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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-106

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

DRAFT

Statistical Review and Evaluation

BIOASSAY (CHEMISTRY)

NDA:	21-106
Name of drug:	Somavert (pegvisomant for injection)
Applicant:	Sensus
Indication:	Acromegaly
Location of electronic datasets	data in hardcopy only
Documents reviewed	Hardcopy submission dated October 1, 2002 (?)
Project manager:	Monika Johnson, Pharm.D. (HFD-510).
Chemistry reviewer:	Janice Brown, Ph.D. (HFD-510)
Dates:	Received 12/4/02; 6-month user-fee goal date 3/31/03
Statistics team leader and primary reviewer:	J. Todd Sahlroot, Ph.D. (HFD-715)
Secondary reviewer:	Karl Lin, Ph.D. (HFD-715)

Keywords: NDA review, other non-clinical

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1 Summary and conclusions

The sponsor submitted an NDA for Somavert on December 22, 2000, for an acromegaly indication. The FDA sent the sponsor an approvable letter dated June 26, 2001, listing a number of deficiencies including chemistry deficiencies. Several of the chemistry deficiencies concerned inadequate acceptance criteria for a Growth Hormone Antagonist bioassay and another for the acceptance of lots. In this Complete Response, the sponsor responded to the bioassay deficiencies by proposing alternative, statistically-based acceptance criteria.

The proposed acceptance criteria for the relative potency bioassay are based on (separate) statistical tests for reference and sample products. The linearity of the relationship between log absorbance and log concentration will be tested and, if the relationship is linear, parallelism of the regression lines will be tested. The most subjective part of the method are the assigned alpha levels, 1% for linearity and 5% for parallelism. The proposed alpha levels require that, in order to accept data from a bioassay, there should be very strong evidence of linearity. Parallelism is assumed unless there is strong evidence *against it*. In the opinion of this reviewer, these alpha levels should provide reasonable criteria for a bioassay of Somavert.

The sponsor proposed criteria for the acceptance of future lots depends critically on the assumption that all sampled lots are good from a chemistry standpoint and therefore can be used to guide the acceptability of future lots.

The sponsor originally submitted relative potency data for 18 lots which was subsequently found to contain some incorrect values. The sponsor eventually submitted corrected data for 48 lots, the 18 original lots and 30 additional lots. Using the sponsor's method and the revised data, this reviewer calculated specification acceptance criteria for relative potency of (78%, 128%). Using tolerance interval methodology, this reviewer calculated specificity limits of (76%, 132%). These limits are similar to the sponsor's proposed criteria of (75%, 133%). As suggested by the data, the calculations assume the within-lot variance is small (even negligible) compared to lot-to-lot variability.

2 Introduction

The sponsor submitted an NDA for Somavert on December 22, 2000, for an acromegaly indication. The FDA sent the sponsor an approvable (AE) letter dated June 26, 2002, listing a number of deficiencies including chemistry deficiencies. Several of the chemistry deficiencies concerned inadequate acceptance criteria for a Growth Hormone Antagonist bioassay and another for the acceptance of lots. The Appendix to this review lists the bioassay deficiencies in the AE letter.

In this Complete Response, the sponsor responded to the bioassay deficiencies by proposing alternative, statistically-based acceptance criteria The chemistry reviewer, Janice Brown, Ph.D., asked Biometrics to review the acceptance criteria for statistical validity.

3 The bioassay

3a Sponsor's proposed acceptance criteria

The FDA AE letter stated "The mean bioactivity acceptance criteria from six plates must have a % CV of ≤ 20%". The sponsor found this criterion to be inadequate due to the complexity of the bioassay and proposed an entirely different set of criteria explained below.

The overall experimental design of the bioassay follows the work of Finney (Probit Analysis, 1973). Detailed descriptions of the actual design can be found elsewhere.[1] The goal of the experiment is to estimate the potency of the Somavert reference product relative to samples consisting of various dilutions of the reference product.. The outcome measure, log absorbance, is regressed on the dependent variable, log concentration, separately for test and reference products. If the regressions are suitably linear and if the lines are parallel, the estimated relative potency of the reference and test products is the vertical difference between the regression lines which is constant for all concentrations.

The sponsor's proposed acceptance criteria for the bioassay is based on (1) assessing the linearity of the relationship between log absorbance and log concentration for reference and sample products and, (2) if linearity is present, to determine whether the regression lines are parallel.

Table 1.2.14.1.-2. shows the sponsor's proposed assay acceptance criteria. All criteria must be satisfied for the bioassay to be accepted.

[1] Final Report: Validation of M00017-01, "Automated Relative Potency Bioassay of Pegvisomant Utilizing the Beckman Biomek 2000 Automated Workstation"

Sponsor's Table 1.2.14.1.-2. Assay Acceptance criteria

Slope to concentration ratio, samples	p<.01
Slope to concentration ratio, reference material(s)	p<.01
Sample response linearity	No significant quadratic term, p>.01
Reference material response linearity	No significant quadratic term, p>.01
Parallel responses	Slopes for test and reference must not be different, p>.05

3b Reviewer comments

The sponsor's method is equivalent to testing parameters $\beta_{1,1}$, $\beta_{1,2}$, $\beta_{2,1}$ and $\beta_{2,2}$ in the following models. One model is for reference (k=1) and one is for the samples (k=2):

$$E(A) = \beta_{0,k} + \beta_{1,k} C + \beta_{2,k} C^2$$

Where A = log (absorbance)
C = log (concentration)

The linear terms are tested using the null hypotheses $H_{1,k}$: $\beta_{1,k} = 0$ (no linear term) vs the alternative $\beta_{1,k} \neq 0$ (with linear term) (k=1, 2). These tests correspond to lines 1 and 2 of the Table. The tests are carried out at α=1%, implying the evidence against the null hypothesis must be very strong in order to reject it.

The quadratic terms are tested by the null hypotheses $H_{2,k}$: $\beta_{2,k} = 0$ (no quadratic term) vs the alternative $\beta_{2,k} \neq 0$ (with quadratic term) (k=1, 2). These tests correspond to lines 3 and 4 of the Table. The tests are carried out at α=1%, implying the evidence against the null hypothesis must be very strong in order to reject it.

If $H_{1,1}$ and $H_{1,2}$ are rejected and $H_{2,1}$ and $H_{2,2}$ are not rejected (together implying each regression equation is a straight line), parallelism of the regression lines is tested by the null hypothesis H_3: $\beta_{1,1} = \beta_{1,2}$ (slopes are equal) vs the alternative $\beta_{1,k} \neq \beta_{1,2}$ (slopes are not equal). The test is carried out at α=5%, implying the evidence against the null hypothesis must be strong in order to reject it. Note that under the null hypothesis the lines are parallel and, if we are to reject this hypothesis, the evidence against the null must be strong (but does not have to be as strong as before). Assuming parallelism in the absence of strong data to

reject it makes sense here since the samples are just dilutions of the test product and could be expected to have equal slopes compared to the reference.

The appropriateness of alpha levels in any experimental setting can be debated. These alpha levels require that, in order to accept data from a bioassay, there should be *very strong* evidence of linearity. Parallelism is assumed unless there is *strong* evidence against it. In the opinion of this reviewer, these alpha levels should provide reasonable criteria for a bioassay of Somavert.

4 Lot specification

4a Sponsor's proposed acceptance criteria

The data from an accepted bioassay will be used to calculate mean relative potency. The corresponding lot will be accepted or rejected based on the following proposed acceptance criteria for relative potency.

Sponsor's table 1.2.13.2

Test	Method number	Acceptance criteria
Potency – Bioassay	400.431	75-133% of Reference Material with fiducial [2] limits of error (p=.05) of not less than 56% not more than 178%

In the AE letter, the FDA stated that the acceptance criteria mean reference IC50 should be 90-110% for the drug product. From the sponsor's Validation Report VPR.02.10FR.01, the procedure is validated to support a specification of 80-125% for the mean with 95% fiducial limits. Based on relative potency data from 18 lots shown in Table 1, these data clearly do not meet the FDA standard for the mean (90-110%) but they are fairly consistent with the sponsor's 80-125% criterion. Only 2 lots have lower fiducial limits that fall just below 80.

However, noting the substantial lot-to-lot variability compared to the variability of the bioassay method itself, the sponsor calculated new (wider) acceptance criteria based on data from the 18 lots. The sponsor formulated the new acceptance criteria by constructing fiducial intervals based on the observed mean (95) and SD (9) of the relative potencies. A confidence coefficient of 2.5 was used. The resulting lower bound of the fidicual interval was 75%. The upper bound was 133%, the geometric reciprocal of 75%.

[2] Fiducial limits are understood to have the same meaning as confidence intervals in this review

Table 1. Relative Potency Data for 18 lots

Lot #	Relative potency (%)	Fiducial limits	
		Lower	Upper
I1812N001-F	100	98	101
I1812N002-F	92	90	95
I1927R001-F	85	82	89
I1825P002-F	93	90	96
I1825P003-F	93	88	97
I1927R003-F	81	79	83
I1927R004-F	83	79	86
I1825P004-F	92	90	95
I1812N003-F	90	87	94
I1825P005-F	85	Not available	
I1825P006-F	98		
I1812N004-F	98		
I1825P008-F	104		
I1825P009-F	99		
I1825P010-F	113		
I1927R005-F	99		
I1825P011-F	93		
I1927R002-F	106	103	108

4b Additional relative potency data

The first week of December, 2002, Pharmacia submitted additional relative potency data for 42 lots per the request of the FDA chemistry reviewer. This reviewer was subsequently notified in a 26 February 2003 e-mail from Rich Wolfe, Director, CMC Operations at Pharmacia (Attachment 2) that these data should have been corrected for certain protein measurements. Attachment 2 contains the original uncorrected data and the corrected data from 48 lots, including the 18 lots in Table 1 and an additional 30 lots.

This reviewer has determined that the data in Table 1 contain both corrected and uncorrected measures. The data for the 10 lots with fiducial intervals are corrected data and agree with the corrected data in Attachment 2. The data for the 8 lots without CI information are uncorrected and are different from the corrected data in Appendix 2.

4c Reviewer's comments

The sponsor's previous calculations used both corrected and uncorrected data from a total of 48 lots. This reviewer re-calculated estimates using only corrected data from all 48 lots, the original 18 lots and 30 additional lots.

Using the sponsor's method, this reviewer obtained a mean relative potency of 92.7% and SD of 7.1%. I used a confidence coefficient of 2.01 equal to the upper .975 percentile of the t distribution with 47 d.f. The resulting 95% fiducial interval was (78%, 128%) where the upper limit 128% is the reciprocal of the lower limit 78%.

Tolerance intervals

The previous calculations treat the mean and SD as known. Because the mean and SD were estimated from a sample, true tolerance limits would be wider due to sample to sample variability. Bowker and Lieberman (Engineering Statistics, Prentice-Hall, Inc. 1972, pp. 312-313) show how to select appropriate coefficients K and CI's (0.927 – 0.071K, 0.927 + 0.071K) such that a fixed proportion of fiducial intervals γ ($0<\gamma<1$) include at least 95% of the distribution. I selected γ=90% and γ=95%.

The reference gives K = 2.29 for γ=90% and K=2.39 for γ=95%. The tolerance intervals are (76%, 109%) and (76%, 110%), respectively. An acceptable set of specificity limits are (76%, 131%) and (76%, 132%) where the lower limits are from the tolerance limits and the upper limits are calculated as 1/(lower limit).

Final remarks

Both methods use the available lot data to calculate new acceptance criteria. The implicit assumption is that all lots contributing to the statistical analysis are acceptable from a chemistry standpoint and therefore can be used to guide the acceptance of future lots. The proposed method should not be used if this underlying assumption is incorrect.

Relative potency appears to have two primary sources of variability: (1) variability of the bioassay (within a lot) and (2) lot-to-lot variability. The sponsor ignored the former in the calculations since it is small relative to the latter. This seems reasonable as long as the fiducial intervals for each estimated relative potency are valid.

The sponsor does not provide any justification for the 95% fiducial limits in the sponsor's Table 1.2.13.2 (56%, 178%). This reviewer cannot find any statistical justification for these fiducial limits.

Appendix 1 – Bioassay deficiencies cited in FDA AE letter (item 3)

a. Submit the specifications for the cell line, including tests for relevant phenotypic and genotypic markers

b. Describe the preparation and characterization of the master and working cell banks for the FDC-P1 cell line

c. Describe how the cell is activated in the presence of human growth hormone

d. The written procedure for the Growth Hormone Antagonist (GHA) bioassay includes acceptance criteria that are not supported by the validation method. Revise the following in the procedure:

i. The acceptance criteria mean reference IC50 for the formulated bulk should be 70-80% for the bulk intermediate and 90-110% for the drug product;
ii. The mean bioactivity acceptance criteria from six plates must have a % CV of ≤ 20%; and
iii. Interwell reproducibility acceptance criteria should be ≤ 15%

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Concur with review

Statistical Review and Evaluation

NDA#:	21-106
Applicant:	Pharmacia & Upjohn
Name of Drug:	Somavert® (pegvisomant for injection)
Indication:	Treatment of Acromegaly
Document Reviewed:	Proposed Labeling dated October 1, 2002
Medical Reviewer:	Robert Perlstein M.D. (HFD-510)

This reviewer's labeling comments for the clinical studies in the NDA can be found in the Statistical Review for the submission dated February 22, 2001. There are no new labeling comments since the current submission contains no new clinical data.

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

Dr. Nevius

cc: Arch NDA 21-106
HFD-510/MJohnson, RPerlstein
HFD-715/LPian, TSahlroot, ENevius, CAnello

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Statistical Review and Evaluation

NDA#:	21-106
Applicant:	Sensus
Name of Drug:	Somavert® (pegvisomant for injection)
Indication:	Treatment of Acromegaly
Document Reviewed:	Submission dated February 22, 2001
Medical Reviewer:	Robert Perlstein M.D. (HFD-510)

Background

Pegvisomant, a PEGylated analog of human growth hormone (GH), is a GH receptor antagonist (GHA). The indication for this application is for treatment of acromegaly with dosing regimens of 10mg, 15mg or 20 mg per day (Study SEN-3614). Study SEN-3611 evaluated doses of 30 mg to 80 mg once weekly in acromegalic patients. Studies SEN-3621, SEN-3621A, SEN-3622, and SEN-3631, evaluated disorders associated with type 2 diabetes. The studies were reported in this application without seeking the indication
Therefore, focus of this review is on study SEN-3614.

Key words: Clinical studies, NDA review, One-study application adaptive randomization

Study SEN-3614

Study Design:

This was a double-blind, randomized, multi-center, placebo-controlled study of pegvisomant in the treatment of acromegaly. Patients were randomized to receive placebo or one of the doses of 10 mg, 15 mg or 20 mg by subcutaneous injection. A single bolus loading dose of either placebo (for the placebo group) or 80mg pegvisomant (for the 3 pegvisomant groups) preceded the once daily treatment dose for 12 weeks.

The objectives of the study were to determine the tolerability and efficacy of pegvisomant therapy in subjects with acromegaly. The hypotheses to be tested are pegvisomant improves both biochemical and clinical aspects of the disease compared with placebo.

The primary efficacy measure was reduction in IGF-I levels. The secondary efficacy measures included the incidence of normalization of IGF-I levels, reduction in acid labile subunit (ALS) and free IGF-I levels, changes in signs and symptoms of acromegaly, changes in ring size, and changes in quality of life.

The tolerability evaluation of pegvisomant included adverse events, clinical laboratory values, and clinically significant changes in MRI results, ECG, physical examinations, and vital signs.

The sample size of 100 patients was based on observations made in study SEN-3611. With an alpha value equal to 0.05 and a power of 0.80, a sample size of 25 patients per treatment group was adequate to detect statistically significant differences in IGF-I of at least 20% between pegvisomant and placebo with a common standard deviation (SD) of 24%.

The random assignment of patients used an adaptive (minimization) randomization procedure. Randomization was stratified according to Visit 2 IGF-I concentrations of low (1.3-2.0 times ULN) or high (>2.0 times ULN) and the investigative site. The Visit 2 (for eligibility) IGF-I assays were conducted at the central laboratory, _____ for all the U.S. sites. Visit 2 IGF-I samples from the European sites were split into two for assessment at the local lab to minimize time to determine patient IGF-I eligibility and the central lab for efficacy analysis.

A total of 7 visits over a span of approximately 14-21 weeks included screening (visit 1), eligibility (visit 2), baseline (visit 3), and 4 visits at weeks 2, 4, 8, and 12 of the double blind treatment phase. Patients were eligible to participate in an open-label extension study after completion of the 12-week study. The 7 visits are depicted as follows:

Screening	Eligibility	Baseline	Double-blind treatment				Open label
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	→
Weeks -4 to -9	Weeks -2 to -4	Week 0	Week 2	Week 4	Week 8	Week 12	

The study included male or female acromegaly patients ≥18 years of age who had an IGF-I value 1.3 times of the age adjusted ULN (upper limit normal) at the eligibility visit (Visit 2).

Efficacy Variables:

The primary efficacy variable was the percent change in IGF-I concentrations from baseline (Visit 3) to Week 12 (Visit 7). Secondary analyses including normalization of IGF-I concentrations; changes in ALS and free IGF-I concentrations; signs and symptoms of acromegaly; ring size; and quality of life.

The primary efficacy assessment was based on the analysis of variance (ANOVA) for the comparison between pegvisomant and placebo performed on the last observation carried forward dataset of the intent-to-treat population. The ITT population was defined as patients who received at least one dose of study medication and had at least one postbaseline efficacy assessment. The percent change in IGF-I concentrations from baseline to Week 12 was the dependent variable and treatment and investigative site were the independent variables. The treatment-by-site interaction was also examined.

The multiple comparison adjustment used a step-down procedure to test pairwise comparisons of pegvisomant to placebo in the order of 20 mg, 15 mg and 10 mg. The procedure will stop at any stage and declare the test dose and the lower dose(s) non significant if the comparison was not significant at the nominal p-value of 0.05.

Change in Conduct of the Study

All patients were intended to receive a bolus loading dose of 80 mg pegvisomant or placebo. However, a total of 24 patients (11 patients in the pegvisomant 10 mg group and 13 patients in the pegvisomant 15 mg group) did not receive the correct bolus loading dose. Instead, these patients received four times their assigned daily dose, i.e., 40 mg and 60 mg of pegvisomant in the 10 mg/day and 15 mg/day groups, respectively. Therefore, a separate subgroup analysis for IGF-I was conducted to assess the effect of these

incorrect bolus-loading doses on the primary efficacy outcome at Week 12

Patient #2401 (placebo group) and Patient #2402 (pegvisomant 20 mg group) were inadvertently administered each other's study medication at Visit 6 (Week 8) and thus took the wrong doses for the remaining 4 weeks of the study. The ITT analysis used the data from these patients without correction or adjustment.

The overall health status score was designed as an 11-point scale, with 0 = worst possible and 10 = best possible; however, the initial CRF was printed incorrectly with a 9-point scale (0 = best possible and 8 = worst possible). Because some data were collected on the incorrect scale before the CRF could be amended, only those data collected on the correct CRF (n = 81 patients) are included in the analysis.

Additional exploratory analyses were conducted on data for GH and IGFBP-3. Statistical testing was based on changes from baseline (Visit 3) to each post-baseline visit in the database for GH and to Visit 7 (Week 12 or final visit) for IGFBP-3.
Pairwise treatment comparisons were derived from analysis of variance using ranks.

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Patient Disposition:

A total of 112 patients were enrolled at 16 study centers. Number of patients randomized to the placebo group, 10mg, 15mg, and 20mg of the pegvisomant groups were 32, 26, 26, and 28, respectively. Four of the 112 patients discontinued prematurely and 108 patients (96.4%) completed the study. Table 1 summarizes patient disposition.

Table 1 Patient Disposition Summary

Discontinuation Reason	Placebo (n=32)	10 mg/day (n=26)	15 mg/day (n=26)	20 mg/day (n=28)	Total (n=112)
Adverse Event	0	0	1[c]	0	1
Protocol Violation	1[a]	0	0	0	1
Lack Efficacy	1[b]	0	0	0	1
Voluntary Withdrawal	0	0	1[d]	0	1
Total	2	0	2	0	4 (3.6%)

[a] #1115, a 31 year old male received placebo for 6 days with pituitary tumor compressing optic chiasm on baseline MRI

[b] #2104, a 37 year old female received placebo for 70 days

[c] #1501, a 42 year old male received drug for 63 days with abnormal liver function test/transaminitis

[d] # 1605, a 43 year old male received drug for 7 days

Demographics and Other Baseline Characteristics:

Of the 112 randomized patients, 63 (56%) were male and 49 (44%) were female. Most patients were Caucasian (82%). The mean age was 47.5 years (range, 20-78 years). The baseline demographics were comparable across the treatment groups.

Baseline levels of IGF-I, GH and baseline weight are displayed in Table 2.

Table 2 Baseline levels of IGF-I, GH and baseline weight

Baseline	Placebo n=31	10 mg n=26	15 mg n=26	20 mg n=28
IGF-I (SD) (min, max)	669.8(287.6)	626.7(250.8)	648.8(293.5)	731.6(204.9)
Stratified IGF-I (SD) (min, max)	High n=14 / Low n=17	High n=11 / Low n=15	High n=10 / Low n=16	High n=15 / Low n=13
GH (SD) (min, max)	8.2 (19.5)	7.8 (10.5)	11.4 (22.6)	8.1 (10.6)
Weight (kg)(SD) (min, max)	91.1 (24.2) (50.0, 158.3)	93.1 (19.6) (61.3, 137.2)	93.4 (18.2) (62.6, 132.0)	92.1 (21.9) (55.3, 135.6)

Primary Efficacy Analysis:

Of the 111 patients in the ITT population, 31, 26, 26, and 28 patients were in the placebo group, 10 mg, 15 mg and 20 mg pegvisomant groups, respectively. The primary efficacy outcome is the mean percent change in IGF-I level from baseline. Table 3 displays the descriptive statistics of IGF-I level and percent change from baseline to Weeks 2, 4, 8 and 12.

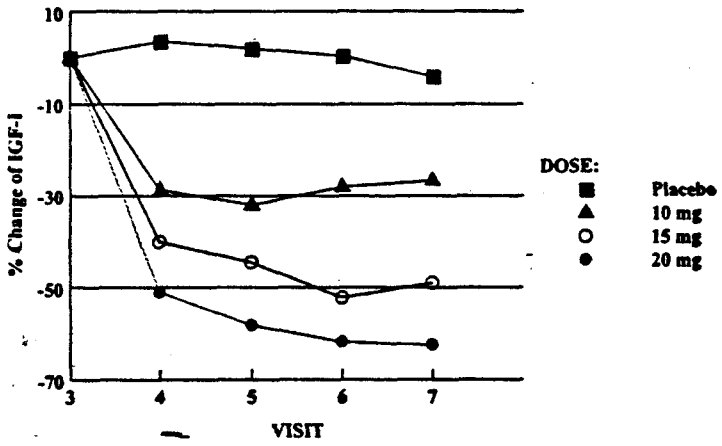
Table 3 Descriptive statistics of IGF-I (μmole/L)

Week	Placebo n=31		10 mg/d n=26		15 mg/d n=26*		20 mg/d n=28	
	Mean (SD)	%Δ (SD)	Mean (SD)	%Δ (SD)	Mean (SD)	%Δ (SD)	Mean (SD)	%Δ (SD)
0	670 (288)		627 (251)		649 (293)		732 (205)	
2	694 (310)	4% (10)	433 (201)	-29% (30)	377 (199)	-40% (24)	363 (175)	-51% (16)
4	673 (273)	2% (14)	416 (213)	-32% (29)	348 (188)	-45% (23)	312 (168)	-58% (17)
8	663 (265)	0.5% (12)	445 (246)	-28% (32)	300 (185)	-52% (24)	287 (175)	-62% (18)
12	640 (288)	-4% (17)	449 (220)	-27% (28)	320 (199)	-48% (26)	279 (183)	-62% (21)

*n=25 at weeks 2, 4 and 8 (patient #1605 had post baseline measurement at week 12 only)

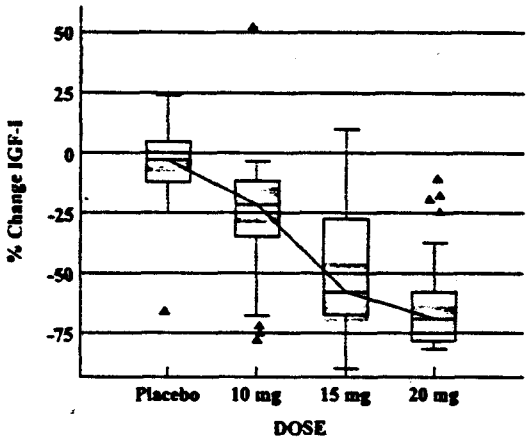
Figure 1 displays the percent change from baseline of IGF-I over time.

Figure 1 IGF-I percent change from baseline over time



The median percent change from baseline of IGF-I is displayed in Figure 2.

Figure 2 Box plot of percent change of IGF-I at endpoint - ITT



The median percent changes of IGF-I at endpoint were -2.9%, -21.4%, -58.0%, and -69.3%, respectively for placebo group, 10 mg pegvisomant group, 15 mg pegvisomant group, and 20 mg pegvisomant group.

The analysis of variance result with treatment, strata for baseline IGF-I (1.3-2.0xULN vs. >2.0xULN), and pooled sites (U.S. vs. Europe) in the model on the intent-to-treat population with LOCF dataset is displayed in Table 4.

Table 4 Primary Efficacy Analysis on percent change (%) of IGF-I from baseline to Week 12 - ITT

Treatment	Placebo n=31	10mg pegvisomant n=26	15mg pegvisomant n=26	20mg pegvisomant n=28
Mean % change (SE)	-4.1 (4.2)	-26.9 (4.6)	-48.4 (4.6)	-62.4 (4.4)
Difference from placebo (SE)		-22.8 (6.2)	-44.4 (6.2)	-58.4 (6.1)
95% C.I.		(-35.2, -10.5)	(-56.8, -32.0)	(-70.5, -46.3)
p-value		0.0004	0.0001	0.0001

Treatment with 10 mg, 15 mg or 20 mg of pegvisomant was statistically significantly better in IGF-I reduction when compared with placebo treatment. The difference from placebo in percent change of IGF-I was -22.8%, -44.4% and -58.4%, respectively.

Secondary Efficacy Analyses

1. Normalization of IGF-I

The sponsor reported incidence of patients in the ITT population who achieved normalized IGF-I concentrations at **some time** post baseline during the study. The percentages were 9.7% (3/31) in the placebo group, 53.8% (14/26) in the pegvisomant 10 mg group, 80.8% (21/26) in the pegvisomant 15 mg group and 89.3% (25/28) in the pegvisomant 20 mg group. However, the protocol definition of normalization was at the "Week 12" post-baseline visit. The reviewer's analysis on the incidence of normalized IGF-I at **endpoint** is displayed in Table 5.

Table 5 Number and percent of patients whose IGF-I concentration became normal at endpoint.

Treatment	Placebo n=31	10 mg pegvisomant n=26	15 mg pegvisomant n=26	20 mg pegvisomant n=28
# (%)	3 (9.7%)	10 (38.5%)	2 0(76.9%)	23 (82.1%)
Fisher's Exact Test		p=0.01	p=0.001	p=0.001

2. Signs and Symptoms of Acromegaly

Mean changes in soft tissue swelling, arthralgia, headache, excessive perspiration, and fatigue were displayed in Table 6. Of the 5 signs and symptoms the 10 mg pegvisomant was different from placebo in fatigue only. The 15 mg and 20 mg pegvisomant groups were different from placebo in soft tissue swelling, excessive perspiration, and fatigue but not in arthralgia or headache.

Table 6 Mean change of signs and symptoms of acromegaly

Treatment	Placebo n=31				10 mg n=26				15 mg n=26				20 mg n=28			
Sign & Symptom	BL	SD	Chg	SD	BL	SD	Chg	SD	BL	SD	Chg	SD	BL	SD	Chg	SD
soft tissue swelling	2.1	1.9	0.3	2.3	2.4	2.4	-0.7	1.6	2.7	2.4	**-1.2**	2.3	2.8	2.3	**-1.3**	1.3
Arthralgia	3.7	2.0	0.1	1.8	3.0	2.0	-0.3	1.8	3.2	2.5	-0.5	2.5	2.8	2.0	-0.4	2.1
Headache	2.1	2.1	0.1	1.6	2.5	2.2	-0.4	1.6	3.0	2.3	-0.3	1.4	2.1	1.9	-0.3	2.0
Excessive perspiration	3.1	2.4	0.1	1.7	3.2	2.2	-0.6	1.6	3.8	2.1	**-1.1**	1.3	3.3	1.9	**-1.7**	1.6
Fatigue	3.2	1.9	**-0.7**	1.5	3.7	1.9	**-0.5**	1.4	4.3	2.5	**-1.3**	1.7	3.9	2.0	**-1.0**	1.6

Bold, p<0.05

3. Ring size

Ring size was measured on the ring finger of the non-dominant hand using standard European jeweler's rings. The alpha-numeric jeweler's sizes (from "A" to "Z6") were converted to a numeric score ranging from 1 to 63. The descriptive statistics of ring size is displayed in Table 7. The 10 mg pegvisomant group was not different from placebo in change from baseline to Week 12 ring

size whereas the 15 mg and 20 mg pegvisomant groups were significantly different from placebo.

Table 7 Change from baseline to Week 12 ring size

	Placebo	10 mg	15 mg	20 mg
n	31	26	26	27
Baseline (SD)	46.80 (9.25)	48.12 (9.24)	48.35 (10.46)	45.15 (11.47)
Change(SD) at Week 12	-0.13 (2.34)	-0.81 (1.63)	**-1.85** (2.03)	**-2.52** (3.27)

Bold, p<0.05

4. Special Laboratory Tests

ALS and free IGF-I were secondary efficacy variables. But, analyses on growth hormone and IGFBP-3 were ad hoc and exploratory in nature. The sponsor's analyses showed that all pegvisomant treatment groups were significantly different from placebo except the GH was not different from placebo for 10 mg pegvisomant-treated patients.

Table 8 Mean (SE) of Special Laboratory Tests at Baseline and Change at Week 12.

	Placebo	10 mg/day	15 mg/day	20 mg/day
	(N = 31)	(N = 26)	(N = 26)	(N = 28)
Baseline ALS (mg/L)	21.5 ± 1.0	22.0 ± 0.95	23.1 ± 1.2	23.3 ± 0.8
Change at Week 12 (mg/L)	-0.5 ± 0.7	-3.1 ± 0.88	-6.4 ± 1.1	-9.5 ± 0.8
Baseline free IGF-I (ng/mL)	7.0 ± 0.6	6.4 ± 0.6	6.2 ± 0.6	6.2 ± 0.5
Change at Week 12 (ng/mL)	-0.2 ± 0.5	-2.5 ± 0.5	-3.6 ± 0.7	-3.9 ± 0.7
Baseline free IGF-I percent (%)	1.2 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
Change at Week 12 (%)	0.0 ± 0.1	-0.2 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1
Baseline IGFBP-3 (mg/L)	5.1 ± 0.2	5.2 ± 0.2	5.5 ± 0.2	5.3 ± 0.2
Change at Week 12 (mg/L)	-0.1 ± 0.1	-0.7 ± 0.2	-1.6 ± 0.3	-1.6 ± 0.2
Baseline growth hormone (ng/mL)	8.7±3.7	7.8±2.1	11.5±4.6	8.1±2.0
Change at Week 12	-0.8±0.9	2.7±1.1	9.2±2.2	14.4±4.1

Covariate and Subgroup:

Figures 3 and 4 display the percent change of IGF-I from baseline to Week 12 by covariates of baseline IGF-I and baseline body weight (kg), respectively. The treatment-by-baseline weight interaction was significant for baseline weight but not for baseline IGF-I.

Figure 3 Percent change of IGF-I from baseline by baseline IGF-I

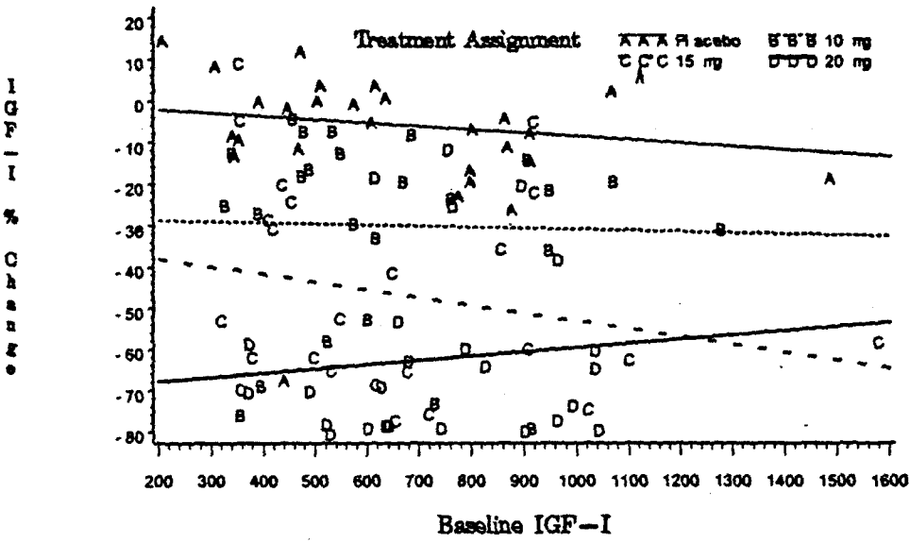


Figure 4 Percent change of IGF-I by baseline weight (kg)

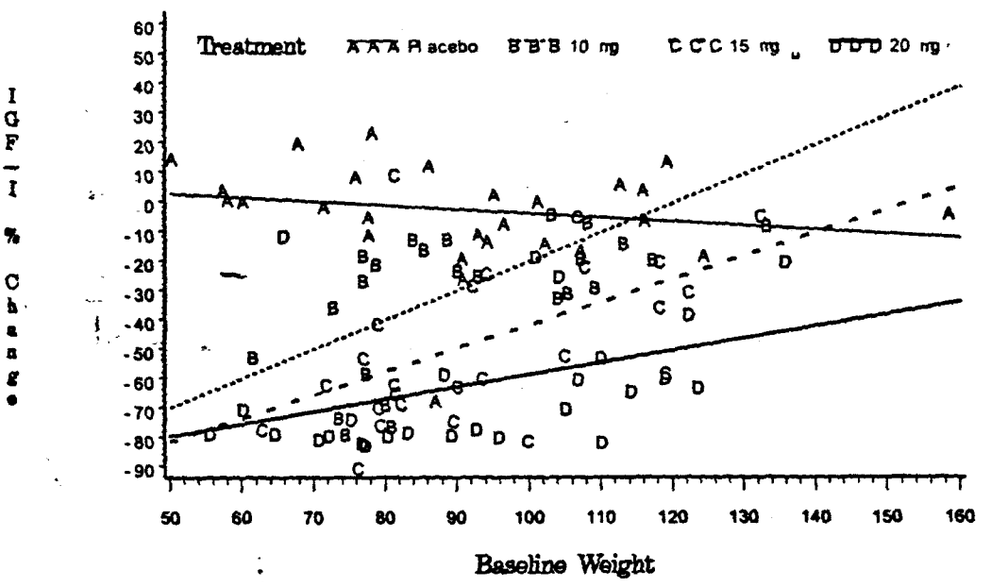
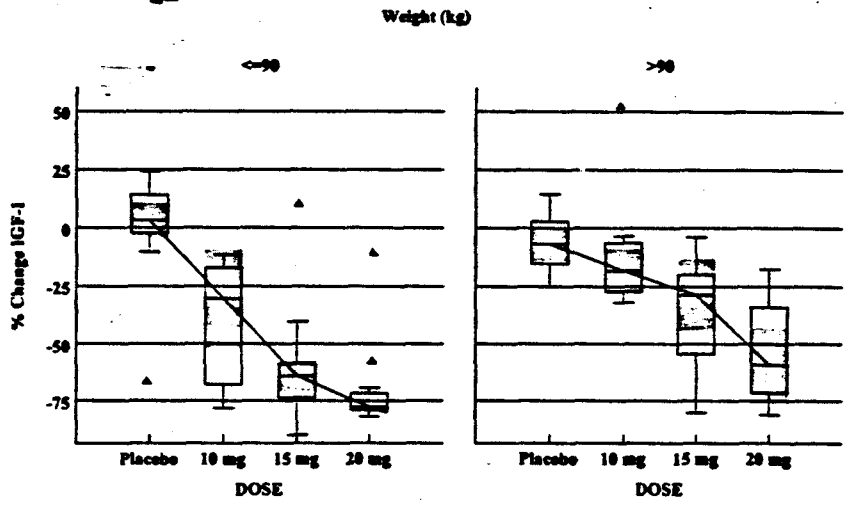


Figure 5 Box plot of % change from baseline IGF-I by median baseline weight (90 kg)



The median percent change from baseline IGF-I for patients with baseline weight of 90 kg or less and greater than 90 kg are displayed in Table 9 and Figure 5.

Table 9 Median percent change from baseline IGF-I by subgroup of baseline weight (≤90, >90 kg)

Treatment	Placebo		10 mg pegvisomant		15 mg pegvisomant		20 mg pegvisomant	
Baseline weight (kg)	≤90	≥90	≤90	≥90	≤90	≥90	≤90	≥90
n	12	15	14	11	13	12	13	13
Median % change	3.2	-6.6	-30.4	-18.3	-64.0	-28.6	-77.6	-59.3

Bolus loading dose validity

The descriptive statistics in IGF-I change from baseline for patients classified by loading dose are displayed in Table 10.

Table 10 IGF-I change from baseline by loading dose

Treatment Bolus dose	Placebo bolus	10 mg 80 mg bolus	**10 mg 40 mg bolus**	15 mg 80 mg bolus	**15 mg 60 mg bolus**	20 mg 80 mg bolus
n	31	16	**10**	14	**12**	28
Baseline IGF-I (SD)	670 (288)	578 (221)	**704 (288)**	592 (233)	**714 (350)**	732 (205)
Mean % change (SD)	-4.0% (16.8)	-25.0% (31.5)	**-29.5% (22.1)**	-51.3% (29.0)	**-44.7% (23.8)**	-62.5% (21.3)
Min, Max						
Median % Change	-2.9 %	-20.4 %	**-23.2 %**	-62.5 %	**-46.0 %**	-69.3 %

Bold, incorrect loading dose

The percent change from baseline to Week 12 of IGF-I by baseline IGF-I for the two loading doses is displayed in Figures 6 for the 10 mg and 15 mg pegvisomant groups. Figure 7 is the percent change of IGF-I by baseline weight.

Figure 6 Percent change of IGF-I by baseline IGF-I

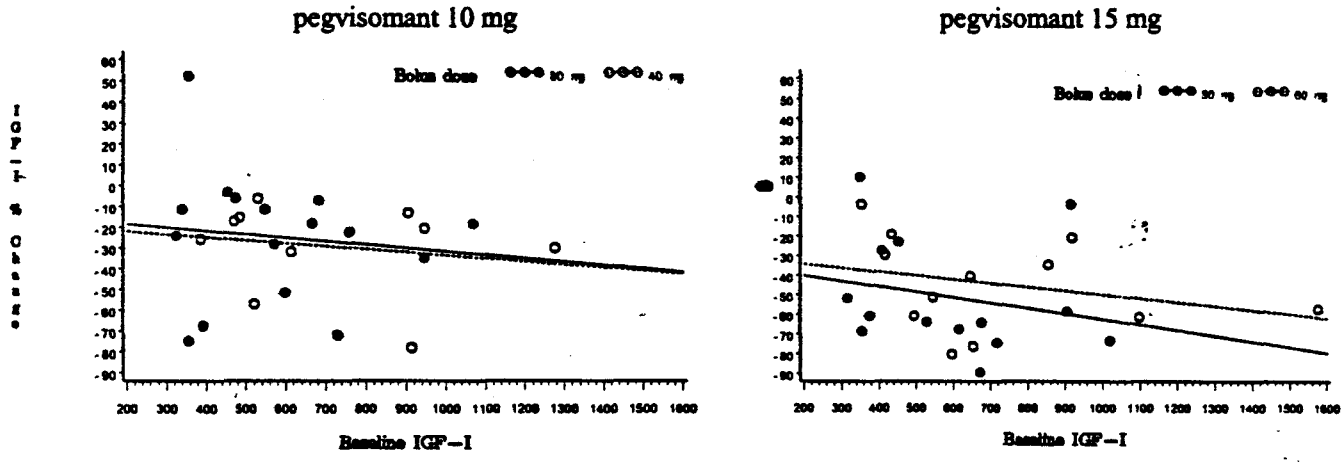
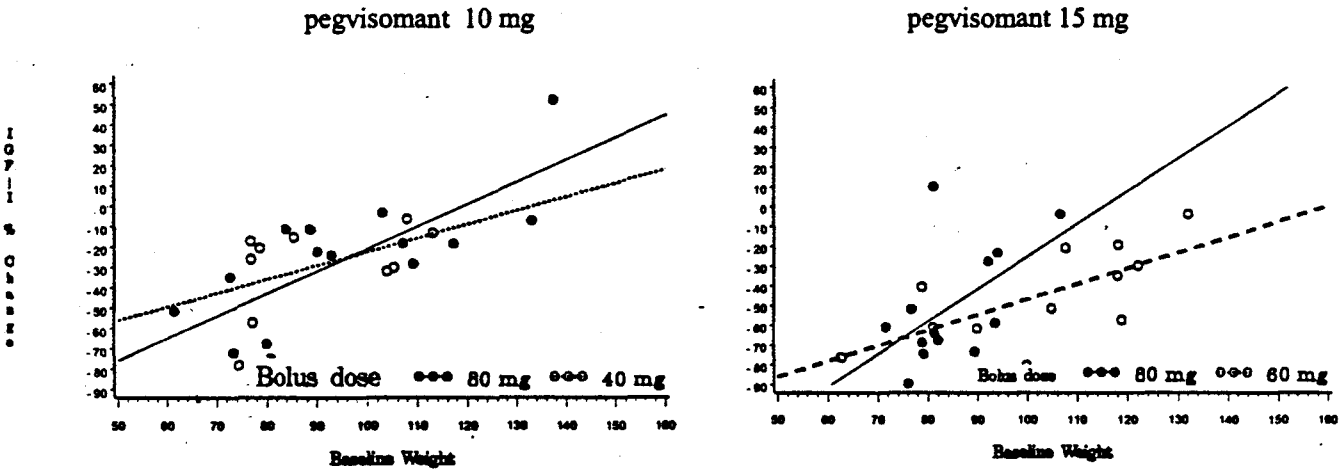


Figure 7 Percent change of IGF-I from baseline to Week 12 by baseline weight



The sponsor conducted exploratory analyses to identify baseline covariates to help determine the initial dose. The Medical Officer, Dr. Perlstein, requested this reviewer to comment on the exploratory analysis results.

The protocol specified primary efficacy analysis was analysis of variance; therefore, there were no prespecified covariates in the primary efficacy analysis. The protocol section describing covariates and subgroup analyses are for exploratory purposes. The covariate section of the protocol stated that "All data may be assessed as to the possible effect of any covariates. Among the covariates that may be examined are baseline IGF-I level, IGF-I study entry strata, baseline growth hormone (GH) level, sex, and baseline body weight." The assessment of possible effect of "any covariate" is considered exploratory.

To select covariates from a set of variables whose relevance is unknown for dosing purposes based on current trial data can introduce bias and produce misleading inference. Covariates selected in this manner can be used to design future trials using similar patient populations.

In Addendum 2, the sponsor explored the effects of age, weight in kg, BMI, baseline growth hormone result, baseline IGF-I, stratification of qualifying IGF-I (low & high), and sex. Two outcomes of interest were whether a patient's IGF-I fell within the normal range and the percent change from baseline IGF-I.

First, the correlation analysis showed 5 out of the 8 baseline characteristics were significant.

The logistic regression models were used to select a subset of the "statistically significant" predictors for IGF-I becoming normal at the final visit (binary variable).

The stepwise regression was used to select predictors for the percent change from baseline IGF-I at the last visit (continuous variable).

To reconcile the results of the regression analysis of the 15 mg pegvisomant group with that of the 10 mg and 20 mg groups, one "outlier" had to be removed from the 15 mg treatment group.

Analyses of the normalization of IGF-I at the final visit with covariates baseline weight (kg) and baseline IGF-I normalized by ULN (IGF-I/ULN) were further explored using cut off points 80.2 kg and 104.0kg, and 1.32520 and 2.05556, respectively, with 3 categories each. The responder table of the number of patients with normal IGF-I at the termination visit was a 3x3x3 table (3 categories each of treatment group, weight and normalized IGF-I) consisting of 27 cells. Cell size ranged from 0 to 6 patients.

The sponsor stated, "These tabulations should be interpreted with caution due to the small cell sizes." As the sponsor pointed out,

these are exploratory analyses based on small samples; therefore, the study results cannot be viewed as confirmatory.

The sponsor's exploratory analysis of dosing selection based on patient weight and baseline IGF-I level is data-driven. The result can be biased and misleading, therefore, it should not be considered for labeling purposes.

Comments on the Electronic Label Dated April 24, 2001

1. IGF-I was the primary efficacy variable and Week 12 was the primary time point for analysis. The clinical studies section reported that "The three groups that received SOMAVERT showed dose-dependent, statistically significant reductions in mean IGF-I ($p<0.0001$), free IGF-I ($p<0.05$), IGFBP-3 ($P<0.05$) and ALS ($p<0.05$) at all post baseline visits (Figure 1)."

   Free IGF-I and ALS were secondary efficacy variables. Analyses of IGFBP-3 and growth hormone (GH) were additional unplanned exploratory analyses. Any statements concerning statistically significant reductions should apply only to the primary efficacy variable, IGF-I at Week 12. For the secondary variables, free IGF-I, ALS, and the unplanned exploratory analysis on IGFBP-3, the p-values should not be displayed.

2. The label reported "Serum IGF-I was normalized during the course of this study in 9.4%, 53.8%, 80.8% and 89.3% of subjects…" The secondary variable was percent of patients with normal serum IGF-I at "the Week 12 post-baseline visit." in the protocol (p.757, Final study report:SEN-3614). The label should report the percentage of patients with normalized IGF-I at Week 12 or endpoint, not at any time point during the study.

3. The label only reported those signs and symptoms that are statistically significantly different from placebo. All the secondary efficacy variables should not be reported as statistically significant since there is no adjustment for multiplicity.

4. The label reported efficacy of a cohort of 38 patients in the open-label study of at least 12 consecutive months in the Clinical Studies section. Because this phase was open label and the 38-patient cohort was not a randomized group, the data could provide valid information for safety but not for efficacy.

Conclusion:

This 12-week, randomized, double blind study of acromegaly patients demonstrated statistically significantly differences between each dose (10 mg, 15 mg, and 20 mg) of pegvisomant injection and placebo in IGF-I reduction. The differences from placebo in mean percent change of IGF-I from baseline to Week 12 were -23%, -44%, and -59%, respectively. For the secondary efficacy variable, normalization of IGF-I, the percentages were 10%, (3/31), 39% (10/26), 77% (21/26), and 82% (23/28), respectively, for the placebo, 10mg, 15mg, and 20mg treatment groups at endpoint.

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

Dr. Nevius

cc: Arch NDA 21-106
HFD-510/CKing, RPerlstein, SMalozowski
HFD-715/LPian, TSahlroot, ENevius, CAnello

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/s/

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S. Edward Nevius
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Concur with review.