CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200677Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	December 14, 2012
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	200677
Applicant Name	Novartis
Proprietary / Established (USAN) Names	Signifor (pasireotide)
Dosage Forms / Strength	300, 600, 900 micrograms in prefilled syringes for twice daily subcutaneous injection
Proposed Indication(s)	Patients with Cushing's disease who require medical therapeutic intervention
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding pasireotide. Please refer to the action package for other reviews containing more detailed discussion. Pasireotide is a new molecular entity (NME), immediate-release injectable drug that is a cyclohexapeptide somatostatin analog developed for the treatment of patients with Cushing's disease (CD). CD is caused by endogenous hypercortisolism as a result of over-secretion of adrenocorticotropic hormone (ACTH) from a pituitary adenoma. The clinical consequences of prolonged exposure to inappropriately high levels of cortisol are diabetes/glucose intolerance, hypertension, weight gain, muscle weakness, and Cushingoid features (moon facies, buffalo hump, central obesity, striae) from fat redistribution.

Naturally occurring somatostatin exerts its effect via binding to five different but related somatostatin receptors (SSTR1-5) and acts on a variety of targets including the pituitary. There are currently two other somatostatin analogues on the market (Sandostatin-octreotide and Somatuline-lanreotide), both approved for acromegaly (and some other non-CD indications for octreotide).

All the somatostatin analogs have similarities, but also have different receptor binding affinities that may result in different efficacy and safety profiles. Pasireotide is more promiscuous in binding somatostatin receptors and has more affinity for SSTR5 than the other analogues. This receptor has a high level of expression in corticotroph tumor cells. The consequence of binding SSTR receptors on the surface of pituitary tumor cells is a reduction in ACTH, which subsequent decline in adrenal cortisol production as measured by urinary free cortisol (UFC). This pharmacological mechanism led to the development of pasireotide for use in CD.

Primary treatment of CD is surgical in nature, but there are high recurrence rates. Further treatment includes unapproved medical therapies, although there is one approved drug therapy-mifepristone- but its use is limited to the treatment of glucose intolerance/type 2 diabetes mellitus of Cushing's syndrome (CS). Other therapies include radiotherapy or bilateral adrenalectomy, which is quite drastic. Therefore, a drug therapy that could lessen the disease burden would be quite welcomed.

The sponsor did demonstrate that pasireotide activation of receptors on the surface of pituitary tumors in some patients resulted in reduction in adrenocorticotropin (ACTH) secretion and subsequent decline in cortisol production as measured by UFC. The expectation is that this would translate into improvement of the biochemical and clinical signs of hypercortisolism which include impaired glucose tolerance/diabetes, hypertension, dyslipidemia, osteoporosis, immune deficiency and abnormal fat distribution.

As I will discuss below, pasireotide has demonstrated efficacy in decreasing UFC as a measure of treatment of CD. However, pasireotide also was associated with the development of glucose intolerance/diabetes/worsening diabetes control in patients. The reason for this, as described by the sponsor, is that SSTR5 receptor stimulation leads to decreased insulin secretion. There is evidence in the data that other clinical manifestations of CD improved in some, but not all patients, including blood pressure control and fat redistribution. Therefore, a paradox exists whereby pasireotide decreases urinary cortisol, a good marker for decreased ACTH secretion, but has an adverse effect on glucose homeostasis which is also one of the main consequences of CD and where corrective therapy would be welcomed. This was a focus of discussion at the November 7, 2012 Advisory Committee (AC) meeting where the general consensus was that use of pasireotide, while possible worsening glucose control, did have enough evidence of other benefits to allow marketing.

The safety profile for pasireotide is similar to that of the other somatostatin analogs and expected, with the exception of the effect on glucose homeostasis and a simultaneous increase in liver transaminases and bilirubin in a few subjects. The simultaneous rise of transaminases and bilirubin is not typical of drug-induced-liver-injury (DILI). Our internal hepatology consultants, and the Advisory Committee hepatologist felt that this clinical manifestation was more likely an effect of SSTR5 activity within hepatocytes and transport systems and was not likely to result in liver toxicity, although the data is limited in this regard.

I believe there is an adequate risk and benefit consideration to allow marketing of pasireotide for CD.

Efficacy

Efficacy is based mainly on Study B2305, a 6-month study in 162 subjects with CD. Please see other reviews for the details of this study. The primary efficacy analysis was the response rate of patients who normalized their mean (m) UFC at Month 6. The pre-specified threshold demonstrating efficacy was the lower bound of the 95% CI, which for responders was expected to exceed 15%. The selection of the 15% threshold took into consideration that spontaneous improvement in CD is an exceedingly rare event and was also following advice

from expert opinion at the time of study conceptualization. This evaluation was agreed to by the Agency, but it should be noted that there are few trials in this population, a limited population which would likely necessitate a single robust trial, and this analysis was knowingly conservative allowing for powering of results that could provide the level of evidence necessary for regulatory purposes. This agreement, since it was in uncharted territory, should not be viewed as precluding consideration, in this specific instance, of other data or evaluations that may be generated. It is also important to consider that this analysis is referred to as a 'non-inferiority' in many of the reviews, but in reality it is not a typical non-inferiority trial. Non-inferiority trials are typically thought of as an active control trial, not intended to show superiority of the test drug (or intervention), but to show that the new treatment is not inferior to an unacceptable extent to an approved therapy. This trial instead, did not have an active control (or placebo), and the subject's final result was compared to whether the UFC normalized (responder), with the concept that a certain number of 'responders' was necessary to assure that spontaneous improvement was not occurring. Therefore, this trial did not share many of the characteristics of a typical non-inferiority trial. However, this trial did share the concern of non-inferiority trials where assay sensitivity cannot be assured (because of the lack of placebo control), which is why the lower bound was set at 15%.[1] In reality, this trial should be viewed as having a superiority design where the objective is to demonstrate that the lower bound of the confidence interval around the estimated response rate must exclude a certain threshold to assure assay sensitivity. That threshold (15%) can be viewed as very conservative considering that spontaneous resolution of UFC in CD patients is thought to be exceedingly rare.

Below are the primary results as obtained from Dr. Pian's review (Page 16).

Table 1: 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%]	

Pasireotide dose of 900 µg bid met the primary efficacy criterion, whereas the 600 µg bid dose did not. However, as discussed earlier, this criterion was used to allow for trial design and powering and was considered very conservative. These results also do not reflect the baseline imbalances in mUFC where the pasireotide 600 µg group had higher levels. Also, if one were to consider this a superiority trial with very few 'spontaneous resolutions', a lower bound of 7% (600 µg group) may be reassuring.

While it is not typical that we would consider another potential endpoint, we do look at the totality of the data and consider the trial design in all of our considerations. Therefore, due to the conservative nature of the primary endpoint and the lack of prior precedent upon which to draw, and because normalization by spontaneous improvement of UFC is considered rare, another responder analysis defined as a patient with mUFC ≤ ULN or ≥ 50% reduction from

[1] This trial however did not have an M1 or M2 of a typical non-inferiority trial as there was not an active control agent for comparison.

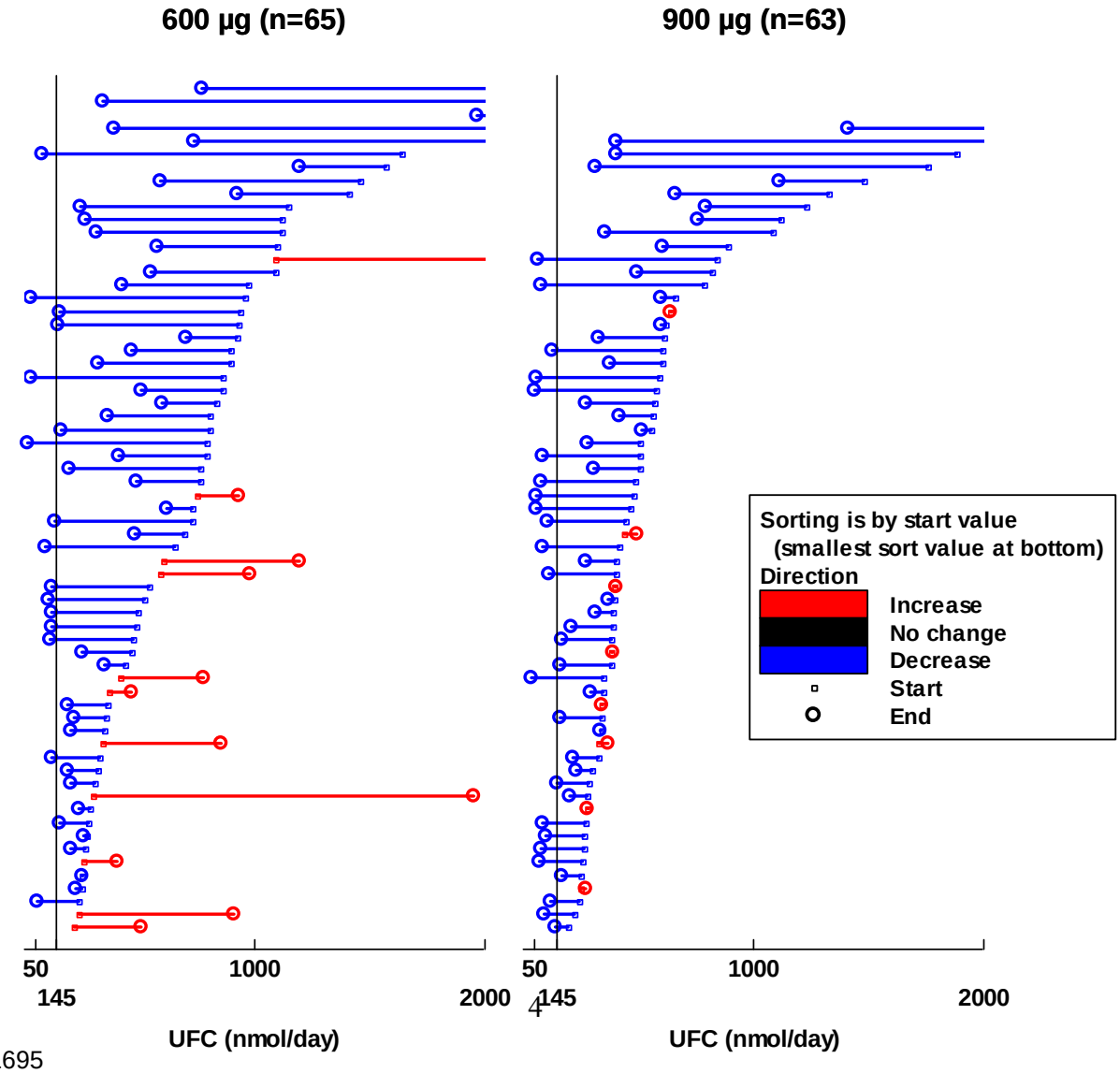
baseline was considered. These results are presented in the table below from Dr. Pian's review (Page 17).

Table 2: Percentage of subjects with mUFC ≤ ULN or ≥ 50% reduction from baseline at Month 6

Treatment	Pasireotide 600µg n=82	Pasireotide 900µg n=80	Total n=162
	n (%) [95% Confidence interval]		
Month 6 (LOCF)	28 (34%) [24%, 44%]	33 (41%) [30%, 52%]	61 (38%) [30%, 46%]
Month 6 (Observed)	24 (29%) [19%, 39%]	29 (36%) [26%, 47%]	53 (33%) [25%, 40%]

Responders are observed with both doses with some suggestion of dose ordering. However, due to imbalances in mUFC at baseline between groups, it may not be appropriate to draw cross-group comparisons. Further investigation by Dr. Pian revealed little correlation between average dose and mUFC decreases and subjects that didn't respond to the 600 µg bid dose had little improvement when the dose was increased. Below is a demonstrative graph from Dr. Pian's review demonstrating individual UFC changes (Page 20).

Figure 1: Individual UFC Changes from baseline to Month 6 in Study B2305



This demonstrates that most subjects had some decrease in UFC. As further discussed in Dr. Pian's review, the highest percentages of responders were in those with the lower baseline UFC values.

Other clinical parameters were evaluated, but not meticulously, and due to a high amount of drop-outs must be viewed cautiously. For most, downward trends were noted. Blood pressure tended to decrease as demonstrated in the table below (Dr. Pian's review, page 29). This should be viewed cautiously as there also was increased use of some categories of antihypertensive medications during the trial.

Table 3: 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)

Applicant's Clinical Study Report

However, there was a subset of patients identified as having hypertension at baseline and not receiving antihypertensive therapy. For this small subset, improved blood pressure was also noted (Dr. Roman's review, page 11).

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

Improvements were also noted in BMI, waist circumference and weight and there was a dose-related trend as noted below:

	6 month		12 month	
Dose pasireotide	600 μg	900 μg	600 μg	900 μg
BMI (kg/m2)	1.2	2.1	2.1	2.8
Waist circumference (cm)	1.9	3.4	4.4	5.6
Weight (kg)	3.1	5.7	5.8	7.7

A Cushing's syndrome health related quality of life questionnaire was also included in the trial. This questionnaire has not been adequately assessed for content validity, clinically important changes were not determined and standard deviations were large, but increases from baseline for both groups were demonstrated indicating improvement.

Use of pasireotide, at both the 600 and 900 μg bid doses demonstrated decreases in mUFC. It should also be noted that some patients that were unable to tolerate the 600 μg bid dose completed the trial receiving 300 μg bid and had evidence of efficacy (i.e. decreasing UFC). While the pre-specified endpoint for the primary analysis was not met for the 600 μg dose, there was improvement, and as discussed above this was not a classic non-inferiority trial compared to a known effective agent. Viewed as a superiority trial with very rare spontaneous resolution of UFC to normal (the 15% threshold to assure assay sensitivity is very conservative and does not seem to based on any data), then the 600 μg could be considered to have demonstrated efficacy. This trial was originally designed with a very stringent endpoint because of the lack of a placebo control. However, due to the rarity of spontaneous remission in untreated patients, and for all the reasons specific to this application that I discussed above, it is appropriate to explore other endpoints in consideration of appropriate dosing. The percentage of patients who achieved mUFC $\leq$ ULN or $\geq$ 50% reduction (an endpoint that should be highly correlated with the primary endpoint) is convincing for both doses of pasireotide. There were secondary endpoints of hypertension control, quality of life improvements and changes in fat redistribution that indicated these changes may be clinically

important. Dose selection is important because as the dose increases, so do tolerability issues. So the lowest effective dose is optimum for continued therapy.

As I will discuss below, despite improvement in UFC and some secondary clinical endpoints, there is a concerning worsening in glucose homeostasis associated with pasireotide use.

Safety

Pasireotide demonstrated adverse effects typical of somatostatin type drugs (e.g. QT prolongation, cholelithiasis). I will focus this section on two additional findings that are of concern: glucose intolerance/diabetes and abnormal liver function tests.

Pasireotide was associated with almost universal increases in subjects' HbA1c. Associated with this was an increase in the use of anti-hyperglycemic medications. Mean fasting plasma glucose values increased similarly for the 600 μg and 900 μg groups to pre-diabetic and diabetic values. Mean HbA1c levels increased from 5.8% at the start of the trial to 7.2% by study end. The percentage of patients with diabetes increased from 34% at baseline to above 50% at trial end. This is demonstrated in the two figures below from Dr. Roman's review (Page 16-17).

Figure 12: Changes in pre-diabetes and diabetes status

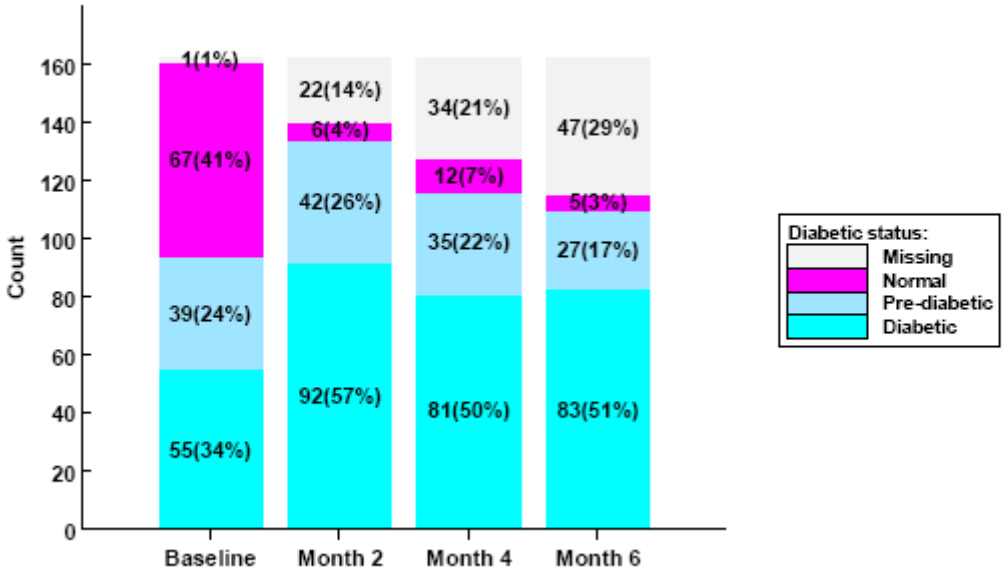
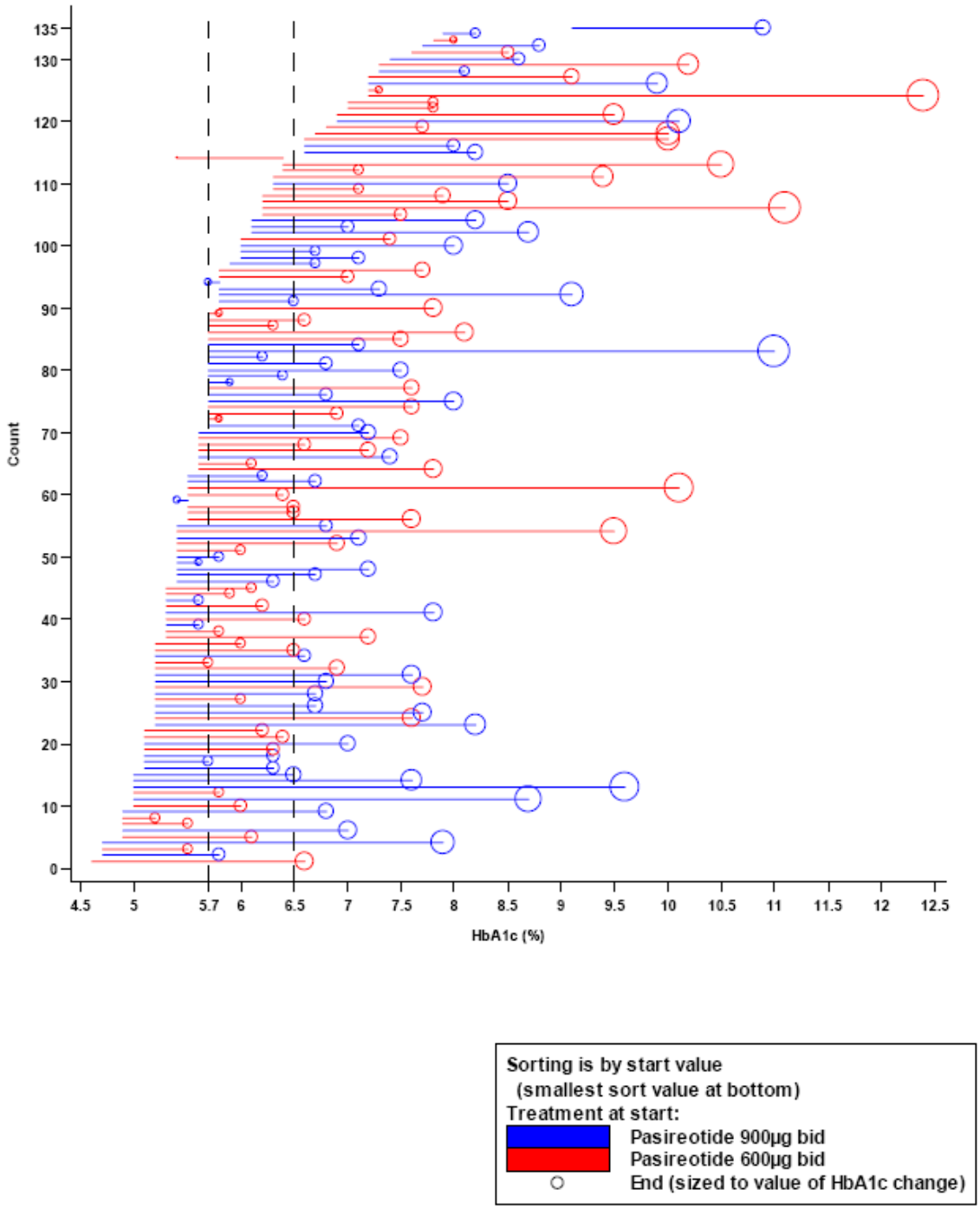


Figure 11: Individual changes in HbA1c from baseline to Month 6



There was a weak positive correlation and coefficient of determination (r^2=0.05) between the change in HbA1c and mUFC change from baseline. This is important as it demonstrates that a dramatic change in mUFC doesn't necessarily mean increased risk for dramatic increases in HbA1c. The changes in HbA1c occurred early during treatment and did not seem to continue to increase over time.

The mechanism of pasireotide-induced hyperglycemia has been characterized by the applicant as being mediated by drug's binding to the somatostatin receptor. The studies performed by the sponsor indicate that SSTR5 and perhaps SSTR2 binding decrease insulin secretion. This would indicate that the decrease in glucose homeostasis is on the basis of decrease insulin and not due to insulin intolerance. This is also important as it could inform which categories of diabetic therapies are selected in treating pasireotide induced hyperglycemia. It is also unfortunate that pasireotide has this effect, as one of the main complications of CD is the resulting hyperglycemia, which pasireotide most likely would not correct.

Within the pasireotide development program one subject with CD and 3 healthy volunteers developed biochemical findings of ALT > 3x ULN and bilirubin >2xULN. These laboratory abnormalities are used in the definition of Hy's law as indicating potential liver toxicity if other potential hepatotoxic factors are eliminated. All of these subjects recovered without sequelae after drug discontinuation and most were not evaluated for other potential hepatotoxic causative agents. It was noted by our internal consultants that the bilirubin increases occurred concomitantly with the increases in liver enzymes, and that this finding is not consistent with hepatocellular injury. As such, while clinicians should bear these findings in mind, they are likely less worrisome than those cases associated with drug use that represent a true finding of Hy's law.

Finally, also noted were several patients that experienced hypocortisolism (8%). This will need to be monitored for by clinicians, but as well as being an adverse effect, this is also a demonstration that pasireotide has the desired (if overly aggressive in these cases) effect for which it is being used.

Advisory Committee Meeting

An Advisory Committee meeting was held on November 7, 2012. The general consensus was that both doses studied caused substantial reductions in mUFC, that changes in clinical parameters, while not definitive, were suggestive of efficacy and that hyperglycemia, while an unfortunate consequence of therapy, was treatable and that potential salutatory effects of pasireotide would outweigh this risk. For the overall question regarding marketing, the committee voted 10 yes, 0 no.

Conclusions and Recommendations

There are very limited therapeutic options available for the treatment of CD. The current interventions have potential worrisome consequences and there is a clear unmet medical need. Pasireotide has clear effects on decreasing mUFC indicating decreasing cortisol levels. While

it is unfortunate that pasireotide has as a consequence of use adverse effects on glucose homeostasis, many of the secondary indices of clinical effect changed favorably, as would be expect from decreased cortisol levels. It is fortunate that the degree of change in UFC does not predict the level of HbA1c change such that there will probably be a population of patients that have robust changes in UFC without changing HbA1c to diabetic thresholds. Also, as Dr. Parks discussed, changes in UFC and HbA1c occur early in treatment which would allow clinicians to make relatively quick decisions regarding whether or not to continue therapy based on whether there is a response in UFC and if the HbA1c changes can be controlled. I agree with the reviewers and the AC panel members that the paucity of effective therapies and the favorable changes noted in secondary clinical endpoints demonstrate there is a place for pasireotide in the therapy of those with CD.

It will be very important to require the sponsor (as part of a PMR) to define appropriate treatment regimens for those with (or developing) glucose homeostasis abnormalities while use using pasireotide.

I recommend approval of pasireotide as noted above.

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/s/

CURTIS J ROSEBRAUGH
12/14/2012