety.

2. Background

Much of the regulatory history and background for pasireotide development have been clearly summarized by Dr. Dragos Roman in his Cross-Discipline Team Leader memo dated 30 November 2012.

Pasireotide is an analogue of the natural peptide hormone somatostatin. Somatostatin and their receptors are distributed throughout the body wherein activation of these receptors regulates endocrine and exocrine secretion. There are 5 SSTRs referred to as sst1, sst2, sst3, sst4, and sst5. While octreotide and lanreotide, both approved for acromegaly (octreotide is also approved for carcinoid and VIPomas), have high affinity for sst2, pasireotide has higher affinity for the remaining SSTRs, especially sstr5, which is highly expressed in ACTH-secreting pituitary adenomas. Prior experience with octreotide and lanreotide provided clues on expected safety concerns; however, the difference in receptor binding affinities also conferred a different safety profile with regard to glucose intolerance.

The clinical program was designed to evaluate the effect of pasireotide on the reduction of urinary free cortisol, an accepted biomarker for screening, diagnosis, and monitoring of treatment response. Because of the rarity of Cushing's disease and its progressive nature, clinical trial designs were limited by the size of the population and the ethics of having a placebo arm. These limitations present challenges to interpretation of both efficacy and safety of pasireotide.

3. CMC/Device

Please see review dated 16 October 2012 authored by Dr. Olen Stephens.

CMC has recommended approval pending final recommendations from Office of Compliance's GMP inspection.

4. Nonclinical Pharmacology/Toxicology

Please see review dated 4 October 2012 authored by Dr. Miyun Tsai-Turton.

Pharmacology/toxicology recommended approval with no additional studies requests postmarketing.

5. Clinical Pharmacology/Pharmacometrics

Please see review dated 25 October 2012 authored by Sang Chung.

Both disciplines have found the NDA acceptable and no postmarketing studies are recommended.

6. Clinical Microbiology

Please see review dated 3 July 2012 authored by Bryan Riley.

Microbiology recommends approval with no additional postmarketing studies.

7. Clinical/Statistical-Efficacy

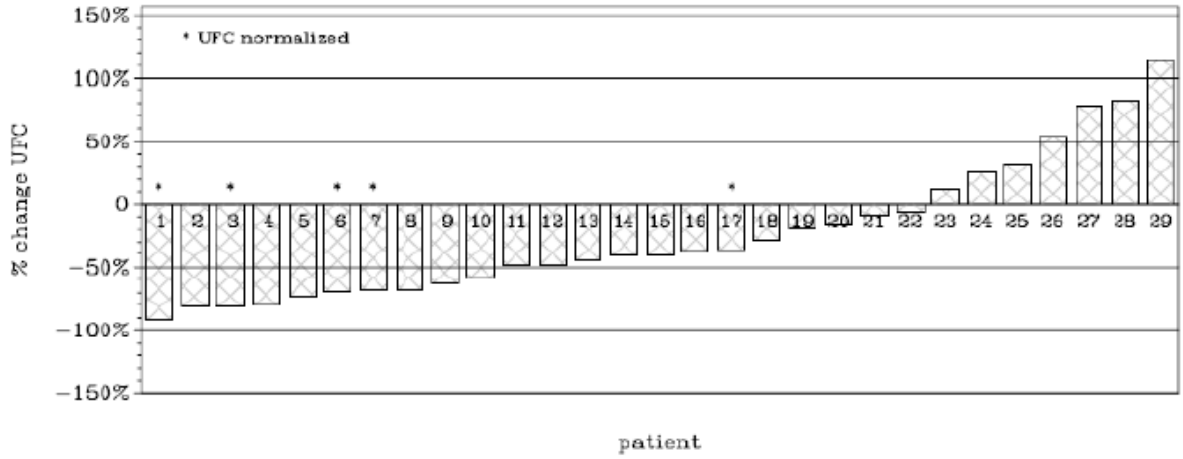
Primary Efficacy Results

The clinical efficacy of pasireotide for the treatment of Cushing's disease was evaluated in one Phase 3 pivotal study (Study 2305) and a Phase 2 proof-of-concept study (Study 2208). Please see reviews by Drs. Pian, Lowy, and Roman for a detailed discussion on their design, conduct, and results.

Dose selection in both of these studies came from PK studies in healthy volunteers and in vitro SSTR5 binding affinity studies. A trough concentration of ~ 2 ng/mL was considered the minimum concentration for receptor binding and was the targeted exposure level for dose selection in the patient population. PK simulation from healthy volunteer studies predicted the 600 ug bid dose to yield approximate peak and trough levels of 16 and 2 ng/mL, respectively.

Study 2208 was a 15-day, open-label, single-arm trial in 39 patients with Cushing's disease evaluating only the 600 ug sc bid dose. The primary efficacy endpoint was normalization of mUFC at the end of 15 days. Primary efficacy analysis was performed on 29 patients as 10 were excluded to due major protocol deviations. Only 5/29 (17.2%) had normalization of mUFC by Day 15. The baseline UFCs in these 5 patients were quite variable, ranging from 299 to 2546 ug/dL with accompanying reductions from baseline ranging from as 36% to a maximum of 92%. The individual response across all 29 patients was also variable as illustrated in the following figure from Dr. Lowy's review.

Figure 1. UFC response in Phase 2 Trial



Clinical Study Report, Figure 11-1

Although the Cmin and max fell within the range of a predicted receptor binding affinity (~5 to 22 ng/mL), the exposure analysis in the 5 responder patients revealed higher PK levels leading the applicant to study a 900 ug bid dose in their Phase 3 trial.

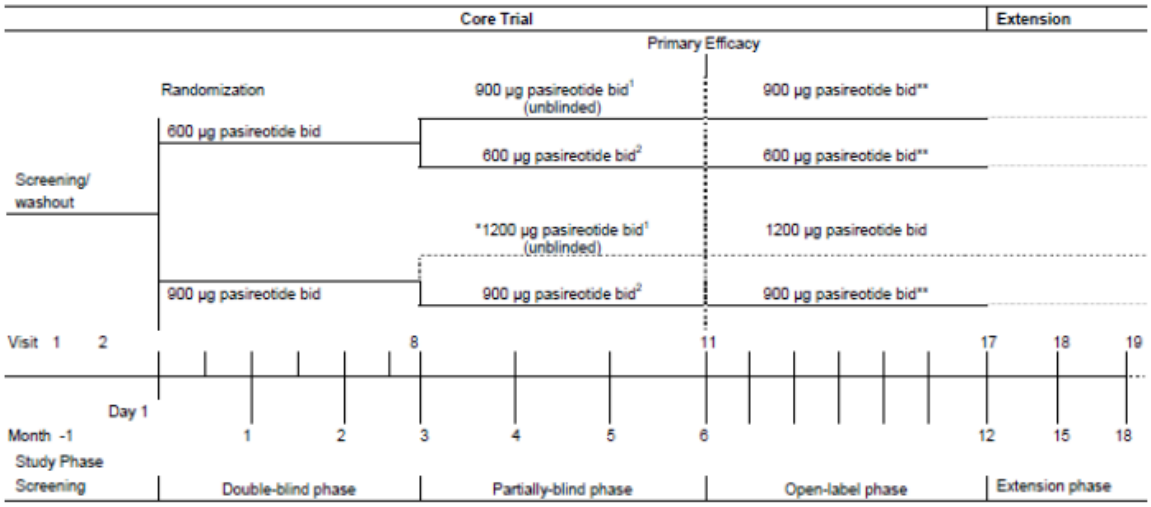
As noted by Dr. Roman, Study 2305 underwent several revisions with input from FDA. Among these revisions included one which extended the original trial duration of 3 months to a 6-month trial with an additional 6-month extension. The extent of treatment and follow-up and the size of the study population should not be overlooked as attributes of this program given the more limited data available for currently employed medical therapies (i.e., smaller studies of shorter duration or case reports).

Study 2305 was a 12-month, randomized, double-blind trial enrolling 162 patients with Cushing's disease who had failed pituitary surgery or were not candidates for surgery. Patients were randomized to the 600 ug or 900 ug bid doses. Keypoints in the timeline of this trial were at:

> Month 3: decision to continue on randomized dose and maintain blind, up-titrate dose and unblind patient/investigator, or discontinue patient from the trial was made based on whether the mUFC was ≤ 2xULN and ≤ the baseline UFC.
>
> Month 6: primary efficacy endpoint analysis performed at this point. Beyond this point all patients were unblinded and entered an open-label treatment period where they would remain on their current dose if a responder. Non-responders could have the dose increased to a maximum daily dose of 1200 ug bid.

A figure provided by the applicant depicting this study design that has also been referred to by FDA staff is repeated here:

Figure 7-1 Design of Phase III study B2305 in patients with Cushing's disease



[1] Patients with baseline UFC ≥ 2xULN and Month 3 UFC >2xULN or baseline UFC < 2xULN and Month 3 UFC > baseline UFC
[2] Patients with baseline UFC ≥ 2xULN and Month 3 UFC ≤ 2xULN or baseline UFC < 2xULN and Month 3 UFC ≤ baseline UFC
* Permitted dose increase if patient had tolerated 900 µg b.i.d.
** During open-label phase dose could be increased by 300 µg at any time if response was lost
All doses could be reduced by 300 µg at any time for tolerability
China only: doses higher than 900 µg b.i.d. were not allowed

A **responder** was defined as any patient who attained a mUFC ≤ ULN at Month 6 and whose dose was not increased after Month 3. Those patients who required an up-titration at Month 3 were counted as non-responders in the primary efficacy analysis, even if the dose increase resulted in normalization of UFC. Those patients who had missing UFC data at Month 6 had their last available value between Month 3 and 6 imputed.

The primary efficacy endpoint was the proportion of responders, summarized as a point estimate with a calculated 2-sided 95% CI. As there was no placebo control arm, determination of what constituted a significant response to treatment was arbitrarily defined as a lower bound in the 95% CI exceeding 15%. Based on recommendations from experts in this field it was acknowledged that spontaneous improvement in Cushing's disease is rare and demonstration of the proportion of responders exceeding 15% could be reasonably attributed to pasireotide.

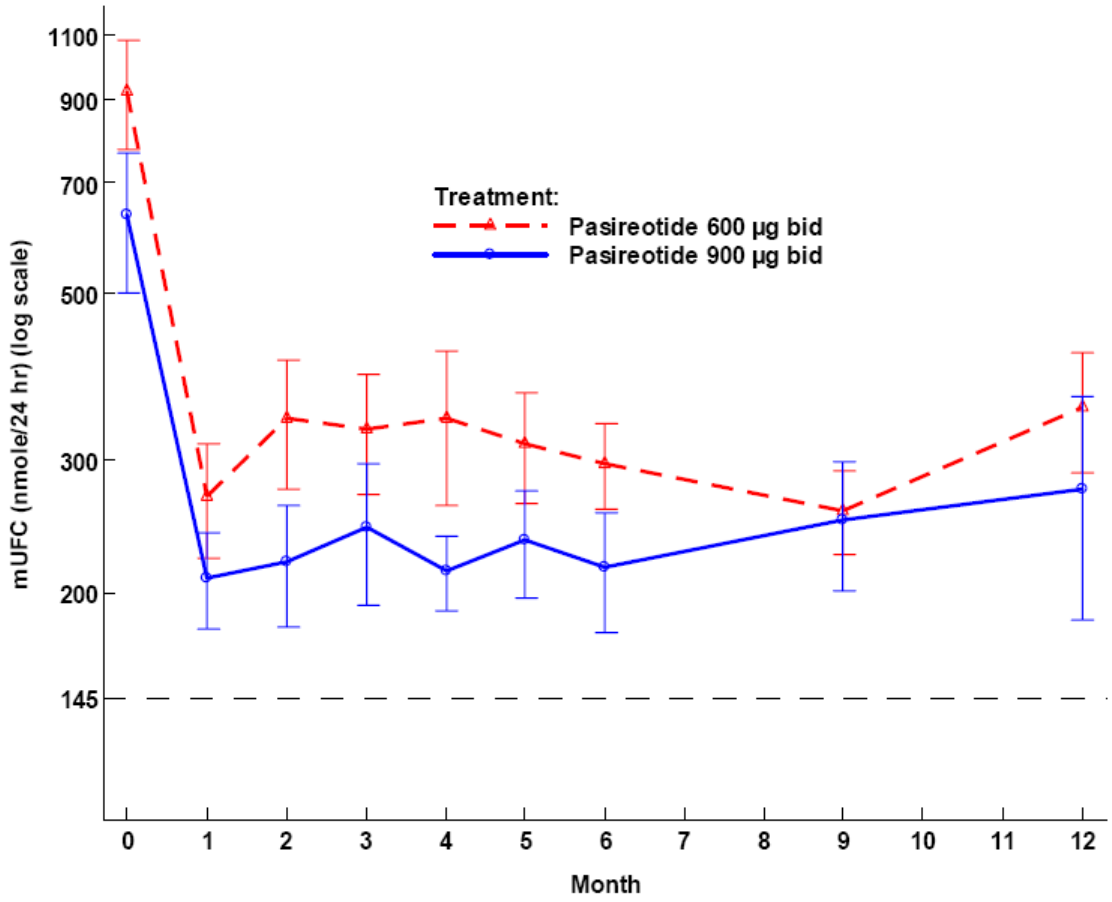
The following table from Dr. Lee Pian's review summarizes the primary efficacy analysis. FDA confirmed the sponsor's analysis and also performed a sensitivity analysis to control for Type 1 error between the two doses. In both analyses, the 900 ug bid dose met the pre-defined criterion for declaring a statistically significant treatment effect.

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%]	

As noted above, the criterion for declaring a statistically significant treatment effect was an arbitrarily set one and the absence of a placebo arm precludes us from declaring that the effect observed with the 600 ug bid dose was also significant. In addition, the trial was not powered to demonstrate a difference in effect between the two doses. And finally, while the trial randomized patients to the two different doses, a numeric imbalance in the baseline UFC might also contribute to the lower rate of UFC normalization in the 600 ug bid group. All these points have been discussed at length in the clinical, statistical and clinical pharmacology review and I will not reiterate them in this memo. Additional exploratory analyses were performed by Novartis and FDA with results supporting a conclusion that the 600 ug bid dose could also be considered a clinically effective dose option. The following figure from Dr. Pian's review does highlight the response to treatment in both dose groups in patients who completed 12 months of therapy. I believe this figure does highlight the difference in baseline mUFC between the two dose groups and the effect on mUFC over time in patients who were responders and remained on therapy for this duration.

Figure 2: Mean (±SE) Urinary Free Cortisol (nmol/24h) at all Time Points up to Month 12 by Randomized Dose Group (Completers, n=39/group)



While relying on these exploratory analyses to conclude effectiveness of drug therapy seems to violate a tenet of clinical trial design, conduct, and interpretation, there was an overall agreement among FDA, applicant, and the advisory committee panel members that the data in the 600 ug bid group does show that for some individuals, the mUFC reduction was clinically relevant and the availability of this dose as a treatment option will allow for individualization of therapy to achieve an optimal benefit-risk profile for any one patient.

There was a difference in interpretation of dose-response between reviewers in the pharmacometrics team and clinical/statistical team which led to different recommendation on recommended start dose. Based on exposure-response analyses, the pharmacometrics reviewers did not believe a proposed initial start dose of 900 ug bid was supported. They further stated that this dose has a higher probability of inducing hyperglycemia over the 600 ug bid dose. Exposure-response relationship was determined by evaluating average trough concentration plotted against the endpoint of interest (probability of normalizing UFC or experiencing hyperglycemia). The statistical reviewed observed data of each of the randomized treatment groups and this analysis did not reach similar conclusions. Given the

high inter-patient variability for drug exposure there is a substantial overlap in exposure levels between these two dose groups which may account for different discipline observations. After discussions with the review team there was agreement that the label did not need to be prescriptive in a start dose but that a recommended dose range with clinical data to guide physicians in selecting dose for initiation and maintenance would be more appropriate.

Secondary Efficacy Endpoints

Other secondary endpoints were evaluated by the applicant including changes in BP, BMI, weight, waist circumference, lipids, physical features (facial rubor, striae, bruising, supraclavicular fat pad, dorsal fat pad, and muscle strength), tumor volume, ACTH levels, and health-related QOL. Caution should be applied when relying on these secondary efficacy endpoints as evidence of pasireotide's effectiveness for a variety of reasons. For the subjective measures, patients or physicians may report improvements perceived because of trial participation and not actual drug effect. The absence of a blinded placebo group limits interpretability of these subjective endpoints. Dropouts and discontinuations can also result in an enriched subgroup of patients for some of these secondary endpoints, especially since data from discontinued patients were not imputed for secondary efficacy endpoints. (b) (4)

The biochemical/objective measures considered included ACTH, serum, and midnight salivary cortisol levels, BP, BMI, weight, waist circumference, and lipid changes. Mean ACTH levels decreased in both treatment groups. Similarly, serum and salivary cortisol levels paralleled the findings of mUFC reduction. Overall, these biochemical changes reflect the pharmacologic mechanism of action of pasireotide and provide no further information on improved morbidity or mortality of Cushing's disease.

In both dose groups there was a mean reduction from baseline in both sitting systolic and diastolic blood pressure.

Table 20 Mean change from baseline in blood pressure by randomized dose group at Month 6

Pasireotide 600 µg bid N=82			Pasireotide 900 µg bid N=80		
n	Baseline mean (SD)	mean (SD)	n	Baseline mean (SD)	mean (SD)
Sitting systolic blood pressure, mmHg					
59	132 (20)	-6.8 (19.4)	57	138 (20)	-11.4 (15.9)
Sitting diastolic blood pressure, mmHg					
59	86 (13)	-4.2 (13.5)	57	89 (11)	-5.0 (11.6)

Clinical Study Report

Adjustments and initiation of anti-hypertensive medications were allowed in this trial at the discretion of the investigators. However, information on use of such drugs and their doses were not systematically recorded beyond a standard data collection for concomitant medication use. In reviewing these data, Dr. Lowy noted that while there was a mean blood pressure reduction, overall use of anti-hypertensives did not decrease and in most classes there

was a slight increase from baseline (Figure 9 in Dr. Lowy's review). This disconnect did raise the possibility that the mean BP reductions were not entirely attributable to pasireotide but may have been due to increases in anti-hypertensive medications.

The applicant noted at the advisory committee that there was a marked reduction in both systolic and diastolic blood pressure from baseline observed in a subpopulation of patients with hypertension who did not receive any anti-hypertensives during the trial (n=16). In the absence of any anti-hypertensive medications, such a reduction was postulated to be due to pasireotide. However, the absence of a placebo arm and the small number of patients does limit one in concluding definitively on the positive effects of pasireotide on treating hypertension associated with Cushing's disease.

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

The effect of pasireotide on BMI, weight, and waist circumference was modest but trended in the direction of improvement. Its effect on lipids was neutral.

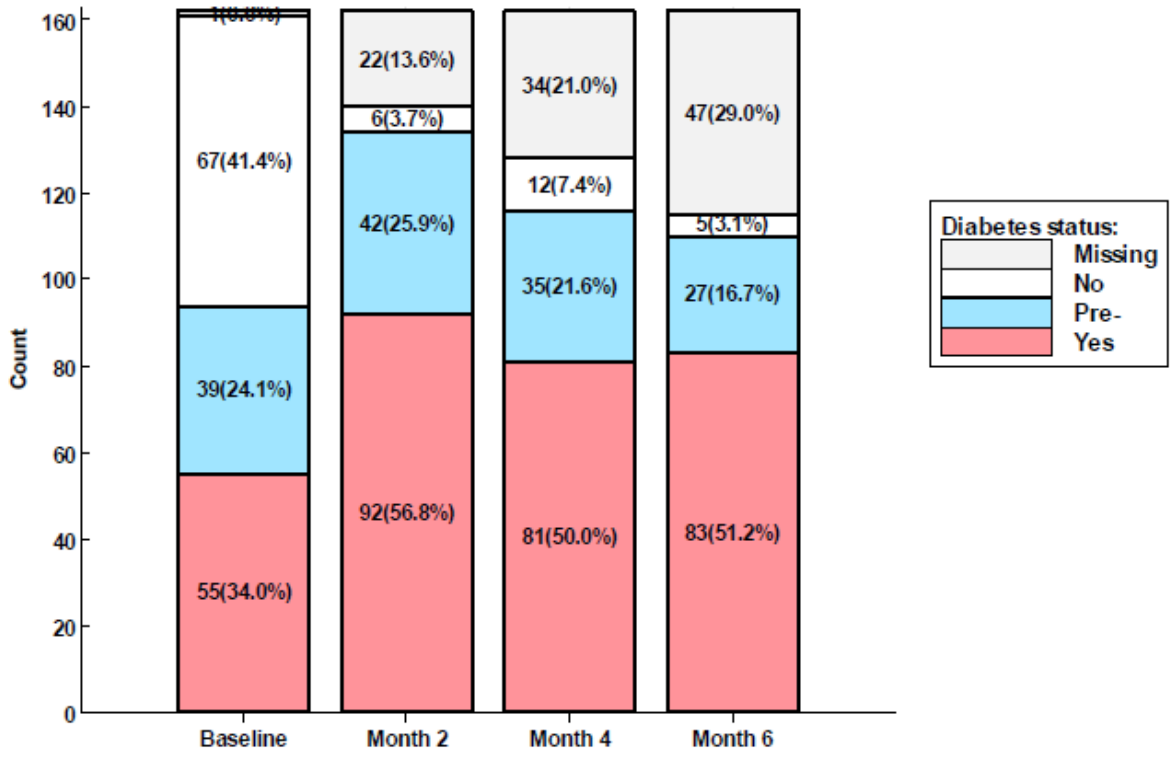
8. Safety

The evaluation of safety of pasireotide was not limited only to the trials in patients with Cushing's disease but also included data from the INDs for acromegaly and gastroenteropancreatic neuroendocrine tumors. Dr. Lowy has provided a detailed review of the clinical safety of pasireotide for which I will highlight only two issues brought before the advisory committee panel – dysglycemia and liver safety. Other safety concerns noted in the class of somatostatin analogues (e.g., QTc prolongation, cholelithiasis) are not approvability issues and while they need to be considered in the safe use of this product, these can be addressed in labeling which is being undertaken by the review team. Please see the specific discipline reviews for further details on safety findings in this program.

Dysglycemia

It was anticipated that pasireotide, like other somatostatin analogues, could cause glucose intolerance and diabetes but the extent to which it did this was not fully appreciated until Trial

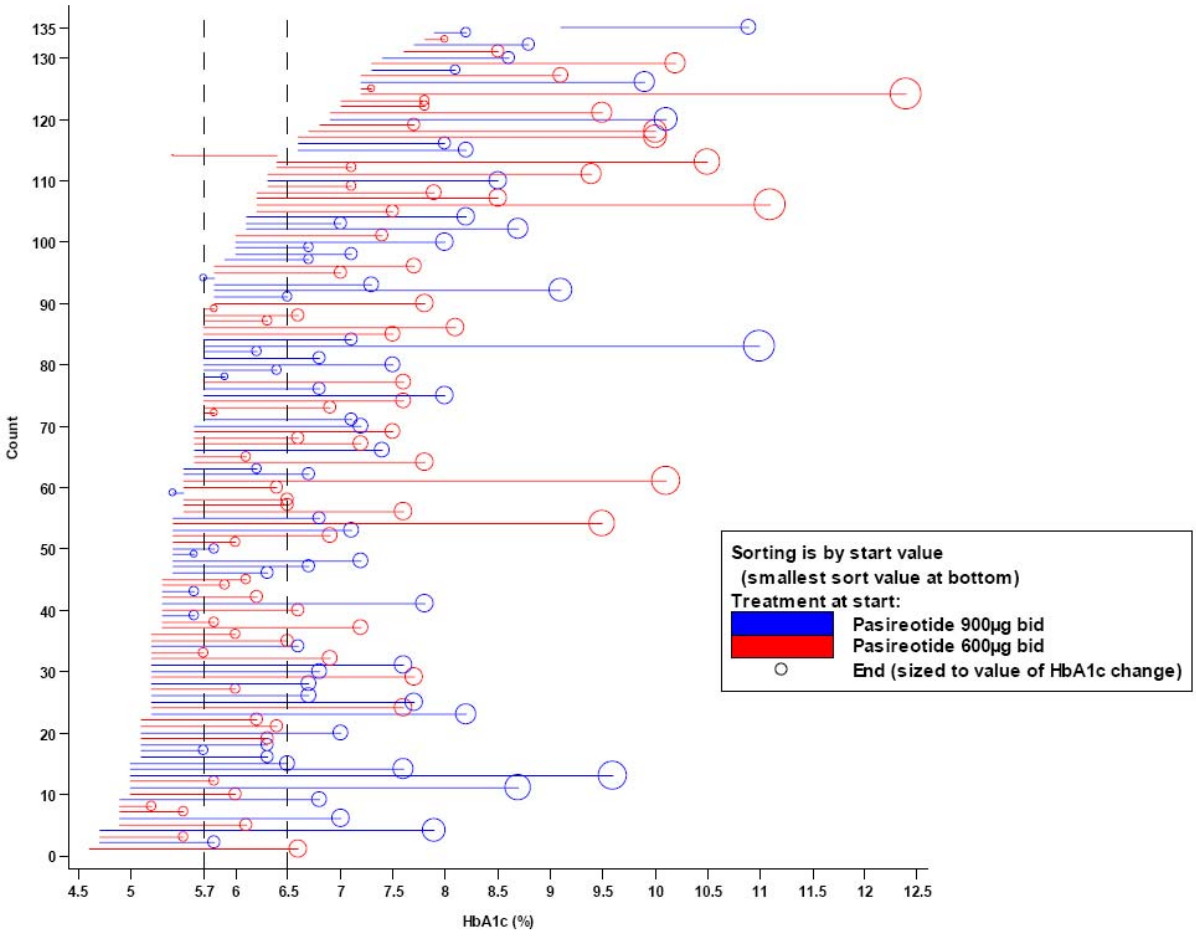
2305 was conducted. In this trial it was observed that the majority of patients had worsening glycemic status over time. The following figure displays the change in glycemic status from baseline at Month 6 in all patients.



At baseline, approximately 41% of patients had normal glycemic status but this proportion decreased to just 3%. Conversely, the proportion of patients with diabetes increased from 34% at baseline to approximately 51% by Month 6. Due to discontinuations, glycemic status was missing in a sizable percentage of patients throughout the trial but many patients discontinued due to poor glycemic control so it would be reasonable to predict even higher percentage of patients with pre-diabetes and diabetes by Month 6 if these patients were able to remain in the study.

To further illustrate the change in HbA1c on any individual in this trial, the following figure displays these data in 135 patients who had baseline and post-baseline values out to Month 6 (or carried forward if missing). Each line represents one patient's baseline and Month 6 HbA1c value. Any horizontal line with the round circle to the right represents worsening glycemic status. No statistical test is necessary to conclude that the vast majority of these patients had worsening glycemic status as one can count all but 3/135 patients displaying the round circle to the right of the line.

Figure 12: Individual changes in HbA1c from baseline to Month 6



Upon recognizing the adverse effect pasireotide had on glucose metabolism, the applicant conducted several mechanistic studies to elucidate the mechanism and evaluate what anti-diabetic therapy could best manage dysglyemia in these patients. Dr. Lowy's review summarizes the results from these studies but in brief, it is postulated that pasireotide impairs insulin secretion and has little effect on insulin sensitivity. A 7-day study evaluating the impact of different anti-diabetic therapies co-administered with pasireotide suggests incretin mimetics (DPP4-inhibitors and GLP-1 analogues) to play a greater role in glycemic management of these patients and metformin to have little impact.

It was suggested that because many patients in Study 2305 were treated with metformin, glycemic status was poorly controlled because of inappropriate therapy selection. However, as noted by the applicant at the advisory committee, management of diabetes in this program was not strictly enforced. In fact, one might argue that diabetes was mismanaged in this program. From Table 38 in Dr. Lowy's review, approximately 47% (n=76) of the 162 patients in the pivotal study did NOT have anti-diabetic treatment during the trial. Upon further inquiry, Dr. Lee Pian provided us with the following information on these 76 patients: 56 (70%) were non-

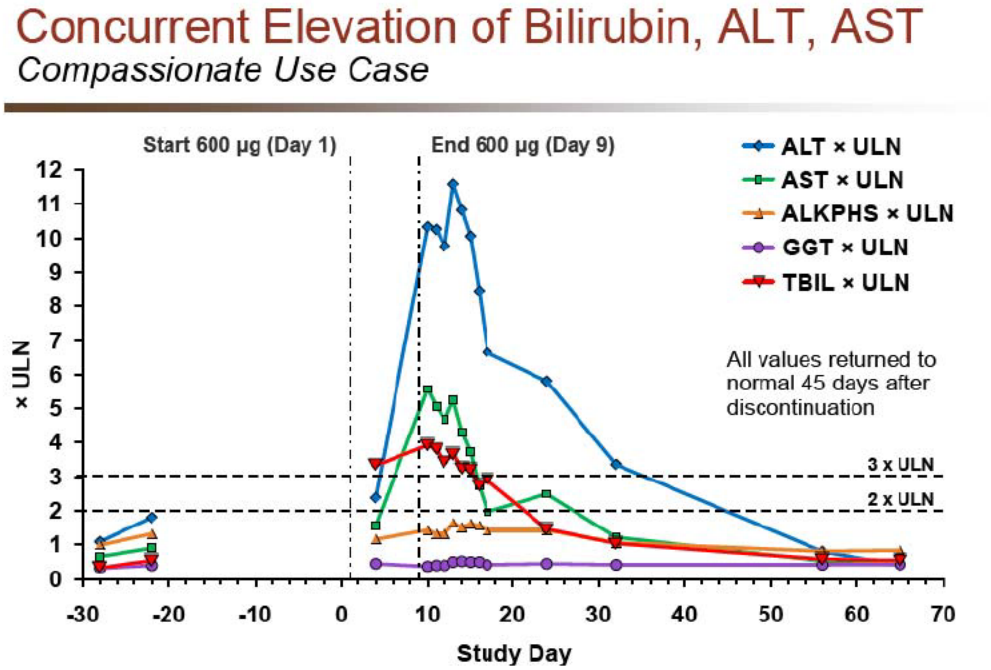
diabetic at baseline and only 5 (7%) remained non-diabetic at Month 6. This would mean that 30% (20) of these patients were either pre-diabetic or diabetic at baseline and why they were not treated at baseline is not clear. Based on Figure 12, it is not unreasonable to assume that some of the remaining 71 patients developed diabetes (or those of the 20 who might have had diabetes at baseline likely worsened) and while diabetes might be managed with diet and exercise alone it is unlikely to work in pasireotide-treated patients. Whatever the reasons for these patients not being appropriately treated, should pasireotide be approved, the adverse effect pasireotide has on glucose metabolism must be clearly conveyed in patient and prescriber information and aggressive monitoring for and treatment of diabetes must be practiced by prescribers.

The FDA review team has discussed extensively the impact of dysglycemia on the approvability of pasireotide. The argument against approval has hinged on the fact that while pasireotide reduces UFC, this remains a laboratory marker of hypercortisolism and not a clinical symptom of Cushing's disease. That hypercortisolemia results in glucose intolerance and dyglycemia challenges the logic of using pasireotide in the treatment of Cushing's disease. A discussion question on this very issue was posed to the advisory committee panel. I will discuss this further under Section 9 and 13 of this memo.

Liver Safety

In 2010 a safety report was submitted to the IND of a patient with Cushing's disease who was receiving pasireotide under a compassionate use IND. This case was of a 37 yo woman whose baseline labs were notable for an ALT that was elevated at 1.8x ULN and alkaline phos of 1.3x ULN. On Day 9 of treatment her ALT increased to 10x ULN and she developed nausea, vomiting, and jaundice. Pasireotide was discontinued on Day 10 and all liver tests normalized 45 days after drug discontinuation. The following figure presented by the applicant at the advisory committee meeting illustrates the time course of this patient's liver abnormalities.

Figure 2. Time course of liver test abnormalities for Subject PHH02010AU13717



Upon receipt of this case additional information was requested of Novartis including an exhaustive search of their entire clinical development program, not limited to just Cushing's disease. No other cases of potential Hy's law was identified in the Cushing's program; however, 3 healthy volunteers did develop ALT elevations > 3x ULN with accompanying bilirubin increase > 2x ULN. These 3 cases are described by Dr. Lowy on pages 95-97 of her review. The ALT elevations and bilirubin in these 3 cases never exceeded 4x ULN and bilirubin increases either preceded or occurred concurrently with the transaminase elevation. No serious clinical sequelae resulted in any of these four cases.

ALT or AST elevations > 3x ULN in the Cushing's disease program occurred in 4.7% of patients; however, the absence of a control limits interpretation of this finding. A controlled study comparing a long-acting preparation of pasireotide to the approved octreotide in 60 patients with acromegaly did not note any difference in rates of transaminitis or hyperbilirubinemia.

The totality of data for liver safety was presented before the advisory committee. Overall, the committee, in particular the hepatologist, did not consider the findings to be evidence for pasireotide-induced serious liver injury. The observation of hyperbilirubinemia preceding or coincident with mild transaminase elevations was not considered to be typical of drug-induced hepatocellular injury.

9. Advisory Committee Meeting

This NDA was presented at the Endocrinologic and Metabolism Drugs Advisory Committee (EMDAC) on November 7, 2012. There was one voting question pertaining to the approvability of pasireotide for Cushing's disease worded as follows:

> 5. Based on the information in the briefing material and the presentations from today, do you believe the applicant has provided sufficient evidence for efficacy and safety to support marketing of pasireotide for the treatment of Cushing's disease?
>
> - If yes, please provide the rationale for your vote and whether any additional studies should be conducted post-marketing.
> - If no, please provide the rationale for your vote and what additional data will be necessary pre-marketing.

A unanimous vote of 'yes' was rendered by the committee. While the transcripts are not yet available, the following points were conveyed by members in their recommendation:

- There are limited options for the treatment of Cushing's disease and this program, while not without limitations and safety concerns, had a robust assessment of the efficacy and safety relative to other available therapies.

- The glycemic risk was acknowledged to be of concern but many members still felt that physicians could either treat with the many available anti-diabetic therapies or discontinue if unable to control. A clinical trial to further investigate the most effective treatment regimen for glycemic control was considered necessary. Some recommended that poorly controlled diabetics have their diabetes optimized prior to initiation of therapy. Careful monitoring throughout treatment was necessary but specifics of monitoring were not outlined.

- The liver safety findings were not of sufficient concern to hinder availability of pasireotide although monitoring of patients while on therapy, including for development to cholelithiasis, was recommended. Specifics were not outlined.

- When asked to discuss whether pasireotide's effect on UFC levels is accompanied by meaningful changes in the clinical signs and symptoms of Cushing's disease, several endocrinologists commented on some of the secondary efficacy findings (e.g., weight loss, physical features) as evidence of a positive correlation.

My general impression of the advisory committee recommendation was that they found the effect of pasireotide on reducing hypercortisolism sufficient enough evidence for expected clinical benefits and that the glycemic risk was one that could be managed or eliminated upon drug discontinuation. Because of the limited therapeutic options for Cushing's disease, several committee members stated that we should not withhold approval to await

the 'perfect' drug when all currently available therapies carry their own unique risks and have been less well-studied than pasireotide.

10. Pediatrics

There is no proposed pediatric development plan for pasireotide and given its orphan status, this NDA is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

Please see reviews by Drs. Lowy and Roman.

12. Labeling

Labeling negotiations are currently underway between FDA and the applicant. A Medication Guide (not part of a REMS) and Instructions for Use were also submitted by the applicant and are currently under review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Novartis was able to demonstrate effectiveness of pasireotide on reducing urinary free cortisol levels, an established biomarker for diagnosing and monitoring response to treatment of Cushing's disease. However, the main goal of treating Cushing's disease isn't just to normalize or reduce elevated cortisol levels. It is to reduce the complications resulting from hypercortisolism – complications which include but are not limited to diabetes, hypertension, infections, depression, osteoporosis, and muscle weakness. Cardiovascular events have a prominent role in the excess morbidity and mortality in these patients; however, the effect of any intervention on Cushing's disease on this long-term complication as well as others (e.g., increase risk of fractures) can not be captured in any clinical development program given the length of follow-up required in a controlled trial of adequate sample size – impractical in an orphan disease. Consequently, this program was limited to reliance on biomarkers or more proximal clinical outcomes.

Pasireotide undoubtedly causes glucose intolerance and this adverse side effect is seen almost immediately with elevations in fasting plasma glucose noted within 2 weeks of drug initiation. Continued exposure to therapy results in worsening glycemic control as evidenced by increasing HbA1c. Even in the absence of a control, one can attribute this effect to pasireotide given the time course of events and also the improvement of dysglycemia upon drug

discontinuation (positive dechallenge). This safety outcome has raised internal discussion on whether a drug should be approved based on improvements of a biomarker but worsening of a clinical outcome of the disease.

Worsening glucose control in the face of reducing cortisol levels seems a contradiction to treatment of Cushing's disease with pasireotide but this also assumes that improvements in glucose metabolism is the only clinical outcome of interest. Other clinical outcomes are of importance and were assessed as secondary endpoints. While data capture of these additional endpoints may limit interpretation and patients' responses were variable, it is conceivable that for some individuals the responses (e.g., improvements in facial appearance as presented in photographs at the AC meeting) represent a clinically meaningful effect of treatment. Similarly, subgroups of patients did have improvements on objective measures such as blood pressure reduction or weight loss which may be important enough outcomes to outweigh the risk of glucose intolerance.

Identifying what characteristics of a patient would respond favorably to therapy while having a low likelihood of developing diabetes was not evident in this program. More likely, the appropriate patient for pasireotide treatment would have to be identified on a case-by-case basis. While this approach is unsettling in a drug regulatory decision, there were findings in this program which favor such a consideration.

A reasonably early timeframe was noted for identifying treatment response to pasireotide and risk of dysglycemia such that decisions can be made by the physician and patient regarding the benefits-risk of continued therapy. Most patients who developed glucose intolerance had a marked rise in fasting plasma glucose within two weeks of initiating therapy. Patients can be instructed to either perform self-blood glucose monitoring or have a fasting plasma glucose test measured within two weeks of drug initiation. If warranted at that time, therapies to treat dysglycemia can be initiated early. If a reduction in mUFC is to be observed, the maximal response occurs within 2 months of initiation of therapy. If a meaningful reduction in mUFC is observed by this timepoint, this also gives the physician and patient another opportunity to assess response to measures to control dysglycemia. Decisions on continuing current treatment, dose-adjustments, or treatment discontinuation can therefore be made within an early timeframe to optimize benefit-risks of pasireotide.

Despite the many available therapies to treat diabetes, it is disconcerting that diabetes wasn't better controlled in this clinical program. However, it was also evident that many patients did not receive any pharmacologic intervention for diabetes. This underscores the importance of reinforced labeling to instruct patients and physicians to aggressively monitor and treat dysglycemia. It also reinforces the need for a postmarketing trial to investigate the most appropriate treatment approach to pasireotide-induced dysglycemia.

I am willing to accept some of the risks associated with pasireotide and to rely upon physician/patient behavior to mitigate these risks in my recommendation to approve pasireotide because of the limited options available to treat Cushing's disease. Currently, patients with Cushing's disease receive off-label medical treatments that have had limited prospective evaluation for safety and efficacy. For example, ketoconazole, an anti-fungal

agent that is a potent inhibitor of steroidogenesis at high doses is commonly prescribed off-label for Cushing's syndrome. Risks of severe hepatotoxicity have been reported with its use along with gynecomastia and potential for drug-drug interactions. Similarly, Korlym which was recently approved to "*control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery*" can only be used in a subset of patients with Cushing's disease and reports of severe hypokalemia, hypertension, rash, adrenal insufficiency and endometrial hyperplasia and bleeding are among the listed safety concerns. In addition, the product contains a boxed warning on the abortifacent effect of the drug. The Korlym program evaluated the efficacy and safety of this product in 50 patients for 6 months, in contrast to the 6-month Phase 3 trial of pasireotide in 162 patients. Table 1 from Dr. Lowy's review summarizes the medical therapies used off-label for Cushing's disease. No therapy in this table or the approved product, Korlym, is without risks and none has been studied as extensively as pasireotide.

The clinical development program of pasireotide provides me with reassurance that the risks of this drug are better characterized than currently available therapies and that this information will enable better labeling for appropriate use of this drug. Furthermore, required studies to be conducted under FDAAA will allow us to capture more safety information postmarketing to continually update the benefit-risk profile of pasireotide.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No REMS is recommended at this time. I believe the safety concerns related to pasireotide can be addressed in labeling, including a Medication Guide. With appropriate monitoring and early management of many of the safety concerns, the risks of therapy can be mitigated.

- Recommendation for other Postmarketing Requirements and Commitments

With my recommendation for approval, I am requiring several postmarketing studies including a clinical trial to evaluate appropriate treatment regimens for managing diabetes in pasireotide-treated patients. The review team is still providing feedback to the firm on the objectives of this trial including the randomization of patients to an insulin-only treatment arm. This trial will be a 52-week trial and with its completion, it is hoped that labeling can be updated to inform physicians on the appropriate anti-diabetic therapies for successful management of pasireotide-induced diabetes.

The applicant will also be required to establish a patient registry and perform enhanced pharmacovigilance. It is recommended that the registry be for a minimum of 5 years from the date of last patient enrollment and will evaluate for the occurrence and features of several serious safety issues of study participants including hyperglycemia resulting in hospitalization, QT prolongation resulting in a CV event, atypical infections and adrenal insufficiency. The enhanced pharmacovigilance plan will include active queries of reporters and expedited reporting to FDA on several serious safety issues of interest.

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/s/

MARY H PARKS
12/13/2012