CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-106

Medical Review(s)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	21-106	APPLICATION TYPE:	Commercial NDA
SPONSOR:	Pharmacia	PROP. BRAND NAME:	Somavert
		GENERIC NAME:	Pegvisomant
		CHEMICAL NAME:	B2036-PEG
CATEGORY OF DRUG:	Growth Hormone (GH) Receptor Antagonist	ROUTE:	Subcutaneous injection
MEDICAL REVIEWER:	Robert S. Perlstein MD, FACP, FACE	REVIEW DATE:	2/12/03

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Dates:	CDER Stamp Dates:	Submission Type:	Comments:
10/1/02, 8/29/02 & 4/30/02	10/2/02, 8/30/02 & 5/1/02	NDA for a New Molecular Entity	Drug developed under IND

Overview:

In June 2001, at the end of the first review cycle, this medical reviewer concluded that Somavert (Pegvisomant), a new molecular entity (more specifically, a GH receptor antagonist) represents a significant advance in the treatment of acromegaly, a serious, "life-shortening" disease, for which currently approved therapies are suboptimal. Given the facts that 1) the observed efficacy of Somavert was excellent, and 2) the possible hepatic safety signal observed will be aggressively monitored, this reviewer concluded that the risk/benefit analysis of the original NDA submission from a clinical perspective favors drug approval. Please refer to the Executive Summary and complete review previously entered in DFS for a comprehensive analysis of the efficacy and safety of Somavert in the treatment of acromegaly. However, because of CMC deficiencies, Somavert was judged to be "Approvable" in June 2001. In August and October 2002, the Sponsor resubmitted the NDA after correction of the CMC deficiencies (and after certain agreements were reached with the Division's Pharmacology/Toxicology reviewers). My clinical review of the resubmission consists of 3 parts A) my new edits of the Sponsor's suggested Package Insert (PI) (which incorporated suggested changes previously made by this reviewer in June 2001) ; B) comments on the Sponsor's 30Ap02 submission containing responses to the Division's requests for "clinical information not required for approval" listed in the Division's 26Jun01 Approvable Letter to the Sponsor; and C) a review of the Sponsor's Safety Update (1June00 through 18July02).

With regard to the Sponsor's proposed PI: 1) efficacy tables/figures were slightly altered; 2) the INDICATIONS section was modified to maintain consistency with the Sandostatin LAR indication; 3) alkaline phosphatase should be included in the list of liver tests (LTs) to be monitored; 4) GH levels should be obtained (at least once) in conjunction with insulin-like growth factor I (IGF-I) levels during dose titration with Somavert and when a maintenance dosage has been achieved to rule out a rapid and/or progressive increase in GH which might be indicative of rapid growth of the GH-secreting pituitary adenoma; 5) a comment regarding the unknown long-term significance of the low titer anti-GH antibodies observed in some patients was added to the immunogencity section; 6) it is acceptable to exclude monitoring of renal function/urinalyses (see ahead*); and 7) a 40 mg loading dose of Somavert is satisfactory (see ahead).**

Conclusions:

1) The Sponsor's proposed PI will need to be further discussed during interactive telcons in the very near future.
2) The Sponsor's responses to the Division's 26Jun01 requests for "clinical information not required for approval" listed in the Division's 26Jun01 Approvable Letter to the Sponsor were satisfactory. In this regard:
a) This reviewer is satisfied with the Sponsor's intention to create a comprehensive database on medical outcomes of patients with acromegaly treated with Somavert in order to carefully follow safety and to assess sustained efficacy (the Somavert patient registry). The database will include continually updated information regarding adverse events, LTs, pituitary tumor size by MRI scans, GH levels, glucose metabolism, renal function/urinalyses*, immunogenicity data, IGF-I levels, and Somavert dosage. In addition, this reviewer agrees with the Sponsor's intention to monitor these same safety (and efficacy) variables during all subsequent Phase 4 studies.
*b) The Division agrees with the Sponsor's request to exclude the need for monitoring of renal function/urinalyses from the Package Insert because of the lack of a renal safety signal during the clinical studies. However, given the nephrotoxicity of uncertain etiology observed during preclinical rat studies, it is essential that careful ongoing documentation of renal function/urinalyses be included in the abovedescribed Somavert patient registry (as well as in all Phase 4 studies conducted by the Sponsor).
c) This reviewer agrees with the Sponsor's plan to explore the development of a validated assay for anti-Somavert antibodies which can be performed in the presence of therapeutic serum levels of Somavert.
d) In view of the comparable pharmacokinetics (PK) and pharmacodynamics (PD), and the very similar clinical efficacy and safety endpoints observed in a relatively small number of patients after 12 weeks of treatment with Somavert 10 mg/day following a loading dose of either 80 mg or 40 mg of Somavert, and in the context of the chronic nature of acromegaly and the recommended frequency of Somavert dose adjustment (6-8 weeks), this reviewer agrees with the Sponsor that any discernible differences between the patients receiving the 40 mg and 80 mg loading doses are not clinically significant, and, therefore, that a 40 mg loading dose is sufficient**.
3) Review of the Sponsor's latest Safety Update (which covered the period between 1Jun00 and 18July02) revealed no new significant adverse events related to Somavert – in particular, abnormal LTs or pituitary tumor growth. As a result of limited drug availability, only 25 acromegalic patients were exposed to Somavert during this period of time. A total of 20 adverse events were reported in 11 patients.

Recommendations:

1) Schedule interactive telcon with Sponsor to discuss PI (scheduled for Wednesday 2/12/03).
2) The Sponsor should continue to actively develop the Somavert patient registry in order to carefully follow safety (especially LTs, pituitary tumor size, renal function/urinalyses and immunogenicity), and to assess sustained efficacy.
3) The Sponsor should continue its efforts to develop a validated assay for anti-Somavert antibodies which can be performed in the presence of therapeutic serum levels of Somavert
4) This reviewer suggests that a straightforward 8-12 week PK/PD study should be accomplished post-approval in a relatively small number of acromegalic patients (~10 per arm) who initially do or do not receive a loading dose of Somavert (e.g., 40 mg), and then are treated with 10 mg/day of Somavert. It is our expectation that the PK and PD results will be comparable, and that the clinical efficacy and safety endpoints observed at the end of the trial will be very similar. In that case, subsequent labeling could be amended excluding the need for any loading dose. Please submit your proposed protocol so that it can be reviewed by the Division's Biopharmaceutics Team.

Recommended Regulatory Action:

X	Approval from a Clinical Perspective
	Not Approvable

Signed: Medical Reviewer: Robert Perlstein MD Date: 7Feb03

Medical Team Leader: David Orloff MD Date: _____

14 page(s) of revised draft labeling has been redacted from this portion of the review.

B. Review of Sponsor's 30AP02 Submission Containing Responses to the Division's Comments/Requests for Information Not Required for Approval Listed in the Division's 26Jun01 Approvable Letter to the Sponsor

Clinical Pharmacology & Biopharmaceutics

2. There is uncertainty as to the cross-reactivity of impurities in the drug product when using the RIA for detection of pegvisomant concentrations in serum. It is possible that some of these impurities are bioactive. Purify these impurities, and evaluate their cross-reactivity with the RIA as well as their bioactivity. Together, these procedures will contribute to the understanding of the active components of pegvisomant.

3. Data show an interaction between octreotide and cyclosporin which may be growth hormone mediated. Since pegvisomant can cause an apparent decrease in growth hormone by blocking receptors, you should conduct an *in vivo* drug interaction study to address any potential pharmacokinetic interaction between pegvisomant and cyclosporin.

4. No data were submitted on the route of elimination of pegvisomant in humans. Provide data showing the route of elimination and/or metabolic pathways of pegvisomant. These data may be the basis for future recommendations of pharmacokinetic studies in special populations (e.g., hepatic and/or renal impairment).

5. To further understand the metabolic effects that pegvisomant may have on other drugs, conduct in vitro metabolism/drug interaction studies as per the guidance, "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro".

See Biopharmaceutics Review.

Clinical

6. Establish a registry of acromegalic patients treated with pegvisomant (Somavert) in order to better monitor the rate of spontaneous reporting of liver test (LT) abnormalities during the initial marketing of pegvisomant.

This reviewer is satisfied with the Sponsor's intention to create a comprehensive database on medical outcomes of patients with acromegaly treated with Somavert in order to carefully follow safety and to assess sustained efficacy (the Somavert patient registry). The database will include continually updated information regarding adverse events, LTs, pituitary tumor size by MRI scans, GH levels (if obtained), glucose metabolism (including the incidence of hypoglycemic reactions, and decrease in requirement for anti-diabetic medications [e.g., oral hypoglycemics, insulin] in acromegalics with diabetes mellitus), renal function/urinalyses*, immunogenicity data (anti-GH antibody data [on drug] and anti-Somavert antibody data [off drug]), insulin-like growth factor I (IGF-I) levels, and Somavert dosage. In addition, this reviewer agrees with Sponsor's intention to monitor these same safety (and efficacy) variables during all subsequent Phase 4 studies.

*The Division has agreed with the Sponsor's request to exclude the need for routine monitoring of renal function/urinalyses from the Package Insert because of the lack of a renal safety signal during the clinical studies. However, given the nephrotoxicity of uncertain etiology observed during preclinical rat studies, it is essential that careful ongoing documentation of renal function/urinalyses be included in the abovedescribed Somavert patient registry (as well as in all Phase 4 studies conducted by the Sponsor). Furthermore, this reviewer endorses the agreement of the Sponsor and the Division's Toxicology Reviewer to monitor renal function during presently ongoing 2 year rat carcinogenicity studies.

7. Obtain additional immunogenicity data (including anti-pegvisomant antibodies***, anti-growth hormone (GH) antibodies, and anti-host cell protein antibodies) when the purity of the to-be-marketed product has improved to an acceptable level.
***Development of a validated assay for anti-pegvisomant antibodies which can be performed in the presence of therapeutic serum levels of pegvisomant should be undertaken.

As noted in my original review, this reviewer agrees with the Sponsor that the efficacy of Somavert was not adversely impacted in the 27 patients (16.9%) in whom low titer, non-neutralizing anti-GH antibodies were detected during active treatment, and the 10 patients in whom anti-Somavert antibodies were detected 1-2 months following cessation of Somavert therapy (all of whom had anti-GH antibodies during active treatment as well).

It is highly unlikely that neutralizing antibodies will be detected after the administration of the much more pure Somavert product (P3 process)

which will soon be marketed. Nonetheless, this reviewer agrees with the Sponsor's plan to 1) explore the development of a validated assay for anti-Somavert antibodies which can be performed in the presence of therapeutic serum levels of Somavert; and 2) continue to collect anti-GH antibody data (on drug) and anti-Somavert antibody data (off drug) as a component of the Somavert patient registry (as well as in all Phase 4 studies conducted by the Sponsor)

8. Consider a three-armed trial comparing the efficacy (e.g., percent reduction in IGF-I levels) of pegvisomant without a loading dose and after loading doses of 40 and 80 mg.

In view of the comparable pharmacokinetics (PK) and pharmacodynamics (PD), and the very similar clinical efficacy and safety endpoints observed in a relatively small number of patients after 12 weeks of treatment with Somavert 10 mg/day following a loading dose of either 80 mg or 40 mg of Somavert, and in the context of the chronic nature of acromegaly (i.e., the usual lack of a need for acute therapeutic changes) and the recommended frequency of Somavert dose adjustment (6-8 weeks), this reviewer agrees with the Sponsor that any discernible differences between the patients receiving the 40 mg and 80 mg loading doses are not clinically significant, and, therefore, that a 40 mg loading dose is sufficient. Furthermore, in this regard, this reviewer agrees with the Sponsor that a statistically rigorous 3 armed trial comparing the effects of a daily dose of Somavert without/with 2 different loading doses (40 mg or 80 mg) of Somavert is not necessary.

On the other hand, this reviewer does suggest that a straightforward 8-12 week PK/PD study should be accomplished post-approval in a relatively small number of acromegalic patients (~10 per arm) who initially do or do not receive a loading dose of Somavert (e.g., 40 mg), and then are treated with 10 mg/day of Somavert. It is our expectation that the PK and PD results will be comparable, and that the clinical efficacy and safety endpoints observed at the end of the trial will be very similar. In that case, subsequent labeling could be amended excluding the need for any loading dose. Please submit your proposed protocol so that it can be reviewed by the Division's Biopharmaceutics Team.

9. Consider a long-term study of the durability of pegvisomant efficacy.

Data from the open label, dose titration, extension studies (SEN-3613A and SEN 3615) (see my original review of the NDA submission) suggest that the efficacy of Somavert is durable, i.e. only a small percentage of patients achieving normalization of IGF-I levels during the titration phase of these studies required upward adjustment of their Somavert dosages to maintain normal IGF-I levels during the subsequent 12 month period.

This reviewer agrees with the Sponsor's plan to obtain additional information regarding the long-term durability of the efficacy of Somavert

in the treatment of hundreds of patients with acromegaly as part of the Tier 2 and 3 portions of the outcome database (the Somavert patient registry) described above under Clinical Question #6.

10. Consider a study comparing the efficacy of pegvisomant and somatostatin analogue (SA) therapy (the primary medical therapy for acromegaly currently available).

This reviewer agrees with the Sponsor's well documented contention that based on historical data as well as retrospective analyses of Somavert clinical trial data that Somavert is superior to SA therapy with respect to both efficacy (and safety), and, therefore, a comparator study is not necessary. In this regard: 1) the mean IGF-I normalization rate for 15 SA studies was 54% compared with 92.6% (SEN-3615) and 97% (SEN-3613A) during the Somavert clinical trials - despite a lower mean pre-treatment IGF-I concentration in the SA studies; 2) a subset of patients (n=13) known to be resistant to SA therapy prior to enrollment in the Somavert clinical trials achieved normalization of IGF-I levels after treatment with Somavert; and 3) in a subset of 44 patients treated with SA therapy prior to enrollment in SEN-3614 (which was washed out prior to initiation of Somavert therapy), 93.2% achieved normalization of IGF-I levels by the end of SEN-3615 (compared with a 38.6% IGF-I normalization rate when these same patients were receiving SA therapy at the time of screening for SEN-3614).

11. Consider a study exploring the utility of adding SA therapy to pegvisomant therapy in patients with clinically and biochemically resistant acromegaly with or without evidence of progressive growth of the underlying GH-secreting pituitary adenoma.

As stated above, Somavert is extremely efficacious in normalizing IGF-I levels (90+%) in patients with acromegaly (i.e, the total number of acromegalic patients resistant to Somavert therapy is expected to be very low), and, therefore, it is highly unlikely that the addition of SA therapy will be necessary. During the Somavert clinical trials, only 1 patient (SEN-3613A) required coadministration of Somavert and Sandostatin LAR in order to normalize IGF-I concentrations. Therefore, this reviewer agrees with the Sponsor's contention that it would not be feasible to conduct a formal study to evaluate the utility of combination therapy with Somavert and SA. In addition, as discussed above under Clinical Question #10, it is highly unlikely that patients resistant to SA therapy will require combination therapy, i.e the vast majority of these patients will respond to Somavert therapy alone.

Finally, in this regard, this reviewer agrees with the Sponsor's plan to monitor the utility of combination therapy with Somavert and SA in atypical patients with acromegaly through the proposed Somavert patient registry described above under Clinical Question #6.

12. Pending approval of this NDA, the following parameters should be monitored prior to the initiation or reinitiation of pegvisomant therapy in patients continuing to receive pegvisomant in clinical trials and subsequently at appropriate intervals. Refer to Enclosure 1 (Package Insert) for further discussion:

a. LTs
b. Renal function
c. IGF-I levels
d. GH levels
e. MRI scans of the sella turcica
f. Incidence of hypoglycemic reactions, and decrease in requirement for anti-diabetic medications (e.g., oral hypoglycemics, insulin) in acromegalics with diabetes mellitus

Since the Division issued the 26Jun01 Approvable Letter to the Sponsor, the Sponsor has submitted 2 protocols (a Sandostatin LAR conversion study and a cardiac mass study). All of the above parameters were included in the safety parameters to be monitored.

C. Review of Safety Update

Review of the Sponsor's latest Safety Update (which covered the period between 1Jun00 and 18July02) revealed no new significant adverse events related to Somavert - in particular, abnormal LTs or pituitary tumor growth.

As a result of limited drug availability, only 25 acromegalic patients were exposed to Somavert during this period of time (all of these patients were enrolled prior to 1Jun00 in the open label extension studies, SEN-3613A and SEN-3615). At the present time, no patients in these 2 studies are receiving Somavert therapy. No new clinical studies were completed (or initiated) during this latest Safety Update period. No deaths occurred and only 1 new serious adverse event (SAE) was reported - urinary incontinence. No subjects prematurely withdrew from a study due to an adverse event.

A total of 20 new treatment-emergent adverse events were reported in 11 patients. The incidence of adverse events in the cumulative 2002 Safety Update are identical/comparable to that of the original 120 day Safety Update (data cut-off 31May00) with respect to gender, age, relatedness, dose and duration of exposure.

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

/s/

Robert Perlstein
2/12/03 06:27:21 PM
MEDICAL OFFICER

David Orloff
2/12/03 06:57:11 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS (HFD-510)

APPLICATION #:	21-106	**APPLICATION TYPE:**	Commercial NDA
SPONSOR:	Sensus Drug Dev. Corp.; Robert Davis, Pharm.D., Exec. V.P. 512-487-2000	**PROP. BRAND NAME:**	Somavert
		GENERIC NAME:	Pegvisomant
		CHEMICAL NAME:	B2036-PEG
CATEGORY OF DRUG:	Growth Hormone Receptor Antagonist	**USAN / Established Name:**	
		ROUTE:	Subcutaneous Injection
MEDICAL REVIEWER:	Robert S. Perlstein MD, FACP, FACE	**REVIEW DATE:**	4/24/01

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
12/26/00	12/26/00	NDA for a New Molecular Entity	Drug developed under IND

RELATED APPLICATIONS (if applicable) None

Document Date:	APPLICATION Type:	Comments:

Overview: Pegvisomant is a new molecular entity - a mutated variant of recombinant human growth hormone (GH) (B2036) which is pegylated to decrease its clearance. It acts as a GH receptor antagonist and was developed by the Sponsor as a new therapy for acromegaly. During a 12 week, placebo controlled trial comparing 3 different daily subcutaneous doses of pegvisomant with placebo in patients with acromegaly, pegvisomant demonstrated excellent efficacy (e.g., a substantial % reduction of insulin-like growth factor I [IGF-I] levels and a large % of patients with normalization of IGF-I levels). In an open label extension trial of ~1 year duration, 92% of patients achieved and/or maintained a normal IGF-I level. Durability of effect was >90%. The overall safety profile for the 160 acromegalic patients exposed to pegvisomant was satisfactory. Two patients (0.8%) manifested hepatic transaminase elevations >10X the upper limit of normal suggesting the potential for hepatotoxicity. GH levels initially increased from baseline, and then remained stable for as long as 18 months. Only 2 patients (with naturally aggressive GH-secreting pituitary adenomas) manifested a clinically significant increase in pituitary tumor volume during pegvisomant therapy.

In that pegvisomant represents a significant advance in the treatment of a serious, "life-shortening" disease, and given the fact that the possible hepatic safety signal will be aggressively monitored, the risk/benefit analysis of this NDA submission from a clinical perspective favors drug approval – following appropriate labeling modifications.

Recommended Regulatory Action:

__X__ Approvable from a Clinical Perspective ___ Not Approvable

Signed: Medical Reviewer: /S/ Date: 4/25/01

Medical Team Leader: _____ Date: 4/26/01

EXECUTIVE SUMMARY

I. Recommendations

I.A Risk/Benefit Analysis and Approvability from a Clinical Perspective

I.A.1 Summary of Risk versus Benefit

Acromegaly, almost always a consequence of a growth hormone (GH) secreting pituitary adenoma, is a serious, life-threatening, uncommon disease which, if not adequately treated, is associated with substantial morbidity and mortality. Presently available therapies do not satisfactorily control acromegaly in as many as 1/3 of patients. GH hypersecretion results in elevated levels of insulin-like growth factor I (IGF-I), the primary mediator of GH action; IGF-I levels are routinely obtained in the followup of patients with acromegaly. Pegvisomant therapy results in 1) IGF-I normalization in ~60% of patients within 2 weeks; 2) normalization of IGF-I in >90% of patients in longer term studies; 3) sustained efficacy/durability of effect as well as very satisfactory durability of dosing (after treatment for a mean duration of ~1 year); and 4) a satisfactory safety profile.

From a safety point of view, pegvisomant was generally well tolerated during the clinical trials. The most concerning safety signals observed were 10-20 fold elevations of hepatic transaminase levels in 2 patients (reversible when drug was withdrawn). Although an extensive analysis of liver tests (LTs) was therefore carried out, which was otherwise reassuring, careful post-marketing surveillance of LTs will be necessary. Other safety issues which did not pose significant problems during the drug development program were: immunogenicity, "effective" GH deficiency, increases in serum GH, acromegalic tumor growth, and insulin sensitivity (in acromegalic diabetics).

I.A.2 Approvability from a Clinical Perspective

In that pegvisomant represents a significant advance in the treatment of a serious, "life-shortening" disease, and given the fact that the possible hepatic safety signal will be aggressively monitored, the risk/benefit analysis of this NDA submission from a clinical perspective favors drug approval – following appropriate labeling modifications.

I.B. Efficacy, Safety and Dosing Recommendations (including Labeling Recommendations, Risk/Management Actions, and Phase IV Studies)

I.B.1 Efficacy Recommendations

- Treat larger number of acromegalics for much longer periods of time in order to hopefully further demonstrate that the anti-acromegalic efficacy of pegvisomant does not wane after years of therapy.
- Consider comparing the efficacy of pegvisomant and somatostatin analogue (SA) therapy (the primary medical therapy for acromegaly currently available) head to head.
- Consider further exploring the utility of adding SA therapy to pegvisomant therapy in patients with clinically/biochemically resistant acromegaly with or without evidence of progressive growth of the underlying GH-secreting pituitary adenoma.

I.B.2 Safety Recommendations

I.B.2.1 Regarding Potential Hepatotoxicity

There is no solid scientific basis for how frequently LTs for injury and function should be monitored in patients receiving pegvisomant based on the results of the clinical trials. This reviewer (and the Agency's Hepatology Consultant) believe that the following recommendations are reasonable and should be incorporated in the label:

Phase IV Commitment:

- **This Medical Reviewer strongly endorses the Sponsor's stated willingness to make a Phase IV commitment to establish a registry of acromegalic patients treated with pegvisomant in order to better monitor the rate of spontaneous reporting of LT abnormalities during the initial marketing of the pegvisomant.**

Other recommendations:

- Every attempt should be made to ascertain the biochemical, phenotypic and genetic factors which predispose to pegvisomant-induced elevation of serum transaminase levels.
- Followup LTs should be obtained in the patients who manifested ALT levels ≥3X ULN during the clinical trials (in particular, the 2 patients whose ALT values were 10-20 fold elevated) to determine if there is any evidence of chronic liver disease.

I.B.2.2 Regarding Immunogenicity

- Development of a validated assay for anti-pegvisomant antibodies which can be performed in the presence of therapeutic serum levels of pegvisomant should be considered.
- Additional immunogenicity data (including anti-pegvisomant antibodies, anti-GH antibodies and anti-vector protein antibodies) in patients receiving pegvisomant produced by the ——— process should be obtained.

I.B.2.3 Regarding Monitoring of IGF-I Levels to Avoid a State of "Effective" GH Deficiency

In that pegviosmant is a potent antagonist of GH action which may result in a state of "effective" GH deficiency, careful monitoring of serum IGF-I levels is necessary in any acromegalic patient being treated with pegvisomant to allow for appropriate dose titration - in order to simultaneously achieve 1) optimal control of acromegaly and 2) avoidance of subnormal age-adjusted levels of IGF-I. Towards that end, the following recommendations should be contained in the label:

[redacted]

I.B.2.4 Regarding Elevations of Serum GH Levels

Serum GH levels consistently peak shortly after initiation of pegvisomant therapy (~2 weeks), reach a plateau, and do not increase further for as long as 18 months. Pegvisomant has significant structural similarity to GH which causes it to cross-react in commercially available GH assays (e.g., GH levels will be spuriously elevated if commercially available GH assays are utilized). In the opinion of this reviewer, the following recommendations should be addressed in the label:

[redacted]

I.B.2.5 Regarding Monitoring of GH-Producing Pituitary Adenoma Size/Volume

The following recommendation should be addressed in the label:

I.B.2.6 Regarding Increased Insulin Sensitivity and Decreased Requirement for Antidiabetic Therapy in Acromegalics with Diabetes Mellitus

Pegvisomant has been shown to increase insulin sensitivity in acromegalics with diabetes mellitus. Therefore, **the following information should be contained in the label:**

- After therapy with pegvisomant has been initiated, acromegalic patients with diabetes mellitus treated with insulin and/or oral hypoglycemic agents may be at risk for more frequent and/or severe hypoglycemic reactions, and may require downward dose adjustments.

I.B.2.7 Regarding Potential Renal Toxicity of the Polyethylene Glycol (PEG) Contained in Pegvisomant

Pegvisomant resulted in tubulopathy/proteinuria in preclinical studies in rats, and PEG has been associated with renal toxicity in human burn patients treated with topical antibiotic cream containing PEG. On the other hand, a renal toxicity safety signal was not apparent during the pegvisomant clinical trials. Nonetheless, in that the number of acromegalics exposed to study drug was small, this Medical Reviewer feels that the **following recommendation should be addressed in the label:**

- Serum BUN/creatinine and complete urinalyses (UA) should be obtained at baseline and at appropriate intervals after the initiation of pegvisomant therapy. In addition, a 24 hour urine collection for creatinine and protein should be obtained at baseline, and at least once during the first year of therapy.

I.B.3 Dosing Recommendations

In the most recent version of the submitted label, the Sponsor proposes that each patient receive a 40 mg loading dose of pegvisomant, followed by a daily dose of 10 mg/day; 5 mg dosage adjustments should then be made every 8 weeks based on the serum IGF-I level 2 weeks earlier (maximum dosage should not exceed 30 mg/day).

This reviewer (and the Division's Biopharmaceutics Reviewer) agree with the proposed dosing regimen (see Section II.D. of the Executive Summary for an explanation).

II Summary of Clinical Findings

II.A Background/Brief Overview of Clinical Program

Acromegaly is an uncommon, chronic, debilitating disorder (almost always resulting from excessive secretion of GH by a non-malignant pituitary adenoma) with very serious consequences if biochemical cure is not achieved. Untreated acromegalics, and acromegalics with persistent disease despite therapy, have a mortality ~2-5 times that of an age-matched cohort from the normal population, as well as a 5-10 year reduction in life expectancy. A substantial number of patients with acromegaly (~30-40%) are not cured with presently available therapies (e.g., surgery and/or radiation therapy and/or medical therapies such as SA therapy).

B2036 is a recombinant protein of human DNA origin. It differs from recombinant human GH (rhGH)/native GH by 9 critically located amino acid mutations. As a result, it is able to act as a growth hormone receptor antagonist (GHRA) (see Section II.A in the CLINICAL REVIEW for a more detailed explanation). B2036 is conjugated with PEG to form pegvisomant, in an attempt to increase its biological half-life. The primary effects of pegvisomant are thought to be 1) reversible binding to the human GHR without the induction of biological activity, and 2) diminished binding of native GH, resulting in reductions of circulating IGF-I levels, and therefore improved symptoms and signs of acromegaly.

Pegvisomant was therefore developed by the Sponsor as an additional anti-acromegalic therapy, in particular for the ~30-40% of acromegalics whose medical needs are currently unmet by existing therapies. Potentially, a greater percentage of acromegalics who have failed surgical and/or radiation therapy may respond to treatment with pegvisomant compared with the percentage of patients who respond to currently available medical therapies.

The efficacy and safety of weekly subcutaneously (SC) administered pegvisomant was evaluated in 1 placebo controlled trial (SEN-3611) and 1 open label extension study (SEN-3613). When it became clear that the efficacy observed after weekly dosing was unsatisfactory, the efficacy and safety of daily SC pegvisomant was assessed in 1 placebo controlled, Phase III, pivotal trial (SEN-3614), and 2 open label extension studies (SEN-3613A and SEN-3615). A total of 160 acromegalic patients were exposed to study drug. See Sections II.B and II.C below.

II.B Summary of Efficacy

II.B.1 Summary/Discussion of Efficacy Studies

II.B.1.1 SEN-3614 - Pivotal Phase III Study

SEN-3614 was a randomized, placebo controlled, double blind, fixed duration (12 weeks) study which compared the efficacy of 3 doses of pegvisomant and placebo in the treatment of acromegaly. Patients were required to have a baseline IGF-I level ≥3X ULN of an age-adjusted reference range after washout from previous medical therapy (e.g., SAs) in order to be included in this clinical trial.

- All 3 doses of pegvisomant produced significant, dose-dependent reductions in baseline serum IGF-I concentrations compared with placebo at each post-treatment time point. **The mean percent reduction in IGF-I at Week 12 was 4% for the placebo group compared with 27%, 50%, and 63% for the pegvisomant 10, 15, and 20 mg/day groups, respectively.**
- In addition, the incidence of patients whose IGF-I concentrations normalized during the study was significantly higher after the administration of all 3 doses of pegvisomant compared with placebo at all treatment visits. **After 12 weeks of treatment, 38.5% of patients in the pegvisomant 10 mg/day group, 75.0% of patients in the pegvisomant 15 mg/day group, and 82.1% of patients in the pegvisomant 20 mg/day group had normalized IGF-I concentrations compared with 9.7% of patients in the placebo group.** In fact, **47 out of 80 patients treated with pegvisomant (58.6%) achieved normalized IGF-I concentrations after only 2 weeks of treatment (including at least 50% of the patients treated with any dose of pegvisomant).**
- With regard to both reductions in baseline IGF-I concentrations and normalization of IGF-I levels, the effects of the 10 mg dosage peaked at 2 weeks, and then plateaued for the remainder of the study. The larger dosages continued to 1) produce greater decrements in IGF-I concentrations, and 2) increase the percent of patients with normalized IGF-I levels for ~4-8 weeks.
- Exploratory regression analyses (by the Sponsor/confirmed by the Division's Statistical Reviewer) suggest that heavier patients (>104 kg) and/or patients whose IGF-I multiple of the upper limit of normal (MULN) value is >2.05 may benefit from a larger dose of pegvisomant (e.g., 15-20 mg) when therapy for acromegaly is initiated.
- Subgroup analyses of acromegalic patients previously receiving SA or dopamine agonist (DA) therapy revealed that treatment with pegvisomant at doses of 15 and 20 mg/day normalized IGF-I concentrations in a significant number of patients who had previously responded suboptimally to SA and/or DA therapy.
- In addition, dose-dependent improvement in several symptoms and signs of acromegaly was observed, with statistically significant differences from placebo noted for soft tissue swelling, excessive perspiration, fatigue and ring size.

II.B.1.2 Open Label Extension Studies

II.B.1.2.1 SEN-3613A

SEN-3613A was an open label, dose-titration, extension study designed to assess the longterm efficacy of daily pegvisomant therapy in acromegaly (which enrolled patients from SEN-3613/SEN-3611). At the first visit in SEN-3613A, an 80 mg SC loading dose of pegvisomant was administered; beginning the next day, the patients initiated therapy with pegvisomant 10 mg SC daily. The dose was then titrated in 5 mg increments every 2 weeks by the participating investigators based on serial IGF-I levels, symptom relief and tolerability (up to 30 mg/day).

- During the ~1 year mean duration of daily pegvisomant therapy in SEN-3613A, IGF-I values decreased 49% further than they did after weekly dosing in SEN-3613. The mean IGF-I level at data cutoff expressed as a MULN was <1 (0.65).
- 35/38 patients (92.1%) manifested normal IGF-I levels during SEN-3613A. The 3 patients who did not achieve normal IGF-I levels had substantial (~60%) reductions in their baseline levels of IGF-I. Seventeen of the these patients had previously achieved normal IGF-I levels as a consequence of weekly pegvisomant therapy during SEN-3613; however, 18 patients required daily therapy with pegvisomant during SEN-3613A to normalize their IGF-I levels (9/18 required pegvisomant 20 mg/day).
- During SEN-3613A, IGF-I normalization was maintained at 403/437 (92.4%) visits – indicating durability of effect; in fact, 25/35 (71.4%) patients manifested 100% durability of effect.
- During SEN-3613A, only 2/35 (5.7%) patients required an upward adjustment of the dose of pegvisomant in order to maintain normal IGF-I levels – indicating durability of dosing.

II.B.1.2.2 SEN-3615

SEN-3615 was an open label, dose-titration, extension study designed to assess the longterm efficacy of daily pegvisomant therapy in acromegaly (which primarily enrolled patients from SEN-3614). At the first visit in SEN-3615, an 80 mg SC loading dose of pegvisomant was administered; beginning the next day, the patients initiated therapy with pegvisomant 10 mg SC daily. The dose was then titrated in 5 mg increments every 8 weeks by the participating investigators based on serial IGF-I levels, symptom relief and tolerability (up to 30 mg/day).

- During the ~12 week mean duration of daily pegvisomant therapy in SEN-3615, IGF-I values decreased 31% further than they did after daily dosing in SEN-3614. The mean IGF-I level at data cutoff expressed as a MULN was 1.
- During daily dosing in SEN-3615, 66/94 (70.2%) patients manifested normal IGF-I levels. The 70.2% rate of IGF-I normalization observed during SEN-3615 does not compare favorably with the 92.1% IGF-I normalization rate observed during SEN-3613A (e.g., the

~12 week mean duration of treatment during SEN-3615 necessitated by the data cutoff date resulted in insufficient time to up-titrate the dose of pegvisomant).

- Thirty seven of these 66 patients had previously achieved normal IGF-I levels as a consequence of daily pegvisomant therapy during SEN-3614; 29 additional patients normalized their IGF-I levels after daily therapy with pegvisomant during SEN-3615.

II.B.1.3 Supportive Studies with Weekly Administration of Pegvisomant

II.B.1.3.1 SEN-3611 and SEN-3613

SEN-3611 (a randomized, placebo controlled, double blind, 6 week study), and SEN-3613 (an open label, dose-titration, extension study) were designed to assess the short and longterm efficacy of weekly pegvisomant therapy in acromegaly. The results of both studies were not satisfactory (e.g., during SEN-3613, only 17/36 [~50%] patients achieved a normal serum IGF-I after a mean duration of therapy of ~23 weeks [most often after treatment with 80 mg/week]). As a consequence, the Sponsor switched to daily dosing of pegvisomant during SEN-3613A and SEN-3614. The significant efficacy observed during those daily dosing trials forms the basis of this NDA submission.

II.B.1.4 Overall Efficacy Conclusions

- Daily pegvisomant appears to be an efficacious short term therapy for patients with acromegaly, including patients who previously had failed medical therapy with SAs (SEN-3614).
- Longterm therapy with daily pegvisomant was also very effective in the treatment of acromegaly during SEN-3613A and SEN-3615.
- The starting dose of pegvisomant (10 mg/day) demonstrated substantial efficacy during both longterm studies. The majority of patients (52.6% in SEN-3613A and 57.4% in SEN-3615) achieved/maintained or maintained normal IGF-I concentrations after therapy with pegvisomant 10 mg/day.
- The durability of effect observed after longterm pegvisomant therapy was excellent. During SEN-3613A, IGF-I normalization was maintained at 403/437 (92.4%) visits (after a normal value had been achieved). In fact, 25/35 (71.4%) patients demonstrated 100% durability of effect.
- During SEN-3613A, only 2/35 (5.7%) patients required up-titration of the dose of pegvisomant to maintain IGF-I normalization (after a normal value had been achieved) - indicating very satisfactory durability of dosing.

II.C Summary of Safety

II.C.1 Summary/Discussion of Safety Issues

II.C.1.1 Exposure and Dosing During Clinical Trials

Pegvisomant was administered to 241 patients (160 with acromegaly, 45 with diabetes mellitus and 36 healthy volunteers). Amongst acromegalics, weekly pegvisomant doses ranged from 30 to 80 mg, and daily pegvisomant doses ranged from 5 to 40 mg. Most acromegalic patients treated with daily pegvisomant therapy received doses between 10 and 20 mg; however, 15 subjects (~10%) required 25 or 30 mg/day and 8 subjects (~5%) required 35 or 40 mg/day.

Twenty four of the acromegalic patients receiving weekly pegvisomant were treated for more than 26 weeks. Eighty four of the acromegalic patients receiving daily pegvisomant were treated for >52 weeks, and 45 were treated >26-≤52 weeks. Overall, 160 acromegalics were exposed to pegvisomant for ~186.2 patient-years. In contrast, the number of patient-years of exposure to placebo in the acromegalic cohort (n=47) was ~9.1, and in the non-pegvisomant (see Clinical Review for definition) acromegalic cohort was ~60.

Conclusions:

- Pegvisomant was administered to 160 acromegalic patients, 84 of whom were exposed to daily doses for >1 year.

II.C.1.2 Reasons for Study Discontinuation, Adverse Effects and Deaths

The majority of enrolled acromegalic patients either completed a placebo controlled study and/or are currently participating in on-going extension studies (85%). The rate of discontinuation due to adverse events was low. Of the 5 (3%) acromegalic patients who withdrew because of non-mortal adverse events, 2 were discontinued because of substantial transaminase elevations (quite possibly related to pegvisomant therapy - see ahead), 1 due to lipohypertrophy at the injection sites, 1 because of severe headaches after <1 week of therapy, and 1 diabetic acromegalic because of substantial weight gain on therapy (?related to enhanced insulin sensitivity?). The latter patient was a hypertensive, insulin-requiring diabetic who died suddenly 5 months after drug discontinuation for unknown reasons (?presumably cardiac?). The deaths of another 5 patients during the pegvisomant studies were not attributable to pegvisomant.

In general, pegvisomant was well tolerated by the majority of subjects. With the exception of a severe hypoglycemic reaction experienced by 1 non-acromegalic diabetic patient (see ahead), none of the 59 reported serious adverse events (SAEs) were considered by this

reviewer to be related to pegvisomant therapy. Another patient who mistakenly injected a larger dose of pegvisomant (80 mg/day) for 1 week suffered no ill effects.

In the acromegalic cohort, overall rates of treatment emergent adverse events (TESS) were comparable in the pegvisomant (85%) and placebo (70%) groups. There were a number of TESS for which the incidence in pegvisomant-treated patients was at least twice as much as that observed in placebo-treated patients. However, these differences must be interpreted with caution, in that many of these complaints are common in acromegalic patients, and there was a substantial difference in the duration of exposure between pegvisomant- and placebo-treated patients. The TESS most likely related to pegvisomant therapy was injection site reaction (11% of the pegvisomant group versus 4% of the placebo group). Of note, a significant incidence of injection site reactions/skin thickening was observed as well during preclinical toxicology studies in rats and monkeys.

Furthermore, additional analyses of TESS in the acromegalic cohort did not reveal any important age-, sex-, duration-, or dose-dependent relationships or associations. Larger sample sizes will be necessary to validate these observations. The majority of TESS were considered mild in severity. The only severe TESS reported in ≥5% of acromegalic patients was headache in the pegvisomant-treated groups.

Conclusions:

- With the exception of a modest incidence of injection site reactions (including 1 patient who withdrew because of lipohypertrophy), and 2 patients withdrawn because of markedly elevated transaminase levels, pegvisomant appears to be a well tolerated drug.

II.C.1.3 Abnormal Liver Tests (LTs)

Two patients (0.8% [2/241] of pegvisomant-treated subjects) developed 10-20 fold elevations of serum transaminase activities during the clinical trials, and were therefore withdrawn from their respective studies One of these patients developed markedly abnormal transaminase levels after initial challenge with pegvisomant, which returned to normal after dechallenge, and increased once again when he was rechallenged. The second patient developed mildy elevated transaminase levels after 4 weeks of therapy that peaked at ~10 weeks. A thorough evaluation (including a liver biopsy) led to a diagnosis of chronic hepatitis (?autommune-related chronic active hepatitis?). In both cases, complete recovery occurred after cessation of pegvisomant.

Additional analyses were performed to further define the incidence, time course and associations of LT elevations during the pegvisomant trials:

- In this regard, the crude incidence rates of elevated ALT values ≥3X ULN (not adjusted for duration of exposure to drug) in the pegvisomant and non-pegvisomant groups were

2.1% (5/241) and 2.1% (3/146). Furthermore, if only acromegalic patients enrolled in the fixed duration (12 week), placebo controlled SEN-3614 study are considered, the incidences of ALT values ≥3X ULN in the pegvisomant and placebo groups were 5% (4/80) and 3.1% (1/32), respectively. Similar percentages were observed if ALT ≥1.9X ULN is used as the cutpoint.

- With respect to most of the patients with ALT values ≥1.9X ULN, the time from the beginning of pegvisomant therapy to the first increase in ALT was ~8 weeks.
- The 2 individuals with marked elevations noted above were the only patients who manifested sustained large elevations of ALT and AST levels. In the 10 subjects with ALT elevations ≥1.9-10X ULN, ALT and AST values peaked, and then returned to normal and remained normal while the patient continued on pegvisomant therapy for 2 to 10 months, or the elevations were only sporadic and infrequent. In addition, in 3 of these patients, a reasonable explanation for transient increases in transaminase levels other than pegvisomant-induced hepatic injury was apparent.
- There was no relationship between the dose or duration of pegvisomant therapy and the change in mean ALT and/or AST levels.
- Only 2 of the pegvisomant-treated subjects with transaminase values ≥1.9X ULN manifested a concomitant elevation in the level of ALP (e.g., the patient described above with a biopsy diagnosis of chronic hepatitis whose ALP increased to 160 in association with marked transaminase elevations, and a second patient with very modest LT abnormalities of unknown etiology which resolved spontaneously), and none manifested a simultaneous increase in serum TBIL. This is reassuring in that the combination of ALT and/or AST elevations ≥3X ULN and TBIL elevation/jaundice is felt by many hepatologists to be an important signal for, or predictor of, serious drug-induced hepatic injury.
- No further elevations of ALT and/or AST were observed after the initiation of pegvisomant therapy in the subset of subjects with elevated baseline transaminase levels; in fact, in the majority of these patients, ALT and/or AST normalized while they were receiving pegvisomant therapy.
- Preclinical hepatotoxicity signals were not apparent in rat and monkey toxicology studies.

Conclusions:

- Pegvisomant was most likely related to the liver dysfunction in the patient who was challenged, dechallenged and rechallenged, and a causal relationship in the patient with chronic hepatitis is possible.
- The mechanism of pegvisomant-induced hepatic injury is unclear.
- It is somewhat reassuring that the incidence of ALT values ≥3X (and ≥1.9X) ULN were comparable in the pegvisomant and non-pegvisomant groups.
- The observation that in most patients ALT elevations returned to normal spontaneously and remained normal on continued drug

therapy is reassuring. However, in that drug tolerance is a well known phenomena, drug causality in these patients cannot be excluded.

- It is reassuring that patients with elevated baseline transaminase levels did not manifest further increases while on pegvisomant therapy.
- It is reassuring that none of the 160 acromegalic patients (and 241 subjects overall) who developed transaminase levels ≥1.9X ULN (in particular the patients with ALT levels ≥3X ULN) experienced simultaneous elevations in serum TBIL.

II.C.1.4 Immunogenicity

Treatment of acromegalics with pegvisomant resulted in a significant incidence (27/160; 16.9%) of low titer, non-neutralizing (e.g., the presence of antibodies did not impact efficacy) anti-human GH antibodies (measured while the patients were on-study). During the longterm study SEN-3613A, only 3/38 patients did not achieve normal IGF-I levels. Anti-human GH antibodies were not detectable in 2 of these patients at any visit - the third patient manifested a low titer (1:8) at only 1/6 study visits, at a time when IGF-I levels were steadily decreasing.

Subsequently, anti-pegvisomant antibodies were determined (by an assay of uncertain validity which can only be performed when pegvisomant levels are less than therapeutic) in 39 patients who had discontinued pegvisomant 1-2 months previously. Ten of these 39 patients had positive titers ranging from 1:8 to 1:256; anti-human GH antibodies had been present in all 10 of these patients (and IGF-I levels had normalized in 9/10*) during therapy with pegvisomant. *The 1 patient (3615-1709) who did not achieve a normal IGF-I level manifested positive anti-human GH antibodies at 2/6 early on-study visits when his IGF-I levels were comparable to baseline, and his starting dose of pegvisomant 10 mg/day had not yet been up-titrated. Several weeks after pegvisomant was discontinued, his anti-pegvisomant titer was 1:8.

Furthermore, minimal evidence of immunogenicity was observed in preclinical studies.

Finally, there were no reports of anaphylactic reactions thought to be related to pegvisomant.

Conclusions:

- Significant immunogenicity does not appear to be a consequence of pegvisomant therapy; however, the decrease in product purity which occurred when the Sponsor switched from the —— production process to the —— production process is of concern (see Chemistry Review).
- Anti-human GH antibodies may be an adequate surrogate for anti-pegvisomant antibodies (in patients where therapeutic levels of pegvisomant preclude measurement of anti-pegvisomant antibodies).

II.C.1.5 Pegvisomant-Induced "Effective" GH Deficiency

During the extension studies, more than 90% of acromegalics treated with pegvisomant achieved normalized IGF-I levels. Only 3 patients required back-titration of pegvisomant to 5 mg/day in order to maintain serum IGF-I concentrations within the normal age-adjusted range.

Conclusions:

- The incidence of pegvisomant-induced "effective GH deficiency" as reflected by decreased age-referenced serum IGF-I levels was small during the clinical trials, and amenable to dosage adjustment.

II.C.1.6 Elevated Serum GH Concentrations

During SEN-3614, GH levels peaked after only 2 weeks of therapy with all 3 dosages, and then plateaued for the remaining 10 weeks of the study. Baseline GH levels doubled after therapy with pegvisomant 15 mg/day and tripled after 20 mg/day. This dose dependent increase in GH appeared to be related to the magnitude of IGF-I reduction caused by increasing the dose of pegvisomant.

An additional analysis of acromegalic patients participating in the 2 extension studies, grouped into 3 cohorts based on how long they had received continuous daily pegvisomant treatment (at least 6, 12 or 18 months), was also performed. GH levels increased between baseline and 6 months, and then plateaued for 6-12 months. The elevations of serum GH once again mirrored the decreases in serum IGF-I concentrations

Conclusions:

- It appears that the elevated GH concentrations observed after 2 weeks of pegvisomant therapy do not increase further for as long as 18 months.
- The clearcut temporal and reciprocal relationship between the changes in serum GH and IGF-I, as well as the lack of a progressive increase in GH for as long as 18 months, suggest that the increase in serum GH concentration observed in acromegalic patients treated with pegvisomant is physiologically related to pegvisomant-induced IGF-I suppression.

II.C.1.7 Change in GH-Secreting Pituitary Adenoma Volume on Serial MRI Scans

Followup MRI scans of 131 acromegalic patients treated with pegvisomant revealed no change in mean tumor volume (mean of 11.5 months between baseline and final MRI) compared with a slight decrease (-0.22 cc) in 37 placebo-treated patients (mean of 2.5 months between MRIs). A minimal increase from baseline (+0.10 cc) was noted in patients with prior surgery alone and no prior surgery or radiation.

In addition, an analysis of the distribution of changes in tumor volume demonstrated that all but 4 patients had a decrease, no change, or a ≤1 cc increase in tumor volume. In 2 patients, tumor volume increased ~1.5 cc after 3-6 months of pegvisomant therapy; however, in both instances, the blinded neuroradiologist reading the final scan did not feel a clinically significant increase in tumor size had occurred. On the other hand, 2 additional patients with acromegaly previously resistant to currently available therapies (detailed narratives included in Clinical Review), demonstrated significant continued tumor growth while being treated with pegvisomant for ~1-2 years (~2.5-3 cc).

Conclusions:

- With respect to the entire cohort of acromegalic patients treated with pegvisomant, there does not appear to be a significant increase in mean tumor volume after a mean duration of therapy of ~1 year.
- The 2 significant outliers observed in the distribution analysis appear to have naturally aggressive pituitary adenomas resulting in 1) progressive tumor growth, and 2) acromegaly clinically/biochemically resistant to currently available therapies as well as pegvisomant. **However, one cannot exclude with certainty at this time a role for pegvisomant in the observed tumor growth.**

II.C.1.8 Increased Insulin Sensitivity in All Acromegalics and Possible Decreased Requirement for Antidiabetic Therapy in Acromegalics with Diabetes Mellitus

During SEN-3613A, acromegalic patients were treated with dose-titrated amounts of daily pegvisomant (10 to 30 mg/day). Mean fasting insulin levels in the entire acromegalic cohort significantly decreased after 6 months of therapy. One diabetic acromegalic patient, a glipizide XL-requiring diabetic, was treated with pegvisomant for a total of 13 months; as a consequence of therapy, hemoglobin A1C normalized and fasting insulin levels decreased - despite discontinuation of the oral agent. A second acromegalic patient with diabetes mellitus manifested

a substantial decrease in insulin requirement associated with a large weight gain after ~3 months of pegvisomant therapy.

Conclusions:

- Treatment with pegvisomant did appear to result in significant improvement in insulin sensitivity in acromegalics with and without diabetes mellitus. One diabetic acromegalic was able to discontinue oral antidiabetic therapy, and a second patient manifested a dramatic decrease in insulin requirement.
- Serious hypoglycemic reactions have not been reported to date in acromegalic patients with diabetes mellitus successfully treated with pegvisomant.

II.C.1.9 Potential Safety Issues (Renal) Related to Pegylation

Both preclinical and clinical data suggest at least the potential of PEG-induced renal toxicity. In a 6 month toxicology study in rats, pegvisomant administration produced histologic tubulopathy associated with proteinuria, granular casts and pyuria clinically (without changes in serum BUN or creatinine) in female rats only. Furthermore, a syndrome resembling ethylene glycol toxicity including renal toxicity has been observed in human burn patients treated with a topical antibiotic cream containing PEG. On the other hand, 3 other PEG-containing medications recently approved by the Agency have been well tolerated without evidence of renal toxicity. However, all of these medications are administered weekly or every other week, and therefore they may not be appropriate comparators for pegvisomant. During the placebo controlled and open label trials conducted as part of the pegvisomant clinical development program, there were no clinically significant changes in serum BUN or creatinine. Furthermore, new-onset proteinuria after the initiation of pegvisomant therapy (~2 times as common in the 20 mg/day group compared with placebo during SEN-3614) did not result in progressive/persistent proteinuria after longterm exposure, and extended exposure to pegvisomant did not exacerbate preexisting proteinuria.

Conclusion:

- There is no evidence from the clinical trials conducted to date that treatment with pegvisomant results in significant renal toxicity; however, the presence of a renal safety signal in the solitary 6 month daily dosing preclinical toxicology study (in rats) is of concern.

II.C.1.10 Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses with Implications Relevant for Safety

Conclusions:

- Drug accumulation does not appear to be a concern after longterm administration of pegvisomant. PK data obtained during the open label extension studies indicates that pegvisomant did not accumulate when administered chronically to acromegalic patients, even when the maintenance dosage was ≥20 mg/day.
- Population PK analysis revealed that that concomitant treatment with lipid-lowering drugs decreased the clearance of pegvisomant by ~30%. The clinical significance of this observation is uncertain.

II.C.1.11 Overall Safety Conclusion

Overall, pegvisomant has been demonstrated to have a satisfactory safety profile. **The primary concern of this reviewer is potential hepatotoxicity.** Careful monitoring of LTs in large numbers of acromegalic patients over time should clarify whether or not the serious (but reversible) elevation of serum transaminase levels in 2 of the 160 acromegalics (241 subjects overall) exposed to the drug was a harbinger of more profound hepatic injury.

II.D Proposed Dosing

In the label, the Sponsor proposes that each patient receive a 40 mg loading dose of pegvisomant, followed by a daily dose of 10 mg/day; 5 mg dosage adjustments should then be [redacted] weeks based on the serum IGF-I level 2 weeks earlier. The maximum dosage should not exceed 30 mg/day. This dosing recommendation is based on the suppositions that 1) ~5 half lives of pegvisomant (e.g., 6X5=30 days=~4 weeks) are necessary to achieve the PK steady state after dosing initiation or a dosing change, and 2) a lag period of ~2 weeks is the time necessary to achieve the maximum PD effect of a given dosage (e.g., reduction in IGF-I level) - after steady state blood levels had been attained.

Comments:

This reviewer (and the Biopharmaceutics Reviewer) agree with the Sponsor's proposed dose regimen.

1) In the label originally proposed by the Sponsor in December 2000, a loading dose of [redacted] mg was recommended; however, in the revised label submitted by the Sponsor in April 2001, a loading dose of 40 mg is recommended. During SEN-3614, 2 subsets of patients were mistakenly loaded with 40 mg and 60 mg of pegvisomant, respectively [redacted]. According to the Division's Biopharmaceutics Reviewer, actual (and simulated) comparative PK/PD analyses of the subsets

receiving different loading doses demonstrate minimal differences between the subsets 2 weeks after the initiation of pegvisomant therapy, and essentially no differences after 4 weeks of therapy. **Therefore, this reviewer (and the Biopharmaceutics Reviewer) agree with the Sponsor that a pegvisomant loading dose of 40 mg would be sufficient.**

2) **There are multiple reasons why the starting dose should be 10 mg** (rather than 15 or 20 mg):

- Acromegaly is a chronic disease
- Substantial efficacy was demonstrated for the 10 mg dosage during short term (12 weeks; SEN-3614)) and long-term (mean duration of therapy ~1 year; SEN-3613A) clinical trials.
- If the 10 mg dosage does, in fact, result in normalized IGF-I levels, drug exposure is minimized (e.g., overexposure to drug is limited by determining the lowest effective dose).
- Possible overtreatment/oversuppression (with reduced IGF-I levels) is less likely.
- At the present time, there are no established predictors of pegvisomant responsivity (e.g., no a priori method is currently available to determine who will need higher doses).

3) The Sponsor's proposal to titrate the dose of pegvisomant every 8 weeks (the regimen utilized during SEN-3615) as opposed to every 2 weeks (the titration scheme used during SEN-3613A) is further supported by the observation that the incidence of IGF-I normalization was comparable in these 2 studies after a mean duration of therapy of ~12 weeks (70.2% [66/94] in SEN-3615 and 71.1% [27/38] in SEN-3613A).

II.E Special Populations

II.E.1 Gender, Racial/Ethnic and Age-Related Differences

There were no apparent gender, racial/ethnic or age-related differences observed in efficacy or safety. However, the number of patients analyzed were too few to draw definitive conclusions.

II.E.2 Pediatric Studies

The safety and effectiveness of pegvisomant in pediatric patients have not been evaluated. The Sponsor was granted a waiver with regard to performing pediatric studies in that acromegaly in children (e.g., gigantism) is exceedingly rare.

II.E.3 Renal and Hepatic Disease

Patients with clinically significant renal and/or hepatic disease were excluded from the pegvisomant clinical trials. Therefore, appropriate subgroup analyses could not be performed. Such studies would be very difficult to accomplish in that acromegalics have a remarkably low prevalence of renal disease (in view of the frequent occurrence of hypertension and/or diabetes mellitus in these patients). Furthermore, it is unlikely that rhB2036 (like rhGH) will accumulate in the presence of renal and/or hepatic disease. The fate of the pegylated lysine moieties formed after the cleavage of the pegvisomant molecule in multiple tissues remains unclear.

II.E.4 Pregnancy Use

Reproduction studies in rabbits using pegvisomant doses up to 10 times the highest recommended human dose have revealed no evidence of fetal harm or impaired fertility. However, in that controlled studies have not been conducted in pregnant women, this reviewer agrees with the Sponsor that pegvisomant should be administered during pregnancy on a very selective basis when it is clearly necessary to control acromegalic manifestations.

APPEARS THIS WAY
ON ORIGINAL

Table of Contents

CLINICAL REVIEW

I. Introduction and Background

I.A General Information

I.A.1 Chemical; Generic; and Proposed Trade Names

B2036-PEG; Pegvisomant; Somavert.

I.A.2 Drug Class

Growth Hormone Receptor Antagonist (GHRA).

I.A.3 Related Drugs

New Molecular Entity.

I.A.4 Sponsor's Proposed Indication

Somavert is indicated for the treatment of [redacted] acromegaly who have had an inadequate response to [redacted] surgery and/or radiation therapy, or for whom surgery or radiation therapy is not appropriate.

I.A.5 Dosage Form, Dosage Regimen Recommended by Sponsor, and Route of Administration

Reconstituted injectable suspension. After the SC administration of an initial bolus loading dose (80 mg), the proposed daily dosage is 10 to 30 mg SC (determined by dose titration).

I.A.6 Brief Overview of Clinical Section of NDA Review

Efficacy was reviewed separately in detail for the pivotal, Phase III study SEN-3614. The efficacy reviews for the other clinical trials (SEN-3613A, SEN-3615, SEN-3611, and SEN-3613) are contained in the Integrated Summary of Efficacy (ISE). A consolidated safety review for all of the clinical trials is found in the Integrated Summary of Safety (ISS).

I.A.7 Milestones in Product Development

No prior FDA reviews or Advisory Committee meetings.

I.A.8 Foreign Marketing Status

Not marketed in any other country. No "turndowns" by the drug regulatory agencies of other countries.

II. Clinically Relevant Findings from Chemistry, Preclinical Toxicology, Biopharmaceutics and Statistical Reviews

II.A Chemistry

See Chemistry Review. B2036 is a recombinant protein of human DNA origin which has significant structural similarities to native human GH and to the rhGH, somatropin. It is produced by mutating 9 amino acid positions in rhGH. As a result of these alterations, the binding characteristics of B2036 at the GHR are altered, and it acts as a GHRA. Specifically, B2036 avidly (and reversibly) binds to the GHR at site 1 (on 1 GHR) but not site 2 (on a second GHR) - thereby 1) preventing the receptor dimerization necessary for the biological activity of GH, and 2) competitively inhibiting the binding of native GH. B2036 is conjugated with PEG (a water soluble polymer of ethylene glycol which primarily covalently binds to lysine) to form pegvisomant, in an attempt to increase its biological half-life. As a result of this pegylation, the avid affinity of B2036 for the GHR at site 1 is somewhat decreased, but not enough to decrease its efficacy as a GHRA. See reference 1.

The Division's Chemistry Reviewer has expressed concern about an increased potential for immunogenicity after the administration of lots of pegvisomant produced by the currently utilized (and "projected for marketing") ——— process. Batches of pegvisomant produced by the ——— process have much higher concentrations of the ——— ——— impurities of pegvisomant, as well as E. coli vector protein (compared with lots of pegvisomant produced by the ——— process). ——— product was utilized during the placebo controlled SEN-3614 study. However, both ——— products were used by patients during SEN-3613A and SEN-3615; therefore, a comparison of immunogenicity between patients receiving solely ——— product and subjects treated only with ——— product is not possible. See Section VI.C.9 regarding the apparent lack of consequential immunogenicity observed during the clinical trials.

II.B Preclinical Toxicology

See Pharmacology/Toxicology Review. In addition, see Section VI.C.13 in ISS for comments about preclinical studies relevant to human safety. In female rats, there was evidence of a renal toxicity signal (e.g., tubulopathy/proteinuria).

II.C Biopharmaceutics Review and Human Pharmacology, Pharmacokinetics (PK) and Pharmacodynamics (PD)

See Biopharmaceutics Review. In addition, see Sections I.B.3 and II.D in the EXECUTIVE SUMMARY for discussion of the proposed dosing regimen, and Sections III, VI.A.5.7.4 and VI.C.12 ahead for additional comments concerning PK/PD issues relevant to efficacy and safety.

II.D Statistical Review

See Statistical Review. The Medical Reviewer collaborated appropriately with the Statistical Reviewer, in particular with regard to the pivotal, placebo controlled, Phase III study SEN-3614 (including the exploratory analyses of predictors of responsivity).

III. Clinical Pharmacology

The PK of pegvisomant were calculated from single dose studies in healthy volunteers/acromegalic patients, and multiple dose studies in acromegalic patients.

- The bioavailability of a SC dose of pegvisomant was 57% compared to an intravenous dose.
- The apparent volume of distribution of pegvisomant was ~7 liters.
- The maximum concentration (Cmax) and area under the curve (AUC) after the SC administration of 10, 15, and 20 mg of pegvisomant increased more than proportionally, indicating possible saturable elimination.
- The route of elimination of pegvisomant has not been established.
- The mean clearance of pegvisomant was ~32 mL/h. The clearance of pegvisomant was directly related to body weight and inversely related to dose.
- The $T_{1/2}$ of pegvisomant was thought to be ~6 days.

Please see **Biopharmaceutics Review** for additional detail and the results of population PK/PD modeling, as well as Section II.C above.

IV. Description of Clinical Data and Sources

IV.A Materials Reviewed

- All clinical data in the original submission received on **12/26/00.** The data were primarily reviewed electronically after the NDA submission was placed on a secure website by CDER personnel.
- Safety Update received on 2/23/01 reviewed electronically.
- Revised proposed label received on 4/23/01.
- Letter from Sensus received on 6/7/00.

- Various email attachments received in 1/01, 3/01 and 4/01 in response to Medical Reviewer's requests (see Section IV.A.2).
- Consultation from Dr. John Senior/Hepatologist/HFD-440 received on 4/13/01
- Reviews for related NDAs, and IND ——— (see Section IV.A.1).

IV.A.1 Related INDs and NDAs

Pegvisomant - IND ———; FDA-approved pegylated drugs: 1) Adagen (Enzon) - NDA 19-818; 2) Oncaspar (Rhone-Poulence-Rorer) - FTN 103411; 3) PEG-Intron (Schering) - BLA 99-14888.

IV.A.2 Correspondence with Sponsor

- 1/18/01: Telcon involving myself, Robert Davis, Pharm.D. (Executive Vice President), and Mike Bernstein (Senior Director, Regulatory Affairs). Requests made by me for additional analyses regarding 1) acromegalic patients with elevated baseline LTs; 2) decreased requirement for antidiabetic therapy during SEN-3614; 3) longterm effects of pegvisomant on levels of IGF-I and GH; and 4) distribution of acromegalic tumor volume changes after pegvisomant therapy.
- 1/18/01: Received email clarifying the contents of various Addendums provided by the Sponsor.
- 1/19/01 and 1/21/01: Additional analyses requested arrive as planned (via secure email).
- 2/23/01: Safety Update arrives as planned.
- 3/21/01, 3/22/01 & 3/23/01: Multiple telcons involving myself and Dr. Davis. Multiple (~22) requests made by me for additional information and analyses (e.g., tabulation of additional LT and urinalysis results, additional information on 2 patients with severe adverse reactions)
- 3/28/01: First portion of additional information requested arrives as planned (via email) and discussed with Dr. Davis by telephone.
- 4/3,4&6/01: Additional information requested arrives as planned (via email) and discussed with Dr. Davis by telephone.
- 4/6/01: Clinical findings with regard to a patient with increased insulin sensitivity associated with a large weight gain after therapy with pegvisomant discussed with on-site investigator (Dr. David Cook) at the University of Oregon Health Sciences Center.
- 4/9,10,11,12,16,20/01: Additional information requested arrives as planned (via email) and discussed with Dr. Davis by telephone.
- 4/23/01: Revised proposed label arrives as planned (via email).

IV.B Table Summarizing Design of Clinical Trials

Table 1. Brief Summary of Clinical Trials

Study Number	# of Sites	Design	Treatment Arms	Duration of Treatment	Patient Type
SEN-3614	16	Randomized, double blind, placebo controlled **Phase III pivotal study	4 treatment arms: Placebo and pegvisomant 10 mg, 15 mg and 20 mg SC DAILY following an 80 mg loading dose of pegvisomant or placebo	12 weeks	Diagnosed acromegaly - washout previous therapy n=112
SEN-3611	6	Randomized, double blind, placebo controlled Phase IIb study	3 treatment arms: Placebo and pegvisomant 30 mg and 80 mg SC WEEKLY	6 weeks	Diagnosed acromegaly - washout previous therapy n=46
SEN-3613	6	Open label uncontrolled extension study	Titration phase: Pegvisomant 30 mg up to 80 mg SC WEEKLY Maintenance phase	Prematurely terminated after mean duration of ~ 23 weeks	Patients completing SEN-3611 n=36
SEN-3613A	6	Open label uncontrolled extension study	Titration phase: Pegvisomant 80 mg loading dose following by pegvisomant 10 mg up to 30 mg SC DAILY (5 mg adj q2wks based on IGF-I levels) Maintenance phase.	Ongoing	Patients completing SEN-3611 and/or enrolled in SEN-3613 n=38
SEN-3615	16	Open label uncontrolled extension study	Titration phase: Pegvisomant 80 mg loading dose following by pegvisomant 10 mg up to 30 mg SC DAILY (5 mg adj q6-8wks based on IGF-I levels) Maintenance phase	Ongoing	Patients completing SEN-3614 n=108

IV.C Patient Demographics

See review of SEN-3614, ISE and ISS.

IV.D Extent of Exposure

See ISS.

IV.E Clinical Background

IV.E.1 Post-Marketing Experience

None - domestic or foreign.

IV.E.2 Literature Search

Literature regarding the various aspects of acromegaly (in particular the mortality associated with inadequately treated disease and the results reported with presently available treatment options), and the discovery and development of GH antagonists, was reviewed for the last 15 years. Appropriate references are cited in the text of this review, and a list of these references appears after signature page.

IV.E.3 Background Information Regarding Acromegaly

Acromegaly is an uncommon, chronic, debilitating disorder almost always resulting from excessive secretion of GH by a non-malignant pituitary adenoma. The clinical presentation is characterized by prograssive coarsening of facial features; soft tissue swelling and acral changes in the hands and feet, organomegaly, hypertension and diabetes. The diagnosis is confirmed by elevated levels of serum IGF-I, and the inability of a glucose load to suppress serum GH. The prevalence of acromegaly has been calculated to be ~50 patients per million, and the incidence is thought to be ~3 cases per million per year. It is therefore estimated that there are currently ~40,000 acromegalic patients in the United State, Western Europe and Japan.

Acromegaly is a disease with very serious consequences if biochemical cure (normalized IGF-I and appropriately suppressed GH levels after a glucose load using sensitive assays) is not achieved. Untreated acromegalics and acromegalics with persistent disease despite therapy have a mortality ~2-5 times that of an age-matched cohort from the normal population, as well as a 5-10 year reduction in life expectancy (2-8). Cardiovascular disease, cerebrovascular disease, respiratory disease and malignancy are the leading causes of death in these patients (1-7). It has recently been shown that biochemical cure following treatment results in mortality rates equivalent to that in matched controls (6,7,9,10); therefore, tight control of the GH/IGF-I axis is now considered to be a desired and required goal of therapy (11).

The 3 existing acromegaly treatment options of surgery, radiation therapy, and medical treatment attempt to achieve control of the GH/IGF-I axis by reducing GH hypersecretion, either by removing or destroying the pituitary adenoma or by reducing GH secretion from the tumor pharmacologically. More often than not, the acromegalic patient presents with a macroadenoma which is more difficult for even a skilled neurosurgeon to completely resect. It has been predicted that if a strict definition of biochemical cure is employed, no more than 30-40% of acromegalics are cured by surgery (10, 12-14). The effects of radiation therapy are delayed and more often than not inadequate when current criteria for a biochemical cure are applied; in addition, radiation therapy results in a very high incidence of hypopituitarism (15-16).

Existing drug therapy consists of DAs (bromocriptine and cabergoline) and SAs (octreotide/sandostatin, lanreotide). Drug therapy has been primarily utilized in surgical failures and after radiation therapy while waiting for an effect. DAs normalize GH and IGF-I in less than 20% of patients and cause significant side effects (17-19). SAs, such as octreotide and lanreotide, require the presence of functional somatostatin receptors in GH-secreting pituitary adenomas in order to inhibit GH secretion. However, presumably because all tumors do not fully express functional somatostatin receptors (20), treatment with octreotide (in either short-acting SC (Sandostatin 300-1500 ug/day SC tid) or long-acting intramuscular (IM) (Sandostatin LAR Depot 10-40 mg IM monthly) formulations results in a normalized IGF-I in only 45-65% of patients and mean GH levels <2.5 ng/mL in only 50% of patients (21-25). Of note, SA therapy results in frequent adverse effects (e.g., the incidence of biliary tract abnormalities including gallstones is >60% and gastrointestinal side effects including diarrhea, abdominal pain or discomfort and nausea are frequent, especially in the initial months of therapy) (26).

Therefore, a substantial number of patients with acromegaly (~30-40%) are not cured with present therapy and, as stated earlier, have a clearly increased mortality (as well as significant morbidity).

B2036 is a recombinant protein of human DNA origin. It differs from rhGH/native GH by 9 critically located amino acid mutations. As a result, it is able to act as a GHRA (see Section II.A for detailed explanation) (1). B2036 is conjugated with PEG (to decrease its clearance) to form pegvisomant (1).

Pegvisomant is therefore being developed by the Sponsor to treat the ~30-40% of acromegalics whose medical needs are currently unmet by existing therapies. Unlike SAs (which require the presence of functional somatostatin receptors in GH secreting pituitary adenomas), pegvisomant blocks the action of GH at the cellular receptor level. Therefore, potentially, a greater percentage of acromegalics who have failed surgical and/or radiation therapy will respond to treatment

3613A (ongoing), SEN-3614 (8/98-2/99), and SEN-3615 (ongoing). (Note: The financial disclosure information for 14 additional I/SI who only participated in the diabetes trials were also reviewed.)

- Twenty eight of the 64 study I/SI participated in SEN-3611, SEN-3613 and SEN-3613A, 62/64 study I/SI in SEN-3614 and SEN-3615, and 26/64 study I/SI in all 5 studies.
- None of the study I/SI were employees of the Sponsor (Sensus Drug Development Corporation).
- All study I/SI provided financial disclosure information to the Sponsor.
- None of the study I/SI had received or will receive an Outcome Payment (payment dependent upon outcome of study).
- None of the study I/SI had or has a Proprietary Interest in pegvisomant (e.g. patent, trademark, copyright, licensing agreement)
- None of the study I/SI had or has an Equity Interest in the Sensus Drug Development Company (e.g. stock ownership, stock options).

Conclusions:

This reviewer believes that the steps taken to minimize potential bias were sufficient, and that the payments made to and/or in behalf of the research efforts of these 4 investigators did not affect the outcome of these clinical trials.

VI. Reviews of Efficacy and Safety for Clinical Studies

VI.A SEN-3614 - Review of Efficacy (see references 27-28)

VI.A.1 Objectives

This investigation was a Phase III, randomized, placebo controlled, double blind, multiple dose, parallel group, multicenter (16 centers) trial designed to evaluate the safety and efficacy of 12 weeks of daily pegvisomant (10 mg, 15 mg, and 20 mg) therapy and placebo in 112 subjects with acromegaly.

VI.A.2 Brief Summary of Clinical Trials Prior to the Pivotal Phase III Study - SEN-3614

Preclinical studies demonstrated significant PD effect (reduced IGF-I levels) and no significant toxicity. In healthy and acromegalic subjects, single doses of 0.3 mg/kg and 1 mg/kg resulted in 24-28% and 26-61% suppression of IGF-I from baseline concentrations, respectively (SEN-3601 and SEN-3602).

SEN-3611 (7/97-10/97) was a Phase IIb, randomized, placebo controlled, double blind, multiple dose, parallel group, multicenter (6 centers) study designed to evaluate the safety and efficacy of 6 weeks of weekly pegvisomant (30and 80 mg) therapy and placebo in 46 subjects with acromegaly. Patients were randomized after previous therapy (e.g., SAs) had been discontinued and washed out. The results revealed a statistically significant difference in mean percent change from baseline in IGF-I concentrations between the placebo and 30 mg pegvisomant groups (0% vs. 16%, p = 0.0426), and between the placebo and 80 mg pegvisomant groups (0% vs. 31%, p = 0.0008). Only 4 patients in the 80 mg pegvisomant group and 2 patients in the 30 mg pegvisomant group achieved normalized IGF-I levels at some time during the study.

The subjects from this study were eligible to enter an open label, dose titration study (SEN-3613; 8/97-2/98). Initially, these patients received weekly doses of pegvisomant individually titrated from 30 to 80 mg/week. Subsequently, the protocol was amended, and patients were switched to daily dosing individually titrated from 10 to 30 mg/day (e.g., 5 mg changes at 2 week intervals based on IGF-I responses)

following an 80 mg bolus loading dose (SEN-3613A; 2/98-present). The change to daily dosing was made 1) because of the lack of efficacy observed in SEN-3611 (and SEN-3613), 2) PK analysis/modeling predicted that trough concentrations of pegvisomant after daily dosing would be raised by ~20% (compared with weekly dosing), thus increasing the drug's potential efficacy, 3) in response to reports from some subjects of decreased symptomatic relief 4-6 days after their last injection, and 4) to reduce the volume of each injection. An 80 mg bolus loading dose was utilized to achieve a steady state more rapidly.

During SEN-3613A, treatment with pegvisomant 10 to 20 mg daily for a mean duration of ~1 year resulted in a normal IGF-I level in 35 (92%) patients, and a 69% mean decrease in IGF-I concentration. Twenty six of 30 patients previously treated with octreotide had not achieved normal IGF-I levels; of note, in 23 (88%) of these subjects, treatment with pegvisomant did in fact result in normalization of IGF-I levels.

Treatment with pegvisomant has been well tolerated during the Phase I/II clinical trials. There has been no apparent trend in the type or frequency of any adverse events across studies with the possible exception of injection site reactions (including itching, bruising, and bleeding). In addition, there has been no significant antibody formation to GH or pegvisomant. Furthermore, MRI scans of the sella turcica has revealed no clinically significant changes in tumor volume (a theoretical consideration because of impaired short loop feedback of IGF-I on GH).

SEN-3614 (8/98-2/99) was therefore designed to confirm the efficacy and safety of daily pegvisomant therapy at the 10, 15 and 20 mg dose levels (following an 80 mg bolus loading dose) in subjects with acromegaly (first observed in SEN-3613A - an open label, non-randomized, extension study) in a 12 week, randomized, double blind, placebo controlled, pivotal trial.

VI.A.3 Study Design

VI.A.3.1 Description of the Study - Including the Choice of Control Groups

Potential study patients were screened to determine eligibility (Visits 1 and 2). Most significantly, at Visit 1, serum IGF-I levels were determined and study subjects were withdrawn from previous medical therapy (if any) for acromegaly; at Visit 2, serum IGF-I levels were repeated - *only patients with serum IGF-I values ≥30% above the ULN were eligible for randomization to 1 of the 4 treatment arms at Visit 3. At Visit 3, 112 subjects with the diagnosis of acromegaly were randomized (in a blinded fashion) to receive daily SC doses of either 10, 15, or 20 mg of pegvisomant or placebo (~25 subjects per group) for 12 weeks after a SC bolus loading dose of either 80 mg pegvisomant (for subjects in the active treatment groups)

or placebo, at 16 investigational centers. Subjects self-administered pegvisomant or placebo SC daily; the bolus loading dose was administered by study personnel. Study assessments for efficacy and safety were accomplished at study Weeks 0 (Visit 3-baseline), 2 (Visit 4), 4 (Visit 5), 8 (Visit 6), and 12 (Visit 7-study termination). The study design (spanning approximately 14-21 weeks for any given patient) is depicted in Table 2.

Table 2. SEN-3614 - Study Design

Screening		Baseline		Treatment		
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
2-5 weeks prior to Visit 2	2-4 weeks prior to Visit 3	Week 0	Week 2 (± 2 days)	Week 4 (± 2 days)	Week 8 (± 2 days)	Week 12 (± 2 days)

The primary measure of efficacy was the percent reduction in IGF-I concentrations, and the most consequential secondary measure of efficacy was the incidence of normalization of IGF-I levels - over the course of the study, in particular after 12 weeks of therapy. The other secondary efficacy parameters are listed in Section VI.A.4.3.2.1.2.

The safety and tolerability of pegvisomant were evaluated based upon the reporting of adverse events, the development of anti-GH antibodies, changes in concentrations of serum GH, clinically significant changes in MRI scans obtained before treatment was initiated and at study termination, and other routine parameters listed in Section VI.A.4.3.2.2.

In addition, levels of serum pegvisomant were obtained at each study visit.

At the completion of the study, subjects were eligible to participate in an open label extension study designed to investigate further the safety, tolerability, and efficacy of daily pegvisomant therapy.

VI.A.3.2 Protocol Amendments

The most significant protocol amendment dealt with an error made in the amount bolused to approximately 50% of the patients in the 10 mg (40 mg instead of 80 mg) and 15 mg (60 mg instead of 80 mg) treatment arms. A protocol amendment was inserted to provide for a subgroup analysis comparing the responses of the patients who received the correct and incorrect bolus doses.

VI.A.4 Materials and Methods

VI.A.4.1 Subjects

VI.A.4.1.1 Subject Selection

The protocol called for the enrollment of ~100 acromegalic patients. In fact, 112 acromegalic patients were enrolled in the study.

VI.A.4.1.2 Inclusion Criteria

Subjects eligible to enter the screening phase (Visit 1) of this study:

- were male or female (females were postmenopausal or surgically
- sterile)
- were 18 years of age or older
- had a diagnosis of acromegaly based on accepted criteria made or confirmed at one of the participating study centers

VI.A.4.1.3 Exclusion Criteria (primary)

Subjects who were excluded from entering the screening/eligibility (Visit 1 and Visit 2) phase of this study:

- had prior treatment with any long-acting SA (e.g., sandostatin LAR, Lanreotide) within 3 months of Visit 1
- had prior treatment with any SA (e.g., sandostatin) within 2 weeks of Visit 2
- had prior treatment with any DAs (e.g., bromocriptine, cabergoline) within 5 weeks of Visit 2
- had the presence of other conditions that could result in elevated growth hormone and/or IGF-I concentrations (e.g., severe hepatic or renal disease, anorexia nervosa, Laron's syndrome, treatment with levodopa or narcotic analgesics, or heroin abuse)
- had a history of relevant drug and/or food allergies or regular treatment with any medication that may be expected to interfere with projected study results
- refused to use adequate contraception to prevent pregnancy during the study

VI.A.4.1.4 Treatment Phase Criteria (eligible for randomization at Visit 3-baseline)

Subjects who were eligible for the treatment phase (Visits 3-7, Weeks 0-12) of the study:

VI.A.4.2.2 Treatments Administered - Dosage and Administration/Method of Treatment Assignment - Randomization

Patients were randomized (using an adaptive/minimization randomization procedure in a blinded fashion) to receive 1 of 4 treatment regimens (see below), after a SC bolus loading dose of either 80 mg pegvisomant (for subjects in the active treatment groups) or placebo.

Placebo: 32 patients
Pegvisomant 10 mg SC daily dose group: 26 patients
Pegvisomant 15 mg SC daily dose group: 26 patients
Pegvisomant 20 mg SC daily dose group: 26 patients

Randomization was stratified according to Visit 2 IGF-I concentrations (low [1.3 -2X ULN] versus high [>2X ULN]), as well as to investigative site to the extent possible.

VI.A.4.2.3 Selection of Doses

See Section VI.A.2 for a discussion of why pegvisomant 10, 15, and 20 mg SC daily following a bolus loading dose of pegvisomant 80 mg SC was selected for the SEN-3614 pivotal Phase III study.

VI.A.4.2.4 Dosage Modification

Not performed during this trial.

VI.A.4.2.5 Concomitant Therapy

During the study, subjects were not allowed to take any prescription or non-prescription medication which was likely to interfere with the projected effects of pegvisomant, GH, or IGF-I including SA (e.g., formulations of octreotide), DAs (e.g., bromocriptine, cabergoline, quinagolide, levodopa), and growth hormone releasing hormone antagonists. Other forms of therapy for the treatment of acromegaly, including surgery and radiation were also prohibited during the study. Narcotic analgesics were specifically excluded as well.

Other medications which were considered necessary for the subject's welfare and would not interfere with the study medication were given at the discretion of the investigator (see Section VI.A.5.5 ahead).

VI.A.4.3 Study Assessments

VI.A.4.3.1 Screening and Pre-treatment Assessments

To confirm subject eligibility and to establish baseline measurements, the following assessments were accomplished during the screening period (Visit 1 and Visit 2):

- verification that acromegaly had been diagnosed appropriately in the past
- medical history (including tabulation of concomitant medications)
- complete physical examination (including vital signs)
- complete blood count (CBC) with differential and platelet count
- complete UA with microscopic examination
- serum chemistry panel, including glucose*, total protein, albumin, globulin, albumin/globulin ratio, total TBIL, ALT (SGPT), AST (SGOT), ALP, GGT, LDH, BUN, creatinine, uric acid, calcium, inorganic phosphorous, cholesterol, triglycerides, sodium, potassium, chloride, CO2
- electrocardiogram (ECG) (actually performed at Visit 3 - baseline)
- serum pregnancy test
- signs and symptoms of acromegaly score (5 individual parameters and total score)
- overall health status rating
- quality of life (QOL) questionnaire(s)
- ring size
- serum IGF-I (at Visit 1 and Visit 2 as discussed in Section VI.A.3.1)
- serum free IGF-I*
- IGF binding protein-3 (IGFBP3)*
- acid labile subunit (ALS)*
- serum GH
- MRI scan (not necessary if performed in last 3 months and available for review; actually performed at Visit 3 - baseline)
- anti-GH antibodies (actually performed at Visit 3 - baseline)
- serum pegvisomant (actually performed at Visit 3 - baseline)

*additional markers of GH action

VI.A.4.3.2 Assessments during Treatment

VI.A.4.3.2.1 Efficacy Parameters

VI.A.4.3.2.1.1 Primary Efficacy Parameter (see Table 3)

- percent change in IGF-I concentration from baseline (Visit 3), especially after 12 weeks of therapy

VI.A.4.3.2.1.2 Secondary Efficacy Parameters (see Table 3)

- incidence of normalization of IGF-I concentration
- reduction in free IGF-I, percent free IGF-I, IGFBP3 and ALS levels
- change in ring size measurement[a]
- change in the signs and symptoms of acromegaly score[b]
- change in overall health status score[c]
- change in QOL score[d]

[a]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 were converted to a numeric score ranging from 1 to 63.

[b]Signs and symptoms of acromegaly were assessed according to five individual signs and symptoms (headache, perspiration, arthralgia, fatigue, and soft tissue swelling), and evaluated on a 9 point ordinal rating scale (0 = absent; 2 = mild; 4 = moderate; 6 = severe but not incapacitating; or 8 = severe and incapacitating). In addition, a total severity score was computed by summing the severity ratings of all five signs and symptoms.

[c]An overall health status score was evaluated with 0 = worst possible and 10 = best possible.

[d]Changes in QOL were assessed with the Short Form Health Status Survey (SF-36) Mental Component Score and Physical Component Score, the Brain Tumor module of the Functional Assessment of Cancer Therapy (FACT-Br) total score, and a specially developed instrument targeted to the signs and symptoms of acromegaly

VI.A.4.3.2.2 Safety Parameters (See Table 3)

Safety assessments were made based on the following:

- adverse event reports
- histories/physical examinations including vital signs
- routine laboratory studies
- ECGs
- anti-GH antibodies
- serum GH levels obtained at appropriate intervals
- MRI scans[e]

[e]High resolution MRI scans of the sella turcica (T1-weighted spin-echo images in the coronal and sagittal planes both before and after intravenous injection of standard dose Gadolinium-DTPA) were obtained at baseline and after 12 weeks of treatment. Imaged tumor volumes were measured by an independent neuroradiologist blinded to the treatment groups. The baseline scans were reviewed at the same time as the Week 12 scans to ensure that measurements were made in a

comparable location. The interobserver coefficient of variation for this method of tumor volume measurement (using calipers and measuring on hard-copy film) is estimated at approximately 3%. A subjective analysis was also made with respect to tumorous involvement of the cavernous sinus, optic chiasm, and sphenoid.

Table 3. SEN-3614 - Flowchart of Baseline and On-Study Efficacy and Safety Parameters*

Evaluations	Screening Period		Treatment Period				
	Visit 1	Visit 2	Visit 3 Baseline	Visit 4	Visit 5	Visit 6	Visit 7
Adverse events			X	X	X	X	X
Medical history		X					
Concomitant meds		X	X	X	X	X	X
Physical exam		X					
Vital signs		X	X	X	X	X	X
Hematology		X	X		X	X	X
Chemistry profile		X	X		X	X	X
:inalysis		X	X		X	X	X
ECG			X				X
Pregnancy test		X					X
GH	X	X	X	X	X	X	X
MRI scan of sella			X				X
Anti-GH antibodies			X			X	X
IGF-I, free IGF-I, ALS, IGFBP-3	X	X	X	X	X	X	X
Ring size	X		X	X	X	X	X
Signs and symptoms of acromegaly score	X	X	X	X	X	X	X
QOL questionnaire	X		X		X		X

*Table partially derived from submission

VI.A.4.4. Statistical Analysis Plan

VI.A.4.4.1 Sample Size Calculation

The targeted sample size of 100 subjects was based on efficacy observations made in SEN-3611 (see Section 8.2 and ISE). Assuming an

alpha equal to 0.05 and power of 0.80, a sample size of 25 subjects per treatment group was adequate to detect statistically significant differences in IGF-I variables of at least 20% between pegvisomant and placebo with a common standard deviation (SD) of 24%.

VI.A.4.4.2 Efficacy Analyses

VI.A.4.4.2.1 General Comments/Population(s) Analyzed

Primary and secondary efficacy analyses were carried out using the intent-to-treat (ITT) population. The ITT population included all subjects who were randomized and received at least 1 dose of study drug, and had at least one efficacy assessment while on treatment. Depending on the extent of subjects with missing assessments at study termination (12 weeks), the ITT population with last observation carried forward (LOCF) was also used. An analysis of the "evaluable population" (e.g., subjects who completed at least 8 weeks of treatment without major protocol violations) was not performed (as indicated in the original analysis plan) because the evaluable population differed from the ITT population by only 1 patient (e.g., 111 [ITT] vs. 110 ["evaluable"]).

Summary statistics (means, medians, SD, standard errors of the mean (SE), and minimum and maximum values for continuous variables, and numbers/percentages of responses in each category for discrete measures) are presented for all primary and secondary efficacy variables at each study visit for each treatment group and for all treatments combined. Study Day 0 (Visit 3) was used as the baseline reference visit for all analyses.

VI.A.4.4.2.2 Primary Efficacy Analysis

The primary efficacy outcome parameter for this study was the percent change in IGF-I concentration from baseline (Visit 3) to Week 12 (Visit 7) (and Week 12 LOCF). The percent change in IGF-I concentration from baseline was computed at each follow-up visit for each subject (e.g., the difference between the IGF-I concentration at any given time point and the IGF-I level at baseline, divided by the baseline IGF-I concentration, and then multiplied by 100).

Statistical analyses were performed to determine the baseline comparability between treatment groups (with respect to all demographic characteristics including baseline IGF-I values). The percent changes in IGF-I concentrations at Week 12 were compared (e.g., pairwise comparisons of each pegvisomant dose versus placebo) using analysis of variance (ANOVA). The effects of pegvisomant and placebo were considered to be significantly different if the calculated p-value was ≤ 0.05 (two-tailed). An expanded ANOVA model which included a treatment-by-site interaction term was investigated to determine the impact on the overall results.

A multiple comparison adjustment (step-down procedure) was utilized in comparing the effects of each of the different pegvisomant doses against placebo. The relative importance of each pegvisomant dose level determined the order of testing (e.g., if the effect of 20 mg/day of pegvisomant was significantly greater than the placebo effect, then the effect of 15 mg/day of pegvisomant was compared with placebo, etc). If a significant difference was not found at any given dosage, all remaining comparisons in the step-down procedure were considered to be non-significant.

Summary statistics and statistical evaluations are presented based on all subjects combined from the 16 investigative sites. Statistical comparisons are derived from appropriate procedures which account for within-site differences between treatments. For analysis purposes only, sites were pooled by continent (Europe vs. US) in order to have ample numbers of subjects to satisfy statistical assumptions when adjusting for site (e.g., representation of all 4 treatment groups).

VI.A.4.4.2.3 Secondary Efficacy Analysis

The secondary efficacy outcome parameters for this study are listed in Section VI.A.4.3.2.1.2, in particular the incidence of normalization of the IGF-I concentration. The statistical analyses performed were similar to the analyses described for the primary efficacy outcome parameter in Section VI.A.4.4.2.2. Note: In that the QOL instruments utilized to analyze the QOL data have never been validated in an acromegalic population, the QOL analyses were considered exploratory, and not definitive.

VI.A.4.4.2.4 Covariates

In the above described statistical analyses for efficacy, covariates may have been added to assess their potential influence in predicting efficacy. The protocol-defined covariates in this study were 1) baseline IGF-I concentration; 2) IGF-I study entry strata (low [1.3-2X ULN] versus high [>2.0X ULN]); 3) baseline GH concentration; 4) gender; and 5) baseline body weight.

VI.A.4.4.2.5 Subgroup Analyses

VI.A.4.4.2.5.1 Projected Subgroup Analyses

- Comparative analyses between treatment groups and placebo (IGF-I variables; ANOVA) were conducted in patients previously treated with SA or DA therapy (and contrasted with the analysis of the entire cohort) in order to assess the effect of prior alternative therapy on the efficacy of pegvisomant at Week 12.
- The change in IGF-I concentrations between Visit 1 and Visit 2,

and Visit 1 and Visit 3, were compared in order to determine whether the cessation of previous therapy for acromegaly resulted in an appropriate increase in IGF-I concentrations between Visits 1 and 3.

VI.A.4.4.2.5.2 Unanticipated Subgroup Analyses (Original Protocol Amended)

- As per protocol, all patients randomized to receive pegvisomant should have received an 80 mg bolus loading dose of pegvisomant. However, a total of 24 subjects (11 subjects in the pegvisomant 10 mg/day group and 13 subjects in the pegvisomant 15 mg/day group) did not receive the correct bolus loading dose (e.g., the patients in the 10 mg/day group received a 40 mg loading dose, and the patients in the 15 mg group received a 60 mg loading dose). Therefore, comparative analyses between treatment groups and placebo (IGF-I variables; ANOVA) were conducted in patients who received the correct bolus loading doses (and contrasted with the analyses of the entire cohort, and analyses of the patients who did not receive the correct bolus loading doses) in order to assess the effect of these incorrect bolus loading doses on the efficacy of pegvisomant at Week 12 (see Section VI.A.5.7.3.3). Additionally, a separate PK evaluation was conducted to determine the impact of the bolus loading dose error. Serum pegvisomant concentrations in subjects with and without the dosing error were compared by dose group and visit.

- Subject #2401 (placebo group) and Subject #2402 (pegvisomant 20 mg/day treatment group) were inadvertently administered each other's study medication supplies at Visit 6 (Week 8), and, as a result, took the wrong doses for the remaining 4 weeks of the study. Consequently, the IGF-I level of 1 patient rose and the IGF-I level of the other patient declined between Visit 6 (Week 8) and Visit 7 (Week 12). The primary ITT analysis uses the data from these subjects without correction or adjustment. However, in view of the dosing error, an additional separate analysis of the incidence of normalization of IGF-I in a "modified ITT population" was conducted

VI.A.4.4.3 Safety Analyses

All subjects who were randomized and received at least 1 dose of study drug were evaluable for safety. Adverse events, including intercurrent illnesses, were both tabulated and summarized by treatment group and body system using COSTART preferred terms. Physical examination results (including vital signs), clinical laboratory tests (including blood glucose values and liver function tests), ECG results, and tumor volumetric changes observed on serial MRI scans are presented in subject data listings, and summarized with simple descriptive statistics by dose group and visit in tables and graphs. **In addition, unplanned exploratory analyses (pairwise treatment comparisons derived from ANOVA) were conducted on accumulated GH data.**

VI.A.4.4.4 Data Quality Assurance

The Sponsor states that accurate, consistent, and reliable data were ensured through the use of standard practices and procedures. _____ performed all data management procedures including a series of logic and consistency checks on the database to ensure acceptable accuracy and completeness, and a database audit prior to database lock. The final database was then transferred to _____ for analysis and reporting (except for the QOL exploratory analyses - see Section VI.A.5.7.2.5).

VI.A.5 Results

VI.A.5.1 Subject Eligibility and Treatment Assignment

A total of 112 patients with acromegaly were enrolled at 16 study centers in the United States and Europe. Thirty two subjects were randomized to the placebo group, 26 subjects each to the 10 mg/day and 15 mg/day pegvisomant groups, and 28 subjects to the 20 mg/day pegvisomant group. All 112 patients were included in evaluations of drug safety, and 111 patients were included in the ITT analysis of the primary efficacy outcome parameter.

VI.A.5.2 Patient Disposition

Of the 112 patients enrolled/treated in this trial, 108 (96.4%) completed the study, and 4 (3.6%) prematurely discontinued. Three of the 4 patients who discontinued prematurely were included in the ITT analysis (LOCF was utilized for patients #1501 and #1605) of the primary efficacy outcome parameter: 1) patient #2104 received placebo for 70 days, and withdrew from the study because of lack of efficacy; 2) patient #1501 received pegvisomant 15 mg/day for 63 days, and was discontinued from the study because of an adverse event (significant transaminitis) - see ISS); and 3) patient #1605 received pegvisomant 15 mg/day for 7 days at which time he voluntarily withdrew from the study because of lack of efficacy and intolerable headaches. The fourth patient (#1115) (who was not included in the ITT analysis of the primary efficacy outcome parameter) received placebo for 6 days, and was discontinued from the study because of a belatedly discovered protocol violation (pituitary tumor compressing optic chiasm on the baseline MRI scan). See Table 4.

Table 4. SEN-3614 - Patient Disposition*

Termination Status	Placebo n=32	10 mg/d n=26	15 mg/d n=26	20 mg/d n=28	Total Patients n=112
Subjects completing the study					
Yes	30(94%)	26(100%)	24(92%)	28(100%)	108(96%)
No	2 (6%)	0	2 (8%)	0	4 (4%)
Total patients	32	26	26	28	112
Reasons for discontinuation					
Adverse event	0	0	1(50%)	0	1(25%)
Protocol violation	1(50%)	0	0	0	1(25%0
Lack of efficacy	1(50%)	0	0	0	1(25%)
Voluntary withdrawal	0	0	1(50%)	0	1(25%)
Total discontinued	2	0	2	0	4

*Table derived from submission

VI.A.5.3 Protocol Violations

Most of the protocol deviations during the study were minor (e.g., early or late study assessments, isolated missed measurements, isolated missed doses, and doses taken before the clinic visits and laboratory tests (instead of after visits). Patient #1409 (unbeknownst to the Sponsor) had previously participated in SEN 3611, but not the extension studies, SEN 3613 or SEN 3613A - his last dose of pegvisomant 80 mg/week was 9/30/97 and his first dose of placebo during SEN 3614 was 1/13/99.

As previously noted in Section VI.A.4.4.2.5.2, 22 patients did not receive the correct bolus loading dose. In addition, as noted in Section VI.A.4.4.2.5.2, 2 patients were inadvertently dispensed each other's study medication supplies at Visit 6 (Week 8).

One patient (in the placebo group) was prematurely discontinued from the study after 6 days because of a protocol violation (see Section VI.A.5.2), and was not included in the ITT analysis of the primary efficacy variable.

None of the protocol deviations confounded the results of the study once adjustive measures were tested and applied.

VI.A.5.4 Patient Demographics and Baseline Characteristics

As depicted in Table 5, the acromegalic patients randomized to the 4 treatment arms were well matched with respect to demographics and baseline characteristics. Of the 112 subjects enrolled, 56% were male and 44% were female. The mean age was 47.5 years (range 20-78 years; 73% were between 30-60 years). The majority were Caucasian (82%). The total of the mean scores for the 5 symptoms and signs of acromegaly for all subjects was 15.1 (rated on a 0-40 scale with lower scores indicating less severity). The mean IGF-I level for the ITT efficacy population was 670.4 ng/mL (see Table 8 ahead).

There were no apparent differences between groups (data not shown) with regard to the prevalence of patients with histories of preexisting organ system disease, excepting a history of hepatic disease (e.g., no subject in the pegvisomant 15 mg/day group reported a history of preexisting hepatic disease in contrast to a prevalence of 19% in the placebo group, 12% in the pegvisomant 10 mg/day group, and 18% in the pegvisomant 20 mg/day group). The most common preexisting abnormality in all of the treatment groups was a history of endocrine disease (e.g., ~50% of patients in all pegvisomant treatment groups had a history of partial or complete hypopituitarism). Of note, the prevalence of either type 1 or type 2 diabetes mellitus was ~20% in all 4 treatment groups.

At the screening physical examination, 73-89% of subjects in each treatment group were noted to have abnormal findings (data not shown). Mean vital sign measurements (temperature, systolic and diastolic blood pressure, and pulse rate), height, and weight (including body mass index) at baseline also did not differ substantially between treatment groups (data not shown). Thirty-four percent of all subjects had abnormal ECG findings at screening; however, once again, no differences were observed between treatment groups (data not shown).

The mean duration of acromegaly (± SEM) was 8.1 ± 0.7 years (range, 0.3-41.6 years), for which the vast majority of patients had previously received surgical, radiation, and/or drug treatment (see Tables 6 and 7). More specifically, 80-85% of patients had previously received surgical therapy with/without radiation therapy or drug therapy, ~60-80% of patients had received SA therapy, almost always in addition to surgical therapy or radiation therapy, and ~50% of patients had received conventional radiation therapy with/without surgical therapy or drug therapy. At the time of study initiation, the mean time since the patients' last surgery and radiation therapy, respectively, was 5.6 ± 0.57 years (n=93) and 6.8 ± 0.93 years (n=63). Importantly, there was very little difference observed between treatment groups with regard to the types of therapy previously received.

Only 13 patients had previously received neither surgery nor radiation therapy prior to study entry. Of these, 9 had previously received only drug therapy, and 4 were naïve to any therapy (1 patient [#1707] in the placebo group; 1 patient (#1402) in the pegvisomant 10 mg/day group; and 2 patients (#1405 and #2513) in the pegvisomant 15 mg/day group).

Baseline data for efficacy and safety variables are depicted in Tables 8 and 12 (e.g., further information on baseline IGF-I values, as well as baseline free IGF-I, ALS and IGFBP-3 levels), and the ISS (e.g., baseline GH values, tumor volumes determined by MRI scans, and clinical laboratory parameters including LTs and glucose values).

APPEARS THIS WAY
ON ORIGINAL

Table 5. SEN-3614 - Baseline Patient Demographics*

Characteristic	Placebo (n=32)	Pegvisomant 10 mg/d (n=26)	Pegvisomant 15 mg/d (n=26)	Pegvisomant 20 mg/d (n=28)	Total Subjects (n=112)
Gender [n (%)]					
Male	19 (59.4)	15 (57.7)	14 (53.8)	15 (53.6)	63 (56.3)
Female	13 (40.6)	11 (42.3)	12 (46.2)	13 (46.4)	49 (43.8)
Age (years)					
Mean	49.8	46.5	45.6	47.5	47.5
Range	25-78	26-71	24-78	20-74	20-78
Race [n(%)]					
Caucasian	26 (81.3)	22 (84.6)	22 (84.6)	22 (78.6)	92 (82.1)
Hispanic	3 (9.4)	3 (11.5)	2 (7.7)	3 (10.7)	11 (9.8)
African descent	1 (3.1)	0 (0)	2 (7.7)	1 (3.6)	4 (3.6)
Asian	2 (6.3)	1 (3.8)	0 (0)	1 (3.6)	4 (3.6)
Other	0 (0)	0 (0)	0 (0)	1 (3.6)	1 (0.9)
Signs and symptoms:**					
Soft tissue swelling					
Mean	2.1	2.4	2.7	2.8	2.5
Range					
Joint pain					
Mean	3.7	3.0	3.2	2.8	3.2
Range					
Headache					
Mean	2.1	2.5	3	2.1	2.4
Range					
Perspiration					
Mean	3.1	3.2	3.8	3.3	3.3
Range					
Fatigue					
Mean	3.2	3.7	4.3	3.9	3.7
Range					
Overall health status***					
Mean	5.8	5.9	5.7	5.9	5.8
Range					
Ring size					
Mean	47.3	48.1	48.3	45.1	47.2
Range					
IGF-I (ng/mL)	(n=31)	(n=26)	(n=26)	(n=28)	(n=111)
Mean	669.8	626.7	648.8	731.6	670.4
Range					

** Rated as 0=absent; 8=worst possible, *** Rated as 0=worst possible; 10 =best possible

*Table partially derived from submission

Table 6. SEN-3614 - Previous Acromegaly Therapy by Individual Therapy Type*

Previous Therapy**	Placebo (n = 32)	Pegvisomant 10 mg/day (n = 26)	Pegvisomant 15 mg/day (n = 26)	Pegvisomant 20 mg/day (n = 28)
Surgery	26 (81.3)	22 (84.6)	22 (84.6)	23 (82.1)
Conventional radiation	17 (53.1)	11 (42.3)	14 (53.8)	15 (53.6)
Gamma knife radiation	3 (9.4)	0 (0.0)	3 (11.5)	1 (3.6)
SA	24 (75.0)	15 (57.7)	21 (80.8)	21 (75.0)
Dopamine agonist	17 (53.1)	15 (57.7)	9 (34.6)	14 (50.0)
Other***	1 (3.1)	1 (3.8)	0 (0.0)	0 (0.0)

Data shown are n (%).
** Previous therapy categories are not mutually exclusive.
*** Placebo Patient #1409 received pegvisomant in SEN-3611.
***10mg/day Patient #1305 received stereotactic multiple arc radiotherapy (SMART).
*Table derived from submission

Table 7. SEN-3614 - Previous Acromegaly Therapy by Therapy Combination*

Previous Therapy**	Placebo (N = 32)	Pegvisomant 10 mg/day (N = 26)	Pegvisomant 15 mg/day (N = 26)	Pegvisomant 20 mg/day (N = 28)
Surgery plus radiation	18 (58.1)	9 (34.6)	15 (57.7)	15 (53.6)
Surgery without Radiation	8 (25.8)	13 (50.0)	7 (26.9)	8 (28.6)
Radiation without Surgery	2 (6.5)	2 (7.7)	1 (3.8)	1 (3.6)
Drug therapy only	3 (9.7)	1 (3.8)	1 (3.8)	4 (14.3)
No previous therapy	1 (3.2)	1 (3.8)	2 (7.7)	0 (0.0)

Data shown are n (%).
**Surgery and radiation categories could also include drug therapies.
*Table derived from submission

VI.A.5.5 Concomitant Therapy

Approximately 91% of subjects (102/112) reported the use of concomitant medications during the study period. There were no substantial differences between treatment groups in the incidence of concomitant medication use. The most frequently used medications were anti-inflammatory/anti-rheumatic products (not including steroids) (20-30%), "hypopituitary replacement medications" (e.g., systemic corticosteroids [~30-40%], thyroid preparations [~30%], and sex hormones [including testosterone] [~20-30%]), and antihypertensives (in particular angiotensin converting enzyme inhibitors) (10-30%). In addition, with regard to the presence of acromegaly, it is important to note that 8 patients were receiving

insulin therapy, and 9 patients were being treated with oral antidiabetic agents.

VI.A.5.6 Compliance

The Sponsor reports that lack of compliance was not a significant problem during this study. A small number of patients reported missing isolated doses or taking study medication before clinic visits instead of after visits. There were no apparent differences between treatment groups in the incidence of missed doses. Assessment of the validity of this claim is, however, difficult.

VI.A.5.7 Efficacy Results

VI.A.5.7.1 Primary Efficacy Analysis - Percent Change from Baseline in Serum IGF-I Concentrations

Mean IGF-I concentrations at baseline (Visit 3) were markedly elevated, and comparable between treatment groups (see Tables 5 and 8 and Figure 1). It should be noted at this point that several European patients who were thought to have appropriately elevated IGF-I levels at Visit 2 (based on assays performed at local European laboratories per protocol), and who were therefore randomized and dosed, were later found to have normal IGF-I concentrations at baseline (Visit 3) (when IGF-I assays were performed in bulk at the central laboratory (e.g., 3 patients in the placebo group, 3 patients in the pegvisomant 10 mg/day group, 1 patient in the pegvisomant 15 mg/day group, and 1 patient in the pegvisomant 20 mg/day group). Normal values at baseline were not considered to be a protocol violation by the Sponsor (e.g., it was set forth in the protocol that qualification criteria at Visit 2 were to be based on the results from local laboratories in the case of European patients). Therefore, no adjustments were made to the ITT analysis with respect to these 8 retrospectively normal IGF-I values at baseline. The Division's Statistical Reviewer does not feel additional analyses are necessary.

The percent change from baseline in serum IGF-I concentrations is presented in Table 8 and Figure 2.

- Statistically significant reductions in IGF-I concentrations compared with placebo were observed at every post-baseline time point after the administration of all 3 dosages of pegvisomant (all p-values = 0.0001).
- A dose-response relationship was clearly apparent as early as Week 2, and persisted through the Week 12 assessment (Figures 1 and 2).
- The effects of the 10 mg dosage peaked at 2 weeks, and then plateaued for the remainder of the study (a persistent 25-30% reduction in baseline IGF-I concentrations). The larger dosages

continued to produce greater decrements in IGF-I concentrations for ~8 weeks.

- By Week 12, IGF-I levels were reduced from baseline by 4% in the placebo group, 27% in the pegvisomant 10 mg/day group, 48% in the pegvisomant 15 mg/day group, and 63% in the pegvisomant 20 mg/day group.
- The administration of pegvisomant 20 mg/day resulted in significantly greater reductions in IGF-I levels than those observed after treatment with pegvisomant 10 mg/day at all visits, and the 15 mg dose was significantly better than the 10 mg dose from Week 8 onward.
- In addition, pegvisomant 20 mg/day was significantly more efficacious than the 15 mg dose at Weeks 4 and 12.
- There were no statistically significant treatment-by-site (pooled) interactions.

APPEARS THIS WAY
ON ORIGINAL