

**Table 8. SEN-3614 - Change From Baseline in IGF-I Concentration by Visit - ITT Efficacy Population\***

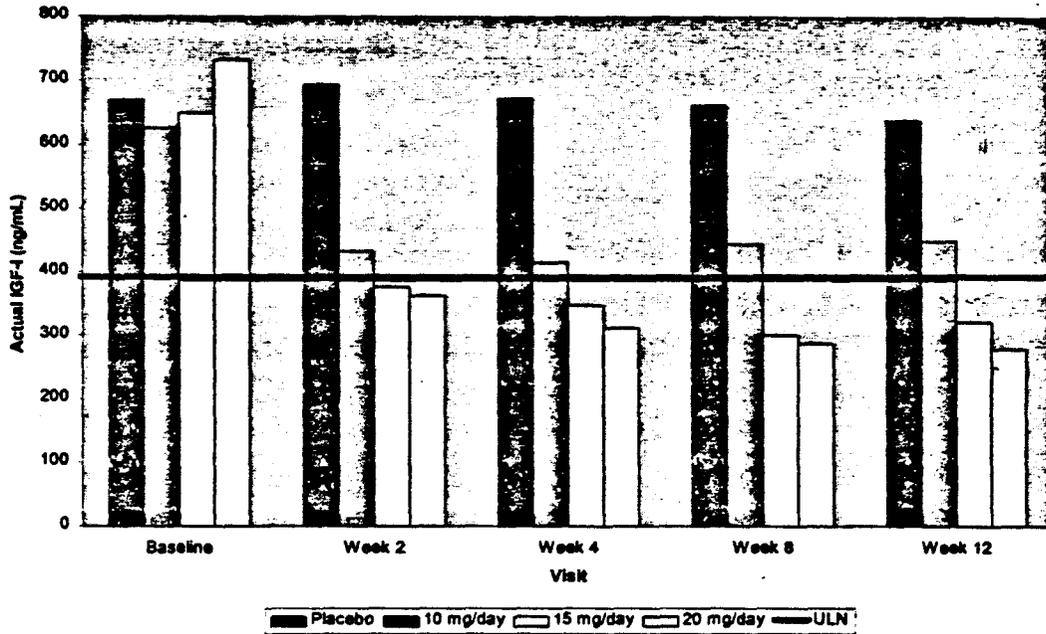
IGF-I (ng/mL)	Placebo	10 mg/d	Pegvisomant 15 mg/d	20 mg/d
<b>Baseline</b>				
N	32	26	26	28
Mean	669.8	626.7	648.8	731.6
Range				
<b>Week 2</b>				
N	31	26	26	28
Mean	694	433.1	376.9	362.9
Range				
Mean % change from baseline (SE)	3.5 (1.82)	-28.6 (5.80)	-39.4 (4.65)	-51.2 (3.11)
p-value vs placebo		0.0001	0.0001	0.0001
p-value vs 10 mg/d			0.1969	0.0013
p-value vs 15 mg/d				0.1078
<b>Week 4</b>				
N	31	26	26	28
Mean	673.1	415.6	347.8	312.1
Range				
Mean % change from baseline (SE)	2.1 (2.47)	-32.0 (5.63)	-44.6 (4.68)	-58.2 (3.14)
p-value vs placebo		0.0001	0.0001	0.0001
p-value vs 10 mg/d			0.0755	0.0003
p-value vs 15 mg/d				0.0168
<b>Week 8</b>				
N	31	26	25	28
Mean	662.6	444.5	300.5	287.2
Range				
Mean % change from baseline (SE)	0.5 (2.12)	-28.0 (6.35)	-52.2 (4.80)	-61.8 (3.43)
p-value vs placebo		0.0001	0.0001	0.0001
p-value vs 10 mg/d			0.0011	0.0001
p-value vs 15 mg/d				0.0800
<b>Week 12 (Final visit)</b>				
N	31	26	24	28
Mean	639.7	449.1	320.9	278.8
Range				
Mean % change from baseline (SE)	-4.0 (3.02)	-26.7 (5.46)	-50.1 (5.45)	-62.5 (4.03)
p-value vs placebo		0.0001	0.0001	0.0001
p-value vs 10 mg/d			0.0048	0.0001
p-value vs 15 mg/d				0.0155
<b>Week 12 (Final visit) (LOCF)**</b>				
N	31	26	26	28
Mean	639.7	449.1		278.8
Range				
Mean % change from baseline (SE)	-4.0 (3.02)	-26.7 (5.46)	-48.3 (5.18)	-62.5 (4.03)
p-value vs placebo		0.0001	0.0001	0.0001
p-value vs 10 mg/d			0.0038	0.0001
p-value vs 15 mg/d				0.0102

\*\*LOCF only applies to 15 mg/d group

Drop-out patient 1605 (15 mg/day) - last visit set to Week 4; Drop-out patient 1501 (15 mg/day) - last visit set to Week 8

\*Table derived from submission

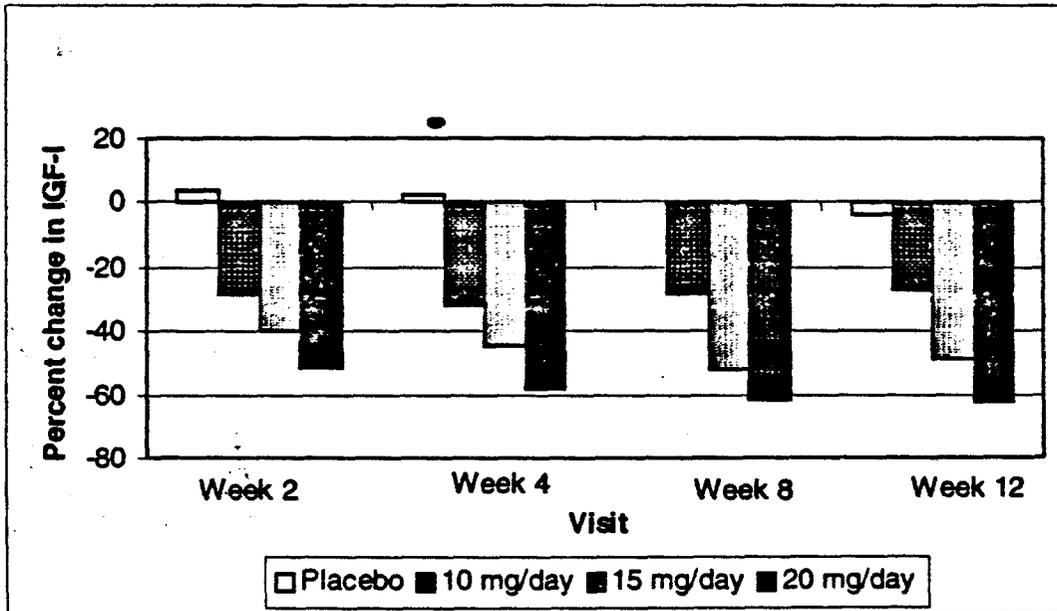
**Figure 1.\* SEN-3614 - Serum IGF-I Levels\*\* Before and After Therapy with 3 Dosages of Pegvisomant**



\*Normal age-adjusted IGF-I values: ages 16-24: 182-780; ages 25-39: 114-492; ages 40-54: 90-360; age 55+: 71-290.

\*\*Superimposed horizontal line represents a mean weighted average age-adjusted ULN for IGF-I for all of the treatment groups taken together.

**Figure 2. SEN-3614 - Percent Change IGF-I From Baseline**



## VI.A.5.7.2 Secondary Efficacy Analyses

### VI.A.5.7.2.1 Normalization of IGF-I Concentrations

The percent of patients with normalization of serum IGF-I concentrations is presented in Table 9 and Figure 3; individual serum IGF-I values are presented in Figure 1:

- The incidence of patients whose IGF-I concentrations became normal during the study was significantly higher after the administration of all 3 dosages of pegvisomant compared with placebo at all treatment visits ( $p \leq 0.001$ ).
- Forty seven 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).
- A dose-response relationship was clearly apparent as early as Week 2, and persisted through the Week 12 assessment.
- 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 increase the percent of patients with normalized IGF-I levels for -4-8 weeks.
- After 12 weeks of treatment, 10 (38.5%) patients in the pegvisomant 10 mg/day group, 18 (75.0%) in the pegvisomant 15 mg/day group, and 23 (82.1%) in the pegvisomant 20 mg/day group had normalized IGF-I concentrations compared with three (9.7%) subjects in the placebo group (p-values in Table 9).
- Of the 111 subjects included in the ITT population, 63 (56.8%) achieved normalized IGF-I concentrations at some time post baseline during the study: three (9.7%) in the placebo group, 14 (53.8%) in the pegvisomant 10 mg/day group, 21 (80.8%) in the pegvisomant 15 mg/day group, and 25 (89.3%) in the pegvisomant 20 mg/day group.
- The 20 mg dose was statistically superior to the 10 mg dose from week 4 onward, and the 15 mg dose was statistically superior to the 10 mg dose from week 8 onward.
- There were no significant interactions noted between site (pooled) and treatment.

The IGF-I normalization results were further examined as follows:

- 1) There appeared to be no differences between gender or age groups in the number of patients who achieved normal IGF-I concentrations.
- 2) When the data of the 2 patients who were inadvertently given each others medication supplies at the Week 8 visit are excluded, the incidence of IGF-I normalization essentially remains unchanged from the original analysis.

3) Twenty five out of 28 patients (89.3%) treated with pegvisomant 20 mg/day achieved a normalized IGF-I level at some time during the study. Two of the 3 patients who did not achieve a normalized IGF-I level did manifest clinically significant responses (e.g., serum IGF-I concentrations fell from 1,032 ng/mL (age adjusted ULN 360 ng/mL) and 761 ng/mL (age adjusted ULN 290 ng/mL) to 420 ng/mL and 478 ng/mL, respectively, at the conclusion of the study.

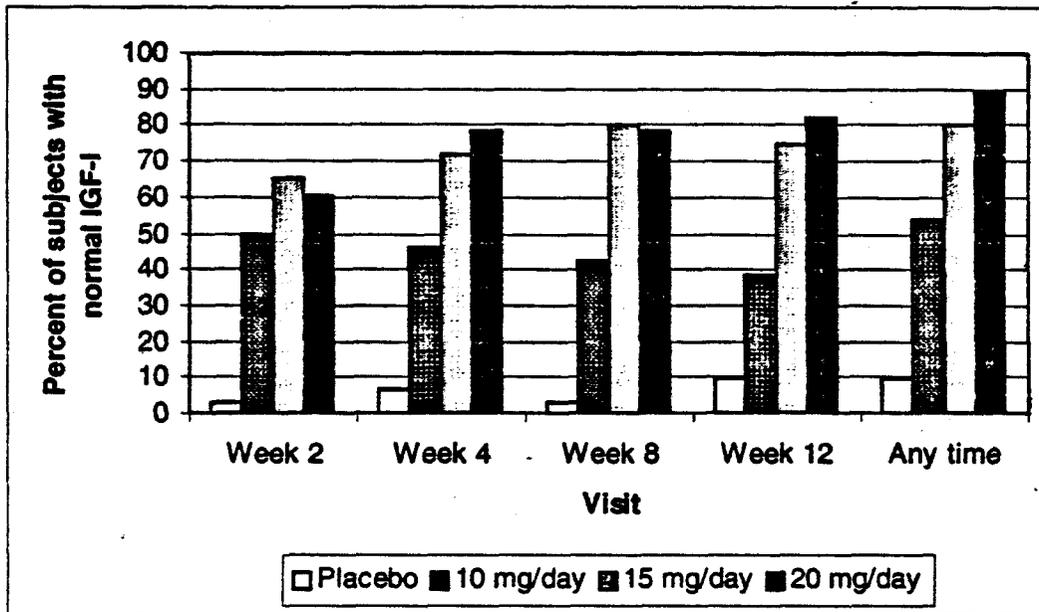
4) The incidence of IGF-I normalization achieved in patients treated with pegvisomant 10 mg/day (53.8%) was almost identical to the incidence of IGF-I normalization observed after the administration of the same dose of pegvisomant (52.6%) in the phase II daily dosing extension study (SEN-3613A), demonstrating a similar magnitude of drug effect across protocols and patients.

**Table 9. SEN-3614 - Percent Normalization of IGF-I Concentrations - ITT Efficacy Population\***

Normalized IGF-I	Placebo (n=31)	Pegvisomant		
		10 mg/d (n=26)	15 mg/d (n=26)	20 mg/d (n=28)
<b>At week 2</b>				
n (%)	1 (3.2)	13 (50)	17 (65.4)	17 (60.7)
p-value vs placebo		≤0.001	≤0.001	≤0.001
p-value vs 10 mg/d			0.261	0.438
p-value vs 15 mg/d				0.683
<b>At week 4</b>				
n (%)	2 (6.5)	12 (46.2)	18 (72)	22 (78.6)
p-value vs placebo		≤0.001	≤0.001	≤0.001
p-value vs 10 mg/d			0.055	0.014
p-value vs 15 mg/d				0.613
<b>At week 8</b>				
n (%)	1 (3.2)	11 (42.3)	20 (80.0)	22 (78.6)
p-value vs placebo		≤0.001	≤0.001	≤0.001
p-value vs 10 mg/d			0.006	0.007
p-value vs 15 mg/d				0.874
<b>At week 12</b>				
n (%)	3 (9.7)	10 (38.5)	18 (75.0)	23 (82.1)
p-value vs placebo		0.0157	0.0001	0.0001
p-value vs 10 mg/d			0.0072	0.0010
p-value vs 15 mg/d				0.4618
<b>Any time post-baseline</b>				
n (%)	3 (9.7)	14 (53.8)	21 (80.8)	25 (89.3)
p-value vs placebo		0.0009	0.0001	0.0004
p-value vs 10 mg/d			0.0207	0.0018
p-value vs 15 mg/d				0.2900

\*Table derived from submission

Figure 3. SEN-3614 - Normalization of IGF-I



**VI.A.5.7.2.1.1 Covariate Analyses Related to Percent Change from Baseline in Serum IGF-I Concentrations and Percent Normalization of Serum IGF-I Concentrations**

**VI.A.5.7.2.1.1.1 Analyses Contained in Formal Submission**

With regard to the percent change from baseline in serum IGF-I concentrations, ANCOVA showed no statistically significant effects for baseline IGF-I levels, IGF-I entry strata, baseline GH levels, or gender as covariates. On the other hand, baseline body weight was a statistically significant covariate in the pairwise treatment comparisons. The importance of baseline body weight as a predictor of responsivity is further supported by 1) a population PK analysis which demonstrated that increased baseline body weight increases the clearance of pegvisomant (see Section VI.A.5.7.4 ahead), and 2) the exploratory analyses described in Section VI.A.5.7.2.1.1.2.

With regard to the percent normalization of serum IGF-I concentrations at any time post baseline, ANCOVA showed no significant effect for baseline IGF-I levels employed as a covariate (e.g., the analysis produced results very similar to the original ANOVA).

**VI.A.5.7.2.1.1.2 Exploratory Analyses Contained in Addendum 2 to SEN-3614 (performed by the Sponsor and confirmed by the Division's Statistical Reviewer)**

Exploratory analyses were carried out by the Sponsor to examine the effects of 6 baseline characteristics on the percent of patients with normalization of serum IGF-I concentrations (e.g., percent of responders) after 12 weeks of therapy with pegvisomant during SEN-3614 (LOCF). The 6 baseline characteristics were weight, "normalized" IGF-I level (expressed as a MULN), IGF-I level, GH level, gender and age. Logistic regression modeling was used (separately for each pegvisomant treatment group) to regress the proportion of responders onto the potential predictors. In the 10 mg/day treatment group, baseline weight and baseline IGF-I expressed as MULN were statistically significant predictors of IGF-I normalization. In the lowest weight category (<80 kg), 67% of patients were responders compared with 50% of patients in the intermediate weight category and 0/8 patients in the highest weight category (>104 kg). In the lowest IGF-I MULN category (<1.33X ULN), 67% of patients were responders compared with 17% of patients in the intermediate IGF-I MULN category (>1.3 ≤2.05X ULN) and 13% of patients in the highest IGF-I MULN category (>2.05X ULN). In the 15 and 20 mg/day treatment groups, no baseline characteristics were statistically significant predictors of response. However, in the 15 mg/day treatment group, there was a trend for patients in the highest weight category and, to a lesser extent for patients in the highest IGF-I MULN category, to respond less well to pegvisomant therapy than patients with lesser baseline weights and IGF-I MULN values, respectively. Nonetheless, the percent of patients achieving a normal IGF-I level within 12 weeks in the highest weight or highest IGF-I MULN category was much larger if these patients were treated with 15 or 20 mg/day as opposed to 10 mg/day. See Table 10.

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**Table 10. ISS - Number and Percent of Patients with Normal IGF-I at Termination Visit by Percentile Categories for 1) Baseline Body Weight and 2) Multiple of Upper Limit of Normal for Baseline IGF-I**

Dose (mg/day)	Category	Multiple of ULN Percentile			Weight Percentile		
		Endpoint IGF-I		Total N	Endpoint IGF-I		Total N
		Not Normal n (%)	Normal n (%)		Not Normal n (%)	Normal n (%)	
10	Bottom	4 (33.3)	8 (66.7)	12	3 (33.3)	6 (66.7)	9
	Middle	5 (83.3)	1 (16.7)	6	4 (50.0)	4 (50.0)	8
	Top	7 (87.5)	1 (12.5)	8	8 (100.0)	0	8
15	Bottom	2 (18.2)	9 (81.8)	11	1 (14.3)	6 (85.7)	7
	Middle	2 (22.2)	7 (77.8)	9	1 (10.0)	9 (90.0)	10
	Top	2 (33.3)	4 (66.7)	6	4 (50.0)	4 (50.0)	8
20	Bottom	0	4 (100.0)	4	1 (10.0)	9 (90.0)	10
	Middle	2 (16.7)	10 (83.3)	12	2 (28.6)	5 (71.4)	7
	Top	3 (25.0)	9 (75.0)	12	2 (22.2)	7 (77.8)	9

Note: The percentiles for the categorization of the baseline multiple of the upper limit of normal were:  $\leq 1.32520$  for the bottom;  $> 1.32520$  and  $\leq 2.05556$  for the middle; and  $> 2.05556$  for the top.

Note: The percentiles for the categorization of the baseline weight (kg) were defined as follows:  $\leq 80.2$  kg for the bottom;  $> 80.2$  kg and  $\leq 104.0$  kg for the middle; and  $> 104.0$  kg for the top.

The effect of these baseline characteristics on the percent change from baseline in serum IGF-I concentrations was determined as well. The results were not nearly as clearcut as described above. However, it was observed that, in any given treatment group, patients in the highest weight category had the smallest reductions in serum IGF-I levels after 12 weeks of pegvisomant therapy.

These preliminary/exploratory analyses suggest that heavier patients ( $> 104$  kg) and/or patients whose IGF-I MULN value is  $> 2.05X$  ULN may benefit from a larger dose of pegvisomant (e.g., 15-20 mg) when therapy for acromegaly is initiated.

#### VI.A.5.7.2.2 Symptoms and Signs of Acromegaly Score and Overall Health Status Score

As can be seen in Table 11, after 12 weeks of therapy with pegvisomant, the scores for all 5 individual signs and symptoms of acromegaly were decreased in the 3 pegvisomant treatment groups. The decreases in scores were generally dose dependent. The changes from baseline to Week 12 in scores for soft tissue swelling, excessive perspiration, and fatigue were significantly different when compared with those for the placebo group in the pegvisomant 15 and 20 mg/day treatment groups. Categorical scores (improved, worsened, no change) were similarly improved.

**Table 11. SEN-3614 - Signs and Symptoms of Acromegaly at Baseline and Week 12\***

Parameter	Treatment Group			
	Placebo (N = 31)	10 mg/day (N = 26)	Pegvisomant 15 mg/day (N = 26)	20 mg/day (N = 28)
Baseline soft tissue swelling	2.1 ± 0.4	2.4 ± 0.5	2.7 ± 0.5	2.8 ± 0.4
Change in soft tissue swelling from baseline at Week 12	+0.3 ± 0.4	-0.7 ± 0.3	-1.2 ± 0.5	-1.3 ± 0.3
Pairwise p-value (vs. placebo)		NS	<0.05	<0.001
Baseline arthralgia	3.7 ± 0.4	3.0 ± 0.4	3.2 ± 0.5	2.8 ± 0.4
Change in arthralgia from baseline at Week 12	+0.1 ± 0.3	-0.3 ± 0.4	-0.5 ± 0.5	-0.4 ± 0.4
Pairwise p-value (vs. placebo)		NS	NS	NS
Baseline headache	2.1 ± 0.4	2.5 ± 0.4	3.0 ± 0.5	2.1 ± 0.4
Change in headache from baseline at Week 12	+0.1 ± 0.3	-0.4 ± 0.3	-0.3 ± 0.3	-0.3 ± 0.4
Pairwise p-value (vs. placebo)		NS	NS	NS
Baseline excessive perspiration	3.1 ± 0.4	3.2 ± 0.4	3.8 ± 0.4	3.3 ± 0.4
Change in excessive perspiration from baseline at Week 12	+0.1 ± 0.3	-0.6 ± 0.3	-1.1 ± 0.3	-1.7 ± 0.3
Pairwise p-value (vs. placebo)		NS	<0.05	<0.001
Baseline fatigue	3.2 ± 0.4	3.7 ± 0.4	4.3 ± 0.5	3.9 ± 0.4
Change in fatigue from baseline at Week 12	+0.7 ± 0.3	-0.5 ± 0.3	-1.3 ± 0.3	-1.0 ± 0.3
Pairwise p-value (vs. placebo)		<0.05	<0.001	<0.05
Baseline total score	14.2 ± 1.3	14.8 ± 1.6	17.0 ± 1.7	14.9 ± 1.3
Change in total score from baseline at Week 12	+1.3 ± 1.1	-2.5 ± 0.8	-4.4 ± 1.2	-4.7 ± 0.9
Pairwise p-value (vs. placebo)		<0.05	<0.05	<0.001

Data shown are mean ± SEM.

\*Table derived from submission

Overall health status was rated as improved in 55% of patients treated with pegvisomant 20 mg/day for 12 weeks - a statistically significant change when compared to the effects of placebo.

### VI.A.5.7.2.3 Ring Size

The mean change from baseline (in derived ring size score) at Week 12 was  $-0.1 \pm 0.43$  in the placebo group;  $-0.8 \pm 0.32$  in the 10 mg/day group;  $-1.9 \pm 0.41$  in the 15 mg/day group; and  $-2.5 \pm 0.63$  in the 20 mg/day group. As seen in Table 12, the improvements in ring size were significantly greater in the patients treated with pegvisomant 15 or 20 mg/day compared with the effects of placebo (as were the effects of pegvisomant 15 or 20 mg/day compared with pegvisomant 10 mg/day).

**Table 12. SEN-3614 - Pairwise Treatment Comparison P-values for Ring Size\***

Parameter	Plac. v. 10 mg/day	Plac. v. 15 mg/day	Plac. v. 20 mg/day	10 mg/day v. 15 mg/day	10 mg/day v. 20 mg/day	15 mg/day v. 20 mg/day
Ring Size	0.1568	0.0010*	<0.001*	0.0235*	0.0031*	0.4626

Comparison is based on changes from baseline (Visit 3) to Visit 7 (Week 12).

\* Statistically significant at the 0.05 level.

\*Table derived from submission

**VI.A.5.7.2.4. Changes in Free IGF-I, Percent Free IGF-I, ALS and IGFBP-3 (additional markers for GH action)**

Acromegalic patients treated with pegvisomant had greater decreases than those treated with placebo in ALS, free IGF-I, percent free IGF-I, and IGFBP-3 at all visits. These changes from baseline to the end of the study were generally dose-related. See Tables 13 and 14.

**Table 13. SEN-3614 - Results of Special Laboratory Tests at Baseline and Week 12\***

Parameter	Treatment Group			
	Placebo (N = 31)	10 mg/day (N = 26)	15 mg/day (N = 26)	20 mg/day (N = 28)
Baseline ALS (mg/L)	21.5 ± 1.0	22.0 ± 0.95	23.1 ± 1.2	23.3 ± 0.8
Actual change in ALS from baseline at Week 12 (mg/L)	-0.5 ± 0.7	-3.1 ± 0.88	-6.4 ± 1.1	-9.5 ± 0.8
Baseline free IGF-I (ng/mL)	7.0 ± 0.6	6.4 ± 0.6	6.2 ± 0.6	6.2 ± 0.5
Actual change in free IGF-I from baseline at Week 12 (ng/mL)	-0.2 ± 0.5	-2.5 ± 0.5	-3.6 ± 0.7	-3.9 ± 0.7
Baseline free IGF-I percent (%)	1.2 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
Actual change in free IGF-I percent from baseline at Week 12 (%)	0.0 ± 0.1	-0.2 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1
Baseline IGFBP-3 (mg/L)	5.1 ± 0.2	5.2 ± 0.2	5.5 ± 0.2	5.3 ± 0.2
Actual change in IGFBP-3 from baseline at Week 12 (mg/L)	-0.1 ± 0.1	-0.7 ± 0.2	-1.6 ± 0.3	-1.6 ± 0.2

Data shown are mean ± SE.

\*Table derived from submission

**Table 14. SEN-3614 - Pairwise Treatment Comparison P-values for Special Laboratory Tests\*\***

Parameter	Plac. v. 10 mg/day	Plac. v. 15 mg/day	Plac. v. 20 mg/day	10 mg/day v. 15 mg/day	10 mg/day v. 20 mg/day	15 mg/day v. 20 mg/day
Free IGF-I	0.0020*	<0.001*	<0.001*	0.2375	0.0197*	0.8027
IGFBP-3	0.0139*	<0.001*	<0.001*	0.0136*	<0.001*	0.3590
ALS	0.0152*	<0.001*	<0.001*	0.0167*	<0.001*	0.0256*

Comparison is based on changes from baseline (Visit 3) to Visit 7 (Week 12).

\* Statistically significant at the 0.05 level. \*\*Table derived from submission.

### VI.A.5.7.2.5 QOL - Exploratory Analyses

Exploratory analyses of data from the 3 QOL instruments did not reveal statistically significant differences among the 4 treatment groups.

### VI.A.5.7.3 Subgroup Analyses

#### VI.A.5.7.3.1 Previous SA and/or DA Therapy

Forty nine patients had received prior therapy with a SA, 12 patients had received prior therapy with a DA, and 3 patients had received both concurrently - all of these drugs were washed out prior to randomization to 1 of the 4 treatment groups in SEN-3614.

An analysis of the 49 acromegalic subjects previously treated with SA therapy reveals that the decreases from baseline in serum IGF-I concentrations (-25%, -55% and -66%) and the incidences of normalized IGF-I levels (22%, 82%, and 86%) in the 10 mg/day, 15 mg/day and 20 mg/day treatment groups, respectively, after 12 weeks of pegvisomant therapy, were very similar to the responses observed in the entire cohort (see Tables 8 and 9). Results of the subgroup analysis combining patients who previously were treated with SA therapy, DA therapy or both (n=61) were very similar to the above described analysis of the 49 patients previously treated with SA therapy. It would appear then that prior medical therapy for acromegaly does not alter the response to pegvisomant treatment.

In addition, at Visit 1, 44%, 25% and 50% of the acromegalic subjects randomized to the 10, 15, and 20 mg/day pegvisomant treatment groups, respectively, had normal IGF-I levels while receiving any dose of SA therapy. In contrast, after 12 weeks of pegvisomant therapy, the incidence of IGF-I normalization in the same 3 groups of patients was 22%, 82% and 86%, respectively. These results suggest that pegvisomant may be more effective than SA therapy in lowering IGF-I concentrations; a properly designed study comparing these 2 medical therapies needs to be performed to validate this observation.

#### VI.A.5.7.3.2 Washout Period Appropriateness

IGF-I concentrations increased at Visit 2 (after cessation of the previous therapy at Visit 1), and no further changes in IGF-I levels were noted between Visits 2 and 3. These data confirm that the washout periods were sufficient to provide a stable IGF-I value  $\geq 30\%$  above the ULN.

#### VI.A.5.7.3.3 Effect of Bolus Loading Dose Error

The extent of IGF-I reduction and the incidence of IGF-I normalization were similar in the cohorts who received an incorrect bolus loading dose and the entire cohort. Moreover, serum pegvisomant

concentrations were found to be similar in patients who received the correct loading dose and those who did not. These additional analyses indicate that the loading dose error did not adversely impact the validity of the study.

#### VI.A.5.7.4 PK/PD Analyses with Implications for Efficacy (See Section VI.C.12) (performed by the Sponsor and confirmed by the Division's Biopharmaceutics Reviewer)

##### VI.A.5.7.4.1 Drug Doses, Steady State Drug Concentrations and Dosing Recommendations

During SEN-3614, pegvisomant concentrations increased in a dose-dependent manner. PK analysis revealed that patients treated with pegvisomant 10 mg/day and 15 mg/day achieved mean steady state serum pegvisomant concentrations of ~7,000 ng/mL and 16,000 ng/mL, respectively, by Week 8. Patients treated with pegvisomant 20 mg/day attained mean serum pegvisomant concentrations of 27,000 ng/mL by Week 12 (which still appeared to be increasing slightly at that time). (Note: The relatively long time periods required to achieve steady state [-8-12 weeks] may be a reflection of the method of administration [e.g., SC], and daily administration of a drug with a long  $T_{1/2}$ .)

The  $T_{1/2}$  of pegvisomant was thought to be ~6 days. It was felt that ~5 half lives (e.g., ~30 days~4 weeks) were necessary to achieve the steady state after a dosing change. In addition, a lag period of ~2 weeks was estimated as 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. This provides the basis for the Sponsor's recommendation in the label to measure serum IGF-I levels 6 weeks after a change in pegvisomant dose, and then further titrate the dose according to those results. See Sections I.B.3 and II.D in the EXECUTIVE SUMMARY.

##### VI.A.5.7.4.2 Drug Clearance Issues Impacting Efficacy

Mean systemic clearance of pegvisomant was estimated to be ~32 mL/h. The systemic clearance of pegvisomant was found to be dependent mainly on body weight and the administered dose of pegvisomant.

- A significant linear relationship was found between pegvisomant clearance and body weight. Systemic clearance increased by 0.51 mL/h for each kg increment in body weight greater than the average body weight of 94 kg for acromegalics in SEN-3614. Thus, a heavier individual may have a greater clearance rate than an individual of lower body weight. The role of body weight as an important

predictor of PD response (e.g., reduction of IGF-I levels) has previously been discussed (see Section VI.A.5.7.2.1.1).

- A significant linear relationship was found between clearance and dose. Clearance decreased by 0.81 mL/h for each mg increment in dose above 15 mg/day. Thus, an individual receiving a dose greater than 15 mg/day will have a decreased clearance rate compared with an individual receiving a dose lower than 15 mg/day.

#### VI.A.5.7.5 SEN-3614 Efficacy - Summary/Discussion

All 3 doses of pegvisomant produced substantial dose-dependent reductions in baseline serum IGF-I concentrations which were significantly different from the minimal changes observed after the administration of 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 MULN value is >2.05 may benefit from a larger dose of pegvisomant (e.g., 15-20 mg) when therapy for acromegaly is initiated.

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.

Subgroup analyses of acromegalic patients previously receiving SA or DA therapy revealed that 1) prior medical therapy for acromegaly did not adversely impact the subsequent response to pegvisomant therapy, and 2) 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.

Population PK analyses showed that systemic clearance of pegvisomant was dependent mainly on body weight and the administered dose of pegvisomant.

#### VI.A.5.7.6 SEN-3614 Efficacy - Conclusions

Pegvisomant appears to be an efficacious short term therapy for patients with acromegaly, including patients who previously had failed medical therapy with SAs.

#### VI.A.5.8 SEN-3614 Safety Results

Safety results from SEN-3614 (as well as all other studies) are discussed in the ISS.

#### VI.B SEN-3611, SEN-3613, SEN-3613A and SEN-3615

The efficacy results of these studies are summarized in the ISE, and safety data from these studies are included in the ISS.

#### VI.C Integrated Summary of Safety (ISS)

##### VI.C.1 ISS Database (incorporating Safety Update)

The ISS database for the pegvisomant program consists of 260 individuals including 167 patients with acromegaly, 45 patients with diabetes mellitus, and 48 healthy volunteers. The number of subjects by study (in 12 of the 13 clinical trials conducted by the Sponsor) is summarized in Table 15 (the 2 acromegalic patients who received pegvisomant on a compassionate use basis in SEN-3603 are not included in Table 15 because case report forms were not designed for this study; no SAEs were reported for either of these patients).

Three of the studies (SEN-3613, SEN-3613A and SEN-3615) were open label, dose titration, extension studies designed to assess the longterm safety/efficacy of pegvisomant in acromegaly. As can be seen in Table 15, nearly all patients who participated in these extension studies had previously been treated with pegvisomant during a short term, placebo controlled study (SEN-3611, SEN-3614). It was therefore possible for acromegalic patients to participate in more than 1 study and receive more than 1 dosage of pegvisomant.

With respect to the data presented/analyzed in the ISS (including the information contained in the Safety Update submitted in February 2001), the cutoff date for information from the ongoing extension studies (SEN-3615 and SEN-3613A) was 31May2000 (when all patients were taken off pegvisomant due to cessation of drug production). Of particular note, LT results available to the Sponsor as of 31May00 were analyzed in acromegalic

patients with normal baseline LTS who subsequently experienced elevations  $\geq 1.9X$  ULN) (see Section VI.C.8.2).

**Table 15. ISS Database**

Study	Total	Unique	Patients from previous studies
<b>Healthy volunteers:</b>			
SEN-3601	36	36	None
SEN-3623	12	12	None
<b>TOTAL</b>		<b>48</b>	<b>None</b>
<b>Acromegalic patients*:</b>			
SEN-3602	6	6	None
SEN-3611	46	43	3 from SEN-3602
SEN-3613	36	1	34 from SEN-3611
(extension)			1 from SEN-3602/SEN-3611
SEN-3613A	38	0	30 from SEN-3611/SEN-3613
(extension)			4 from SEN-3611
			2 from SEN-3602/SEN-3611
			1 from SEN-3613
			1 from SEN-3602/SEN-3611/SEN-3613
SEN-3614	112	111	1 from SEN-3611
SEN-3615	108	6	100 from SEN-3614
(extension)			1 from SEN-3603
			1 from SEN-3611
<b>TOTAL</b>		<b>167</b>	
<b>Diabetic patients:</b>			
SEN-3621	9	9	None
SEN-3621a	5	5	None
SEN-3622	6	6	None
SEN-3631	25	25	None
<b>TOTAL</b>		<b>45</b>	
<b>TOTAL SUBJECTS</b>		<b>260</b>	

\*Study SEN-3603 does not appear in the ISS database

## VI.C.2 Exposure Data

With regard to the 260 individuals enrolled in the pegvisomant clinical trials, 241 received pegvisomant and 19 were administered placebo only. Of the 167 participating acromegalic patients, 160 received pegvisomant (e.g., 120 were treated with pegvisomant only and 40 were treated with pegvisomant after initial randomization to placebo), and 7 were administered placebo only. Of the 160 acromegalic patients treated with pegvisomant, 43 received weekly doses and 152 received daily doses (e.g., a significant number of patients received both weekly and daily doses). Weekly pegvisomant doses ranged from 30 to 80 mg, and daily pegvisomant doses ranged from

5 to 80 mg. Most subjects 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. One patient accidentally took 80 mg/day for 7 days with no untoward consequences.

The duration of pegvisomant therapy was calculated for each dose (and dose regimen) administered. Dose and duration of exposure for all patients (acromegalics, diabetics and healthy controls) are summarized in Table 16.

As seen in Table 16, 52 subjects (including 43 acromegalics and 9 diabetics) received any dose of weekly pegvisomant treatment. Twenty four of these subjects (all acromegalics) were treated for more than 26 weeks. On the other hand, 188 subjects (including 152 acromegalics and 36 diabetics) received any dose of daily pegvisomant therapy. Eighty four of these subjects (all acromegalics) were treated for >52 weeks, and 45 (all acromegalics) were treated >26-≤52 weeks. With regard to "all subjects" treated with daily ± weekly pegvisomant, 85 (all acromegalics) were treated for >52 weeks, 46 (all acromegalics) were treated for >26-≤52 weeks, and 16 (all acromegalics) were treated for >13-≤26 weeks.

In summary, 160 acromegalic patients were exposed to pegvisomant for 186.2 patient-years (193.3 patient-years in 241 "all subjects" population). In contrast, the number of patient-years of exposure to placebo for acromegalics (n=47) (and "all subjects"; n=59) was 9.1 patient-years. (Note: The number of patient-years of exposure in the non-pegvisomant cohort [comprised of the 146 subjects who had LTs measured while exposed to placebo {n=59} and/or after withdrawal of pegvisomant due to limited drug supply {n=87}; see discussion of abnormal LTs in Section VI.C.8.2.2 ahead] was 60 patient-years.) In the acromegalic cohort (excluding patients who only received a single dose), the mean duration of 1) total (daily and weekly) pegvisomant exposure was 61.95 ± 36.18 weeks (n=157, range 0.29-150 weeks), 2) daily pegvisomant exposure was 56.98 ± 27.97 weeks (n=152; range 0.29-116.6 weeks), and 3) weekly pegvisomant exposure was 24.76 ± 12.39 weeks (n=43; range 1.1-42.8 weeks).

**Table 16. ISS - Number (%) of "All Subjects" by Dose and Duration of Exposure to Pegvisomant\***

Pegvisomant dose	Duration (weeks)							Total number of subjects
	≤1	>1 - ≤6	>6 - ≤13	>13 - ≤26	>26 - ≤39	>39 - ≤52	>52	
<b>Daily dosing (n = 188):</b>								
Any dose	2(1)	13(7)	30(16)	14(7)	24(13)	21(11)	84(45)	188 (100)
5 mg	1(1)	0(0)	1 (1)	2(1)	1(1)	0 (0)	1(1)	6(3)
10 mg	1(1)	17(9)	54(29)	39(21)	13(7)	8(4)	16(9)	148(79)
15 mg	1 (1)	13(7)	49(26)	24(13)	5(3)	10(5)	8(4)	110(59)
20 mg	0 (0)	19(10)	57 (30)	18(10)	8(4)	4(2)	14(7)	120(64)
25 mg	0 (0)	3(2)	15(8)	4(2)	3(2)	4(2)	0 (0)	29(15)
30 mg	0 (0)	1 (1)	3(2)	6(3)	3(2)	1(1)	1(1)	15(8)
35 mg	0 (0)	1 (1)	1(1)	3 (2)	0 (0)	0 (0)	0 (0)	5(3)
40 mg	0 (0)	0(0)	0 (0)	1(1)	0 (0)	2(1)	0 (0)	3 (2)
80 mg	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
<b>Weekly dosing (n = 52):</b>								
Any dose	1 (2)	10 (19)	8 (15)	9 (17)	18 (35)	6 (12)	0 (0)	52 (100)
30 mg	1 (2)	22 (42)	14 (27)	1 (2)	0 (0)	0 (0)	0 (0)	38 (73)
40 mg	0 (0)	33 (63)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	34 (65)
50 mg	0 (0)	33 (63)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	33 (63)
60 mg	0 (0)	30 (58)	3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	33 (63)
70 mg	0 (0)	27 (52)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	29 (56)
80 mg	1 (2)	12 (23)	17 (33)	15 (29)	3 (6)	0 (0)	0 (0)	48 (92)
<b>Single dose (n = 42):</b>								
Any dose	42 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	42 (100)
<b>All dose regimens (n = 241):</b>								
Any dose	42(17)	22(9)	30(12)	16(7)	25(10)	21(9)	85(35)	241 (100)

Subjects may appear in more than 1 dose and duration category. Total duration = sum of durations across all doses within a dosing regimen.

### VI.C.3 Demographics

Fifty nine percent of acromegalics studied were male. Mean age of the acromegalic subpopulation was 46.2 years. The majority of all subjects were Caucasian. See Table 17.

## VI.C.7 Vital Signs and Anthropometric Measurements

The mean changes from baseline for blood pressure, pulse, temperature, weight and body mass index were not clinically significant in any subject population during or at the conclusion of any of the pegvisomant clinical trials, in particular the placebo controlled SEN-3614 study. A review of individual data revealed 10/160 acromegalic patients with modest blood pressure elevations above baseline in the pegvisomant-treated cohort compared with 1/47 patients receiving placebo. However, these results must be interpreted with caution in that 1) hypertension is a common finding in acromegaly (~40% of the patients enrolled in SEN-3614 had a history of hypertension at baseline), and 2) these findings were not duration-adjusted (e.g., the pegvisomant-treated patients were on-study 20 times as long as the placebo cohort).

## VI.C.8 Clinical Laboratory Evaluations Including Blood Chemistry/Hematology, Urinalysis, Electrocardiogram and Chest Xray

### VI.C.8.1 All of the Above Excluding LTs

The mean changes from baseline for all of the above laboratory parameters (including renal function parameters [see Section VI.C.11] and blood sugar [see Section VI.C.10.4]) were not clinically significant in any subject population during or at the conclusion of any of the pegvisomant clinical trials, in particular the placebo controlled SEN-3614 study. In the longterm extension study SEN-3613A, baseline mean total serum cholesterol was minimally elevated ( $5.23 \pm 1.1$  mmol/L), but did not change significantly during the course of pegvisomant treatment. In addition, a review of individual laboratory data for selected laboratory parameters by this medical reviewer revealed very few outliers.

### VI.C.8.2 LTs

#### VI.C.8.2.1 General Comments

LTs were monitored at least every 4 weeks during the clinical trials in acromegalic patients when pegvisomant was administered on a daily basis (SEN-3614, 3615 and 3613A). Two patients were withdrawn from their respective studies after 10-20 fold elevations in transaminase levels were observed (see Section VI.C.6.2 for detailed case histories of these 2 patients). One of these patients (3614-1500-1501) developed markedly abnormal transaminase levels after initial challenge with pegvisomant that returned to normal after discontinuation (dechallenge); when he was rechallenged with pegvisomant during SEN-3615, his transaminase levels again increased, and then once again returned to normal after dechallenge. The second patient (3613A-0200-204) developed mildly elevated transaminase levels

after 4 weeks of therapy which peaked at -10 weeks. Pegvisomant was discontinued. ANA was 1:160. Liver biopsy revealed chronic hepatitis (?autoimmune-related chronic active hepatitis?). Transaminase levels normalized 5 months later after a course of immunosuppressive therapy.

In that these findings are suggestive of pegvisomant-induced hepatocellular injury (in particular the first case described), an extensive analysis of the potential association of pegvisomant with LT abnormalities has been performed by the Sponsor and this reviewer.

#### VI.C.8.2.2 Incidence of Any Abnormal LTs in the "All Subjects" Population (with Normal Baseline LTs)

The number and percentage of pegvisomant- and non-pegvisomant-treated subjects in the entire NDA database with any elevation of LTs on therapy (including abnormal values  $>1-1.9X$  ULN) are shown in Table 22. The overall incidence of elevated ALT values was 15.4% in the pegvisomant group and 13% in the non-pegvisomant group.

Since the exposure to pegvisomant in the database (~193 patient-years) is over 20 fold greater than the exposure to placebo (~9 patient years), in this analysis (as well as Table 23 ahead) the placebo cohort has been enlarged to include patients who were withdrawn from pegvisomant during the extension trials (most often because of the study drug shortage); many of these patients were begun on SA and/or DA therapy after pegvisomant was discontinued, but continued to be followed with serial LT determinations. (Note: The Sponsor felt it was appropriate to include these patients in the expanded placebo cohort because almost all of the transaminase elevations observed after the initiation of pegvisomant therapy occurred at ~8 weeks [see Table 24]). Thus, in Tables 22 and 23, the pegvisomant cohort consists of all subjects who had LTs measured while receiving pegvisomant (n=241), and the non-pegvisomant cohort is comprised of all subjects who had LTs measured while exposed to placebo and/or after withdrawal of pegvisomant (n=146). Of note, even with expansion of the blinded placebo cohort, the duration of exposure for subjects in the pegvisomant cohort (~193 patient-years) remains over 3 fold greater than the exposure of the subjects in the non-pegvisomant cohort (~60 patient-years). This creates an unfavorable bias against pegvisomant. Despite this bias, the Sponsor decided not to adjust this analysis for duration of exposure because of the limited number of subjects in each population, and because the incidence of LTs  $\geq 3X$  ULN (and  $\geq 1.9X$  ULN) was similar for the pegvisomant and non-pegvisomant treatment groups (see Table 23).

In addition, there were no significant differences in the incidences of abnormal ALT/AST values in subjects treated with weekly doses of pegvisomant, and subjects who received daily doses of pegvisomant (data not shown).

**Table 22. ISS - Number(%) of Subjects with Any Abnormal LT Values (>1X ULN) During Treatment\***

Laboratory measure	Pegvisomant (n=241)	Non-Pegvisomant** (n=146)
ALT	37 (15.4)	19 (13)
AST	45 (18.7)	16 (11)
ALP	16 (6.6)	14 (9.6)
TBIL	9 (3.7)	4 (2.7)

\*Subjects with baseline elevations above the ULN were excluded on a per test basis.

\*Subjects with elevated values occurring during both a non-pegvisomant and pegvisomant treatment phase were assigned to the treatment group during which the abnormality was first observed.

\*For each test, the number of subjects is presented as the maximum elevation within the described boundaries.

\*\*Assessments were made during treatment with blinded placebo, AND after withdrawal of pegvisomant when serial LT monitoring was continued.

### VI.C.8.2.3 Shift From NORMAL Baseline LTs in the "All Subjects" Population

Table 23 is a shift table which delineates the number and percentage of all subjects in the NDA database with normal baseline ALT, AST, ALP or total TBIL values who subsequently developed elevations of any of these LTS  $\geq 1.9X$  ULN. Subjects are counted only once for each test regardless of the number of abnormal values they may have demonstrated. Therefore, the actual incidence of each category of elevation for each LT is displayed. Table 24 provides the peak value observed for each LT and a very brief case history for each subject listed in Table 23.

As seen in Table 23, the overall incidence of elevations  $\geq 1.9-3X$  ULN,  $>3-10X$  ULN, and  $\geq 1.9X$  ULN for all 4 LTs were similar in the pegvisomant and non-pegvisomant cohorts, despite the aforementioned 3 fold greater duration of exposure in the pegvisomant-treated group. In this regard, the non-duration adjusted incidences of subjects in the entire NDA database with ALT values  $\geq 1.9X$  ULN in the pegvisomant and non-pegvisomant groups were 5.4% (13/241) and 4.1% (6/146), respectively. If ALT values  $\geq 3X$  ULN is used as the cutpoint, the percentages 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  $\geq 1.9X$  ULN in the pegvisomant and placebo groups were 7.5% (6/80) and 6.3% (2/32), respectively. If ALT values  $\geq 3X$  ULN is used as the cutpoint, the percentages were 5% (4/80) and 3.1% (1/32).

**Table 23. ISS - Shift from Normal Baseline LT Values to an Elevation of  $\geq 1.9X$  ULN During Treatment\***

Parameter (unit)	Abnormal Category (X ULN)	All Subjects <sup>†</sup>	
		Pegvisomant N=241 193 patient-years n(%)	Non-Pegvisomant N=146 60 patient-years n(%)
ALT (U/L)	$\geq 1.9-3.0$	8 (3.3)	3 (2.1)
		3614-1300-1313	3631-0002-08
		3614-2500-2515	3614-2600-2602
		3615-2100-2106	3615-2600-2601
		3613A-0600-615	
		3615-1600-1607	
		3613A-0100-103	
		3615-1400-1408	
		3615-2600-2602	
	$>3.0-10$	3 (1.2)	3 (2.1)
		3614-1200-1202	3611-0600-610
		3614-1300-1305	3614-1300-1303
		3614-2500-2512	3613A-0100-106
	$>10$	2 (0.8)	0 (0.0)
		3613A-0200-204	
		3614/3615-1500-1501	
	<b>Total <math>\geq 1.9</math></b>	<b>13 (5.4)</b>	<b>6 (4.1)</b>
AST (U/L)	$\geq 1.9-3.0$	2 (0.8)	4 (2.7)
		3614-1300-1305	3611-0600-610
		3614-2200-2205	3614-1300-1303
			3613A-0100-106
		3615-2600-2601	
	$>3.0-10$	2 (0.8)	0 (0.0)
		3614-1200-1202	
		3614-2500-2512	
	$>10$	2 (0.8)	0 (0.0)
		3613A-0200-204	
		3614-1500-1501	
	<b>Total <math>\geq 1.9</math></b>	<b>6 (2.5)</b>	<b>4 (2.7)</b>
ALP (U/L)	$\geq 1.9-3.0$	0 (0.0)	1 (0.7)
			3614-1300-1303
TBIL (umol/L)	$\geq 1.9 - 3.0$	0 (0.0)	0 (0.0)

\*Subjects are counted only once for each abnormal liver function test, using peak serum concentration in order to determine proper categorization.

<sup>†</sup>All subjects population includes 241 subjects exposed to pegvisomant and 146 exposed to placebo withdrawn from pegvisomant.

**Table 24. ISS - Characterization of Subjects Identified in Table 23 as Having a LT Elevation of  $\geq 1.9X$  ULN During Pegvisomant or Non-Pegvisomant\* Treatment**

Subject ID	Time to first elevation <sup>†</sup>	Peak ALT (0-47)	Peak AST (0-37)	Peak ALP (40-135)	Peak TBIL (0-19)	Comments
<i>Elevations occurring during pegvisomant treatment</i>						
3611-200-204	4 wks	821 (~10 wks)	530	160	normal	Gallstone; chronic hepatitis of unknown etiology; withdrawn
3614-1500-1501	8 wks	904 (~10 wks)	407	normal	normal	Withdrawn; rechallenge positive during SEN-3615
3414-1200-1202	12 wks	220 (~18 wks)	130	normal	normal	Unexplained rise; normalized spontaneously over 3 months; ALT/AST normal for past 5 months on drug
3614-1300-1305	8 wks	144 (~12 wks)	73	137 <sup>†</sup>	26.2 <sup>‡</sup>	Viral illness at time of ALT/AST elevations; incidental ALP and TBIL elevations; normalized over 3-4 months; ALT/AST normal for past 10 months on drug
3614-2500-2512	8 wks	162 (~12 wks)	155	normal	normal	Poorly controlled type 1 diabetic; LTs normalized over 6 months as HbA1c normalized; ALT/AST normal for past 2 months on drug
3614-1300-1313	8 wks	100	95 <sup>‡</sup>	326 <sup>‡</sup> (220 basal)	normal	Alcoholic binge drinker with poorly controlled type 2 diabetes; ALT/AST normal at most recent visit on drug
3614-2500-2515	4 wks	91 (4 wks)	49	154 <sup>‡</sup>	normal	ALP elevated at baseline and throughout study; ALT/AST normalized spontaneously over 2 months; ALT/AST normal for past 7 months on drug
3615-2699-2106	4 wks	129	43	normal	normal	History of alcohol abuse during LT elevations; recurred off drug
3613A-600-615	28 wks	90	63	normal	normal	Mild recurring elevations; ?etiology?
3615-2600-2602	16 wks	133	69	147	normal	Unknown etiology; resolved spontaneously
3615-1600-1607	21 wks	91	51	normal	normal	Isolated single elevation of ALT/AST
3613A-100-103	136 wks	106	normal	normal	normal	Isolated single elevation of ALT
3615-1400-1408	28 wks	109	55	normal	normal	Isolated single elevation of ALT/AST
3614-2200-2205	4 wks	normal	77	normal	19.1 <sup>‡</sup>	No ALT elevation; unknown etiology; AST elevation; TBIL elevated at baseline only

**Table 24 continued\***

*Elevations occurring during placebo or no study drug treatment = non-pegvisomant treatment*

3631-0002-08	8 wks	107	53	normal	normal	Off drug >2mos when elevation occurred; unknown etiology
3611-600-610	4 wks	275	93	normal	normal	Unknown etiology; sporadic but unsustained ALT elevations continued throughout multiple studies
3614-1300-1303	4 wks	288	81	284	20.9	All 4 LTs abnormal; unknown etiology; resolved within 1 mo
3614-2600-2602	8 wks	94	normal	normal	normal	Unknown etiology; resolved spontaneously
3611-0100-106	2 wks	211	93	190	normal	Recurring ALT/AST and ALP elevations before, during and after pegvisomant treatment
3615-2600-2601	4 wks	127	97	124	normal	All elevations off drug; unknown etiology

\*\*Time between visit at which treatment with study drug initiated and visit at which elevation first noted.

†Occurred at a time unassociated with rise in ALT

‡Abnormal at baseline prior to treatment with study drug

\*Table partially derived from submission

Tables 23 and 24 also demonstrate that the only patients with transaminase levels exceeding 10X ULN (but <20X ULN) were the 2 pegvisomant-treated acromegalic patients previously discussed in Sections VI.C.6.2 and VI.C.8.2.1. These 2 patients were also the only subjects to experience sustained large elevations of ALT and AST levels, although these values did eventually normalize once pegvisomant was discontinued. In the 10 subjects with ALT elevations >3-10X ULN (n=3) or ≥1.9-3X ULN (n=7), 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 (e.g., diabetes mellitus out of control, alcoholism). With respect to 8 of the 12 subjects with ALT values ≥1.9X ULN, the time from the beginning of pegvisomant therapy to the first increase in ALT generally ranged between 4 and 12 weeks, with the majority of elevations becoming apparent at 8 weeks (see Table 24).

Finally, it is extremely important to note that none of the pegvisomant-treated patients with transaminase levels ≥1.9X ULN manifested a concomitant elevation of serum TBIL; furthermore, only 2 of the pegvisomant-treated subjects with transaminase values ≥1.9X ULN experienced a simultaneous increase in ALP (e.g., patient 3611-200-204 previously discussed with a biopsy diagnosis of chronic hepatitis whose ALP increased to 160 in association with marked transaminase elevations, and patient 3615-2600-2602 with very modest LT abnormalities of unknown etiology which resolved spontaneously).

#### VI.C.8.2.4 Effect of Pegvisomant Therapy on Subjects with Elevated Baseline Liver Function Tests

Nineteen pegvisomant-treated subjects had elevated ALT and/or AST values at baseline. Two subjects had ALT elevations >3-10X ULN at baseline. Patient 3611-0200-201 was subsequently diagnosed with cholelithiasis; LTs returned to and remained normal after cholecystectomy. The elevations noted in subject 3614-1400-1407 resolved spontaneously once pegvisomant therapy was begun. Another subject (3614-1200-1204) had elevations of ALT and AST  $\geq 1.9$ -3X ULN at baseline of uncertain etiology which also did not persist after initiation of pegvisomant therapy.

The remainder of the subjects had elevations of ALT and/or AST <1.9X ULN at baseline. The majority of these elevations normalized after pegvisomant therapy was started; in 5 patients, the ALT/AST values did not change significantly on-study.

Table 25 summarizes the ALT/AST response during pegvisomant therapy (baseline versus terminal values) in these patients.

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Table 25. ISS

Subjects with Elevated ALT and/or AST at Baseline  
Subsequently Treated with Pegvisomant

Response During Pegvisomant  
Treatment

	ALT	AST
Increased (>15%)	0	0
Unchanged (±15%)	4 1605 (81→91) 1710 (68→65) 704 (85→88) 01-04 (78→68)	1 1304 (41→45)
Decreased (<15%)	0	0
Normalized	7 201 (464→35) 1407 (362→30) 1204 (96→31) 1207 (65→23) 2003 (50→44)  502 (55→30) 109 (70→33)	12 201 (87→22) 1407 (61→32) 1204 (72→31) 1207 (52→28) 2003 (46→35)  01-03 (38→28) 1313 (42→33) 408 (47→17) 409 (41→21) 305 (38→14) 301 (38→31) 1605 (43→39)

VI.C.8.2.5 Change from Baseline in ALT and AST

A very small increase was observed in mean ALT and AST levels in the "all subjects" population when endpoint values are compared to baseline values (see Table 26). However, all of these mean endpoint values for both ALT and AST remained within the normal range.

**Table 26. ISS - Mean Change from Baseline in ALT and AST in the "All Subject" Population\***

Parameter (unit)		All Subjects		Healthy Volunteers		Acromegalic Subjects		Diabetic Subjects
		Peg	Pbo	Peg	Pbo	Peg	Pbo	Peg
ALT (U/L) (0-47)	Baseline	25.8	23.4	22.6	31.7	26.3	21.2	26.6
	Endpoint	30.8	28.2	23.1	29.0	32.5	28	29.6
	Change	5.0	4.8	0.5	-2.7	6.2	6.8	3.0
AST (U/L) (0-37)	Baseline	21.9	21.5	23.0	25.0	21.8	20.6	21.8
	Endpoint	25.7	22.3	24.1	22.9	26.2	22.1	24.8
	Change	3.8	0.8	1.1	-2.1	4.4	1.5	3.0

\*Table derived from submission

There was no relationship between the dose of pegvisomant and the change in mean ALT or AST concentrations (Table 27). Furthermore, an examination of the relationship between duration of treatment and transaminase levels (Table 28) revealed no duration-related effect of pegvisomant on transaminase values.

**Table 27. ISS - Mean Change in ALT and AST Values from Baseline to Endpoint by Dose in "All Acromegalic" Population (SEN-3614)\***

Parameter (unit)		Pegvisomant			
		10 mg/d (n=26)	15 mg/d (n=26)	20 mg/d (n=28)	Placebo (n=32)
ALT (U/L) (0-47)	Baseline	19.6	25.2	32.1	22.0
	Endpoint	37.8	45.0	23.7	22.8
	Change	18.2	19.8	-8.4	0.8
AST (U/L) (0-37)	Baseline	20.7	23.9	21.0	20.3
	Endpoint	32.8	30.5	21.0	20.8
	Change	12.1	6.6	0.0	0.5

\*Table derived from submission

**Table 28. ISS - Mean ALT and AST Values in All Acromegalic Subjects Treated with Pegvisomant by Duration of Exposure\***

Parameter (unit)	Baseline	Months				
		≤3	>3≤6	>6≤9	>9≤12	>12
ALT (U/L) (0-47)	26.3	34.0	27.5	25.2	23.8	23.6
AST (U/L) (0-37)	21.8	27.3	23.5	21.6	20.5	21.4

Date of the lab draw closest to end of duration category was used.

If a subject had a gap in dosing >1 month, each dosing period is treated separately.

\*Table derived from submission

### **VI.C.9 Anti-GH Antibodies (a possible surrogate for anti-pegvisomant antibodies)**

After the pegvisomant drug development program was initiated, it was discovered that the methodology planned to detect anti-pegvisomant antibodies was best utilized in off-treatment serum. However, since pegvisomant shares antigenic epitopes with human GH, it was felt that the measurement of anti-human GH antibodies would be sufficient to screen for a significant humoral response to pegvisomant.

Twenty seven acromegalic patients (16.9% of the NDA acromegalic database) had 1 or more samples test positive for anti-human GH antibodies. The majority of these patients (n=24) manifested isolated or sporadic low titers. In 3 patients who experienced sustained low titers of anti-human GH antibodies, IGF-I levels normalized within 2 months of beginning pegvisomant therapy, and remained normal for the duration of longterm therapy (e.g., immunologically-mediated tachyphylaxis did not occur). During the longterm study SEN-3613A, only 3/38 patients did not achieve normal IGF-I levels (see Section VI.D.2.2.3.1.2). 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.

During the fixed dose, placebo controlled study, SEN-3614, 8/80 pegvisomant-treated patients developed low titers (ranging from 1:4 to 1:64) of anti-human GH antibody (compared with none in the placebo group). As seen in Table 29, there were no apparent dose-related trends. Furthermore, minimal evidence of immunogenicity was observed in preclinical studies.

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

## VI.C.10.2 Elevations in Serum GH concentrations

Elevations in serum GH concentrations in acromegalic patients treated with pegvisomant were expected from the outset of the pegvisomant development program. GH secretion by pituitary somatotrophs is modulated by circulating blood levels of both IGF-I and GH. IGF-I exerts negative feedback directly at the level of the pituitary. Since somatotroph adenomas are not completely autonomous, pegvisomant-induced lowering of serum IGF-I levels could potentially lead to increased pituitary GH secretion. If this was the predominant event after initiation of pegvisomant therapy, presumably, after an initial modest increase in serum GH concentration, levels would not continue to rise, especially as IGF-I levels stabilized in the normal range. On the other hand, GH increases hypothalamic somatostatin release, thereby decreasing additional GH secretion by the pituitary. If pegvisomant penetrated the blood-brain barrier and had access to the hypothalamus, a more rapid and sustained rise in GH secretion from the pituitary would be anticipated (e.g., the hypothalamus would continually perceive a "low" GH concentration because of blockade of its GH receptors and release less somatostatin).

During SEN-3601, the administration of single doses of pegvisomant to healthy volunteers lowered serum IGF-I concentrations, but did not acutely increase serum GH levels. On the other hand, in every study conducted in acromegalics, serum GH concentrations rose in association with the decrease in IGF-I levels induced by pegvisomant treatment.

During the placebo controlled pivotal study SEN-3614, serum GH concentrations increased in a dose-dependent manner in acromegalics treated with pegvisomant. In Figures 4 and 5, the rise in serum GH levels are plotted against the fall in serum IGF-I concentrations in acromegalic patients who received placebo and 3 doses of pegvisomant (10, 15 and 20 mg/d) for 12 weeks. The dose dependent increase in GH appears to be related to the magnitude of IGF-I reduction caused by increasing the dose of pegvisomant. Of note, GH levels peaked after only 2 weeks of therapy with all 3 dosages, and then plateaued for the next 10 weeks. As seen in Table 30, baseline GH levels doubled after 12 weeks of therapy with pegvisomant 15 mg/day and tripled after 20 mg/day.

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Figure 4. ISS - Time Plot of GH vs. IGF-I (SEN-3614)

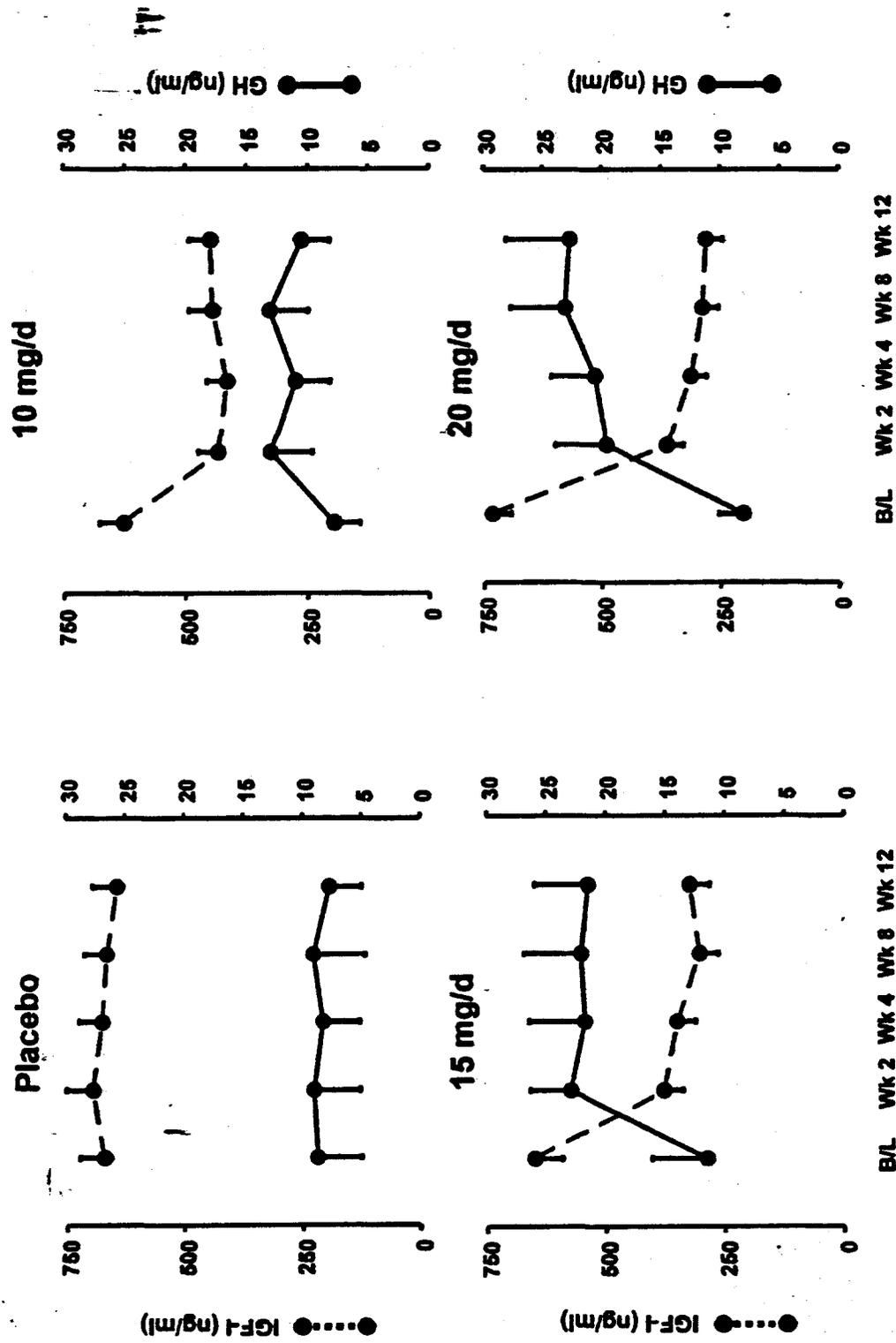
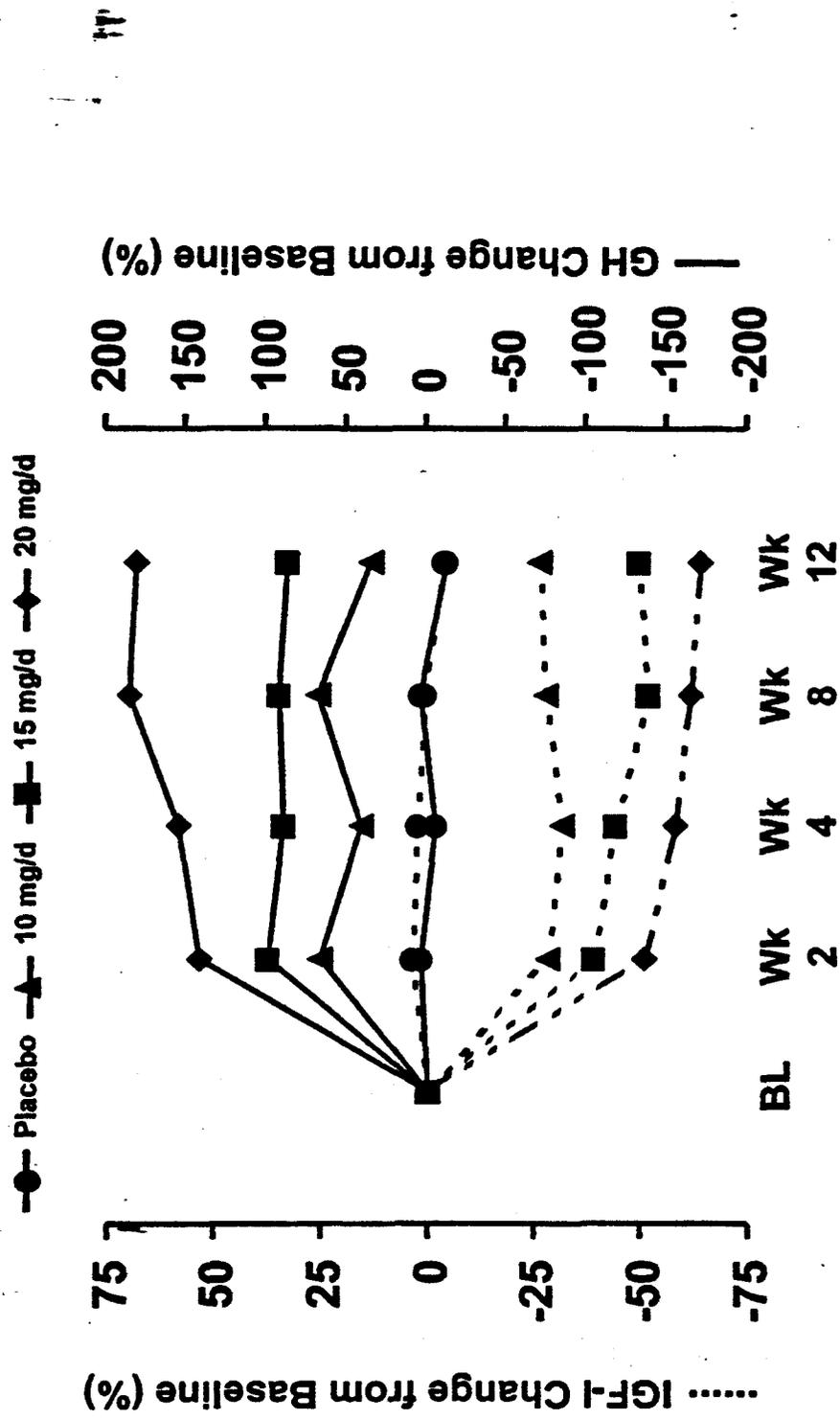


Figure 5. ISS - Time Plot of GH vs. IGF-I (SEN-3614)



**Table 30. ISS - Growth Hormone Levels at Baseline and End of Study (SEN-3614)\***

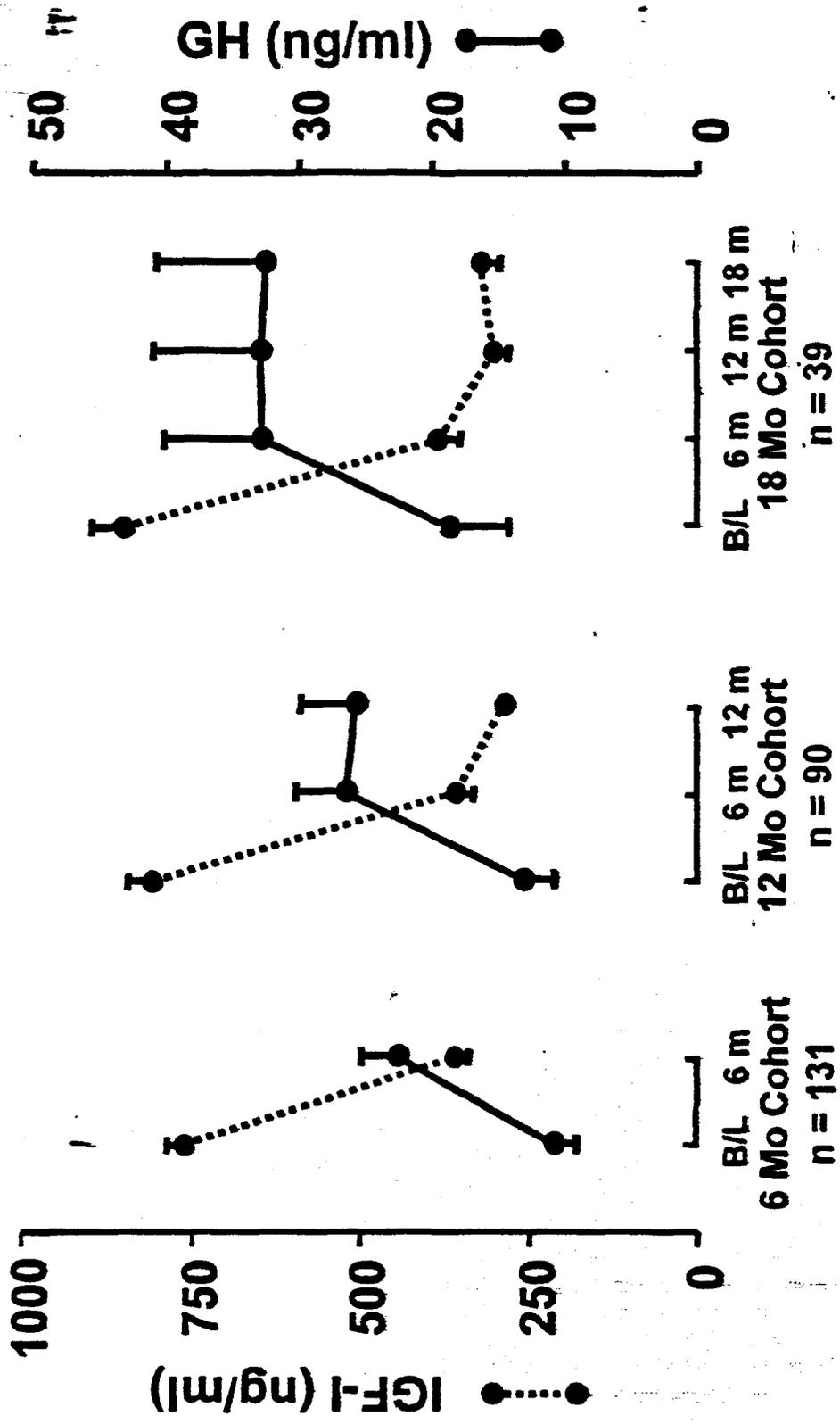
mg/d	Pegvisomant Dosage			Placebo
	10	15 mg/d	20 mg/d	
(n=26)	(n=26)	(n=28)	(n=32)	
Mean baseline growth hormone (ng/mL)	7.8	11.5	8.1	8.7
Change from baseline at Week 12 (ng/mL)	2.7	9.2	14.4	-0.8

\*Table derived from submission

In order to longitudinally evaluate the effect of pegvisomant on serum concentrations of IGF-I and GH over a longer period of time than 12 weeks, an additional analysis was conducted. Acromegalic patients participating in the 2 extension studies (3613A and 3615) were grouped into 3 cohorts based on how long they had received continuous daily pegvisomant treatment (at least 6 months [n=131], at least 12 months [n=90], or at least 18 months [n=39]). All of the patients in the 18 month treatment cohort were also included in the 6 and 12 month cohorts, and all of the patients in the 12 month cohort were also included in the 6 month cohort.

With regard to all cohorts, the baseline GH level was the GH value obtained immediately prior to the initiation of pegvisomant therapy in the patient's first study protocol (most often SEN-3611 or SEN-3614). The mean ( $\pm$  SEM) serum GH concentrations at baseline were  $10.9 \pm 1.5$ ,  $13.2 \pm 2.1$  and  $19.2 \pm 4.3$  ng/mL in the 6, 12 and 18 month cohorts, respectively. GH levels increased by very similar increments in all 3 cohorts (e.g.,  $12.5 \pm 2.1$ ,  $12.5 \pm 3.1$  and  $14.2 \pm 5.7$  ng/mL to  $23.1 \pm 3.1$ ,  $25.6 \pm 4.3$  and  $33.8 \pm 8.6$  ng/mL, respectively [ $p < 0.05$  for within-cohort, baseline vs. final value comparisons]). As can be seen in Figure 6, the elevations of serum GH once again mirrored the decreases in serum IGF-I concentrations (just as they did during the short term [12 week] SEN-3614 study). GH levels increased between baseline and 6 months, and then plateaued for 6-12 months. It is important to note that Figure 6 (provided by the Sponsor) is a bit misleading in that it does not include 2 week and 3 month values for each cohort. As demonstrated in SEN-3614 (Figures 4 and 5), pegvisomant resulted in peak levels of GH after only 2 weeks of therapy in most patients which then remained stable. It would appear then that the elevated GH concentrations observed after 2 weeks of therapy do not increase further for as long as 18 months. Furthermore, in this regard, Table 31 demonstrates that acromegalic patients from SEN-3614 did not manifest further GH elevations during SEN-3615.

Figure 6. ISS - Time Plot of GH vs. IGF-I (SEN-3614/3611 [B/L Values] & SEN-3613A/3615 [6,12,18 Month Values])



**Table 31. IGS - GH vs. IGF-I After Pegvisomant Therapy (SEN 3614/3615)**

Special Laboratory Tests	3614 Baseline	3615 Baseline	3615 Last Visit Cut-off
Growth Hormone (ng/mL)			
N	100	100	88
Mean	9.6	15.7	17.9
SE	1.75	2.38	2.66
SD	17.46	23.78	24.97
Median	4.1	7.3	11.0
Min			
Max			

Further evidence of the inverse relationship between GH and IGF-I levels in acromegalic patients treated with pegvisomant comes from a subgroup of subjects participating in SEN-3613A and SEN-3615 who were withdrawn from pegvisomant and not placed on alternative medical therapy for at least 1 month (n=45). The mean ( $\pm$  SEM) serum GH concentration was  $8.0 \pm 2.5$  ng/mL at baseline, increased to  $15.2 \pm 2.4$  ng/mL at the last visit prior to withdrawal, and decreased back to  $8.3 \pm 2.7$  ng/mL within 30 days of pegvisomant withdrawal (p=NS compared to baseline).

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### VI.C.10.3 Change in GH-Secreting Pituitary Adenoma Volume on Serial MRI Scans

As seen in Table 32, 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). The largest decreases in mean tumor volume in pegvisomant-treated patients were observed in subjects with prior radiation alone (-0.22 cc) and prior radiation and surgery (-0.12 cc). A minimal increase from baseline (+0.10 cc) was noted in patients with prior surgery alone and no prior surgery or radiation. There was no association between the size of the tumor at baseline or the duration of pegvisomant treatment, and the change in tumor volume while on pegvisomant therapy.

In addition, an analysis of the distribution of changes in tumor volume (see Figure 7) demonstrated that all but 4 patients had a decrease, no change, or a  $\leq 1$  cc increase in tumor volume. In 2 patients (patients 2003 and 1205), tumor volume increased ~1.5 cc after 3-6 months of pegvisomant therapy. Both of these patients had very large, irregularly shaped tumours (which are more prone to volume-averaging error when imaged), and, in both instances, the blinded neuroradiologist reading the final scan did not feel a clinically important increase in tumor size had occurred. Two additional patients with acromegaly previously resistant to currently available therapies (see detailed narratives below) demonstrated significant continued tumor growth while being treated with pegvisomant for ~1-2 years (~2.5-3 cc).

Neither of the 2 patients noted above with very significant tumor growth were discussed by the Sponsor in the original NDA submission or the Safety Update. Information about both of these patients was provided to the Division by the Sponsor via a copy of a "Dear Investigator" letter dated 15Jun2000; in addition, the case history of 1 of these patients was recently published (29).

Patient 2201 is a 26 year old Swedish acromegalic female with a pituitary macroadenoma who was originally treated by transsphenoidal adenomectomy in July 1998. She received pegvisomant 15 mg/day between January 1999 and March 1999 while enrolled in SEN-3614 with minimal change in her IGF-I level (878 ng/mL at study termination; GH increased from 8 to 18 ng/mL during SEN-3614). She received no therapy between March 1999 and August 1999. In August 1999, she entered SEN-3615 and was titrated to a pegvisomant dose of 30 mg/day (IGF-I decreased from 1165 ng/mL at baseline to a nadir of 537 ng/mL [still elevated]; GH decreased from 23 to 18 ng/mL after restarting pegvisomant in August 1999). Between December 1998 and March 2000, her tumor volume increased from 5.53 cc to 8.71 cc. It is felt that her tumor grew more substantially between March 1999 and August 1999 (when she was off pegvisomant therapy) than it did between August 1999

and March 2000 (when she was taking pegvisomant). The patient completed a course of radiation therapy in April 2000 because of the tumor growth.

Patient 401 is a 34 year old Dutch acromegalic male with a pituitary macroadenoma who was originally treated by transsphenoidal adenomectomy in February 1997 (IGF-I level post-surgery was 230 nmol/L [age-adjusted ULN 64 nmol/L]). Between February 1997 and February 1998, he was treated with octreotide and also participated in SEN-3611 (IGF-I decreased to 150 nmol/L). In March 1998, he entered SEN-3613A and was titrated to a pegvisomant dose of 40 mg/day. His lowest IGF-I level while being treated with pegvisomant alone between March 1998 and November 1999 was 66 nmol/L (still >ULN). Of note, his tumor grew significantly between July 1997 (2.93 cc) and July 1999 (~5.41 cc) both on and off pegvisomant (associated with new visual field defects). In addition, GH increased from 81 ng/mL (prior to starting pegvisomant in March 1998) to 161 ng/mL in the fall of 1999. In November 1999, therapy with Sandostatin LAR was initiated (in addition to pegvisomant). Since that time, IGF-I levels have normalized, GH levels have decreased to <100 ng/mL, visual field defects have improved and tumor volume has stopped increasing (29).

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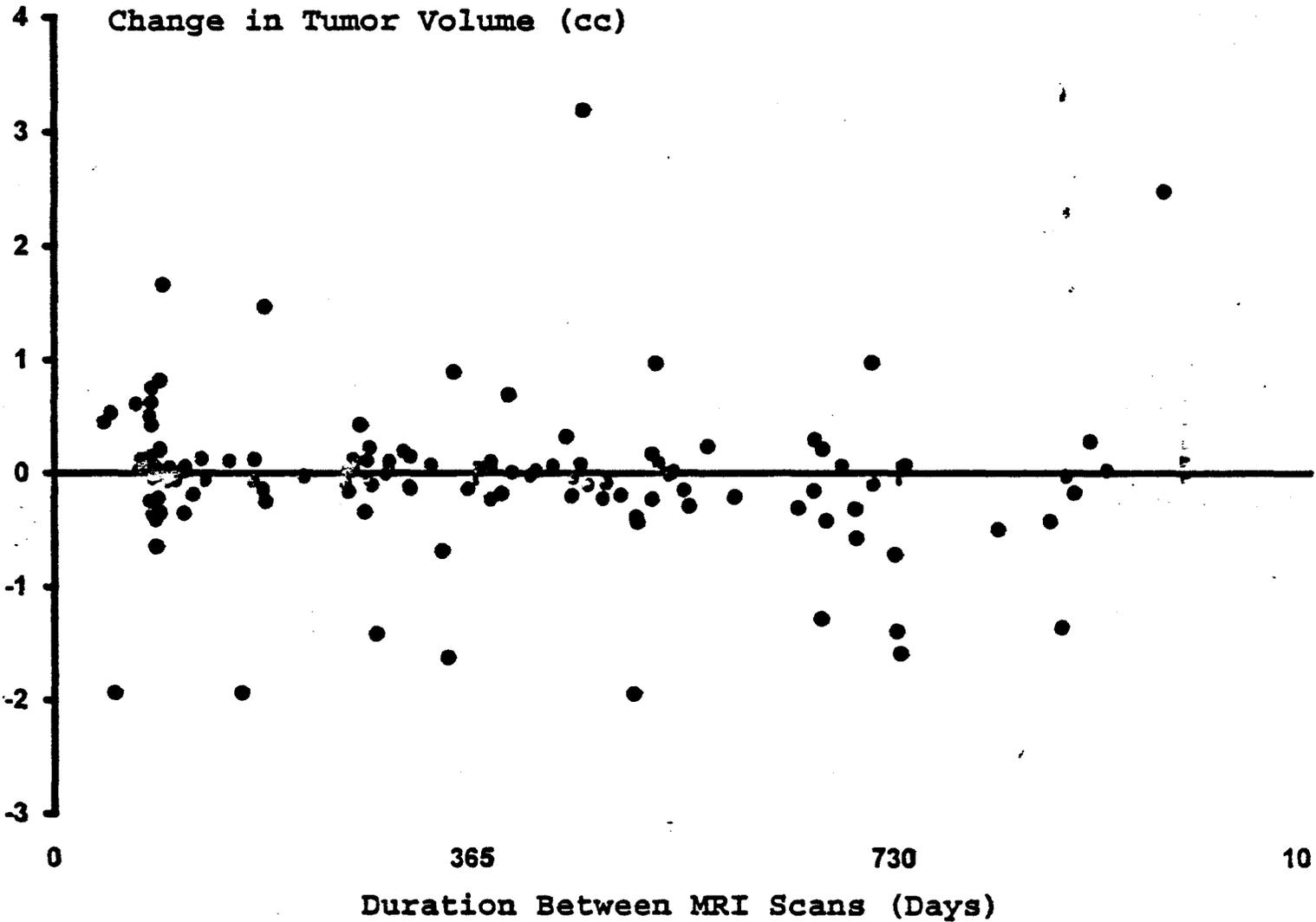
**Table 32. ISS - Mean Tumor Volume (cc±SEM) in Acromegalic Subjects by Prior Therapy\***

Prior therapy	Parameter	Pegvisomant	Placebo
<b>Surgery alone</b>	<b>Number of subjects</b>	<b>42</b>	<b>12</b>
	Duration between baseline and follow-up scan (months)	10.76 ± 1.06	2.74 ± 0.24
	Baseline	2.30 ± 0.38	2.04 ± 0.67
	Endpoint	2.40 ± 0.40	1.74 ± 0.49
	Change from baseline	0.10 ± 0.12	-0.30 ± 0.19
<b>Radiation alone</b>	<b>Number of subjects</b>	<b>9</b>	<b>3</b>
	Duration between baseline and follow-up scan (months)	12.11 ± 1.97	2.32 ± 0.45
	Baseline	2.80 ± 1.57	1.58 ± 0.30
	Endpoint	2.58 ± 1.35	1.50 ± 0.24
	Change from baseline	-0.22 ± 0.22	-0.08 ± 0.11
<b>Surgery + radiation</b>	<b>Number of subjects</b>	<b>69</b>	<b>18</b>
	Duration between baseline and follow-up scan (months)	12.53 ± 1.09	2.25 ± 0.15
	Baseline	2.67 ± 0.49	2.84 ± 0.57
	Endpoint	2.55 ± 0.50	3.07 ± 0.50
	Change from baseline	-0.12 ± 0.08	0.23 ± 0.13
<b>Neither</b>	<b>Number of subjects</b>	<b>11</b>	<b>4</b>
	Duration between baseline and follow-up scan (months)	6.92 ± 1.34	2.71 ± 0.45
	Baseline	0.88 ± 0.28	1.88 ± 0.96
	Endpoint	0.98 ± 0.33	1.82 ± 0.93
	Change from baseline	0.10 ± 0.05	-0.06 ± 0.04
<b>Total subjects</b>	<b>Number of subjects</b>	<b>131</b>	<b>37</b>
	Duration between baseline and follow-up scan (months)	11.46 ± 0.70	2.46 ± 0.12
	Baseline	2.41 ± 0.31	2.37 ± 0.37
	Endpoint	2.37 ± 0.31	2.15 ± 0.31
	Change from baseline	-0.04 ± 0.06	-0.22 ± 0.09

Subjects who received both pegvisomant and placebo appear in both treatment groups.

\*Table derived from submission

Figure 7. ISS - Distribution of Changes in Tumor Volume in All Acromegalic Patients Irrespective of Prior Therapy



#### VI.C.10.4 Increased Insulin Sensitivity in All Acromegalics and Possible Decreased Requirement for Antidiabetic Therapy in Acromegalics with Diabetes Mellitus (and Non-Acromegalics with Diabetes Mellitus)

Increased GH levels more than likely contribute to the defect(s) in insulin action associated with inadequately controlled non-acromegalic patients with type 1 and type 2 diabetes mellitus. Furthermore, excessive GH levels in acromegalic subjects result in significant insulin resistance (e.g., defects in both hepatic and peripheral insulin action); as a consequence, 30-50% of acromegalics develop impaired glucose tolerance and 10-25% manifest overt diabetes mellitus.

Therefore, it was anticipated by the Sponsor that treatment with pegvisomant might result in a decreased requirement for antidiabetic therapy in acromegalics with diabetes mellitus, and increased insulin sensitivity in non-diabetic acromegalics,

In fact, the following was observed in this regard during the pegvisomant development program:

- During the placebo controlled study SEN-3614 (which included 9 patients on oral agents and 8 patients on insulin amongst its enrollees), as well as the extension study SEN-3615 which followed, data was unfortunately not systematically collected with regard to any reductions made in antidiabetic therapy. One diabetic acromegalic patient enrolled in SEN-3615 manifested a significant decrease in insulin requirements associated with a very large weight gain (see Section V.C.5.1). It can only further be said that serious and/or frequent hypoglycemic episodes were not reported.
- During SEN-3613A, acromegalic patients were treated with dose-titrated amounts of daily pegvisomant (10 to 30 mg/day). In 35 acromegalics, mean fasting insulin levels significantly decreased ( $P < 0.02$ ) from  $21.3 \pm 3.39$  mIU/L (at the beginning of SEN-3611) to  $13.6 \pm 1.63$  after 6 months of therapy. Fasting blood sugar decreased from  $5.8 \pm 0.35$  mmol/L to 4.8 mmol/L ( $P < 0.005$ ), hemoglobin A1C levels did not change, and IGF-I levels normalized in 94% of patients (see ISE). One of these patients (patient 3613A-501), a glipizide XL-requiring diabetic, was treated for a total of 13 months; as a consequence of pegvisomant therapy, hemoglobin A1C normalized and fasting insulin levels decreased - despite discontinuation of the oral agent. See references 30-31.
- During SEN-3622 and SEN-3631, mean daily insulin requirements decreased -25-30% in 17 pegvisomant-treated non-acromegalic patients with type 1 diabetes mellitus (20 mg/day SC for as long as 12 weeks) Not surprisingly, there was an ~50% decrease in IGF-I concentrations and GH levels rose slightly. One very severe hypoglycemic episode was reported (altered mental status; patient 3631-0003-02), as well as a number of episodes of modest hypoglycemia during which patients

were able to manifest typical hypoglycemic symptoms (e.g., blocking GH action did not interfere with the ability to respond to/sense hypoglycemia).

## VI.C.11 Potential Safety Issues (Renal) Related to Pegylation

B2036 is conjugated with PEG-5000 (e.g., molecular weight [MW] = 5000) to form pegvisomant, in an attempt to increase its biological half-life. Most often 4-5 PEG moieties attach to each B2036 molecule (less frequently 3 or 6 PEG strands). It has been reported that as the MW of a PEG increases, its renal clearance decreases and terminal half-life increases (32).

Both preclinical and clinical data suggest at least the potential of PEG-induced renal toxicity. A 6 month preclinical toxicology study in rats (SEN-118) indicates that the daily administration of pegvisomant 3, 10 and 30 mg/kg resulted in tubular dilatation and inflammation histologically associated with increased kidney weight, proteinuria, granular casts and pyuria clinically (there were no changes in serum BUN or creatinine) in female rats only; these changes were only reversible in the 3 mg/kg group (human equivalent dosage -0.5 mg/kg). It has long been known that the ingestion of ethylene glycol (a component of antifreeze), usually in alcoholics, results in an anion gap metabolic acidosis, hyperosmolarity, and renal failure. In addition, a similar syndrome has been observed in human burn patients (as well as surgically wounded rabbits) treated with a topical antibiotic cream containing PEG (33).

On the other hand, 3 other PEG-containing medications\* (see Section VI.A.1) recently approved by the Agency have been well tolerated without evidence of renal (or hepatic) toxicity. However, all of these medications are administered weekly or every other week, and therefore they may not be appropriate comparators for pegvisomant. (\* = 1) Adagen - numerous strands of PEG-5000 attached to adenosine deaminase [ADA], and administered weekly to children with severe combined immunodeficiency disease lacking ADA; 2) Oncaspar - 1 PEG-5000 moiety attached to L-asparaginase, and administered every other week to children with leukemia; and 3) PEG-Intron - 1 PEG-12,000 moiety attached to interferon alfa-2B, and administered weekly to patients with chronic hepatitis C).

During the placebo controlled and open label trials conducted as part of the pegvisomant clinical development program, there were no clinically significant changes in mean serum BUN or creatinine (data not shown); in addition, a review of individual data by this medical reviewer did not reveal evidence of significant outliers (data not shown). The baseline prevalence and on-study incidence of proteinuria (by dipstick) during the placebo controlled study SEN-3614 is displayed in Table 33.

Proteinuria first appeared after initiation of pegvisomant therapy in 15.2% (17/112) of enrolled patients, and was most frequently observed after treatment with pegvisomant 20 mg/day (7/28; 25%). On the other hand, if the presence (and amount) of proteinuria is analyzed for these 17 patients during the extension study SEN-3615:

- 11/14 patients originally randomized to active treatment arms during SEN-3614 (including 6/7 receiving 20 mg/day) manifested consistently negative urine protein tests (88 visits), 2/14 had a single additional positive test for proteinuria, and 1 diabetic acromegalic patient had persistent proteinuria (4/13 visits) ranging from 15-30 mg/dl (data not shown);
- the incidence (amount) of new-onset proteinuria detected during SEN-3614 (in the 3/17 patients receiving placebo), was comparable to the frequency (amount) of proteinuria observed in these same patients during the extension study (data not shown).

Proteinuria was present at baseline in 20.5% (23/112) of patients enrolled in SEN-3614. If the presence (and amount) of proteinuria is analyzed for these 23 patients during SEN-3614 and the extension study SEN-3615, 8/23 patients with baseline values  $\geq 100$  mg/dl had persistent proteinuria of the same magnitude, and 15/23 subjects with baseline values  $< 100$  mg/dl manifested much less frequent recurrences of proteinuria, almost always of the same magnitude (4 of these 15 patients had subsequent values greater than the amount determined at baseline, but in every case, follow-up urine protein determinations were negative).

The Sponsor will submit a similar analysis of the results of urine sediment findings (e.g., casts, wbc/hpf, rbc/hpf) in the near future; at that time, this reviewer will comment on these observations in an addendum to this review.

**Table 33. ISS - Incidence of Proteinuria (SEN-3614)**

	Placebo	Peg 10mg	Peg 15mg	Peg 20 mg	All Groups
Treatment arms	32	26	26	28	112
Positive baseline n(%)	5(15.6)	5(19.2)	8(30.8)	5(17.9)	23(20.5)
Positive during rx n(%)	3(9.4)	4(15.4)	3(11.5)	7(25)	17(15.2)
Total n(%)	8(25)	9(34.6)	11(42.3)	12(42.9)	40(35.7)

Finally, it should be noted that the ingestion of a multivitamin containing PEG-8000 and PEG-20,000 has resulted in anaphylaxis (34), and the ingestion of a PEG-containing colon lavage preparation has produced urticaria (35). It is therefore somewhat reassuring that there were no reports of anaphylaxis during the pegvisomant trials (as previously noted in Section VI.C.9).

**VI.C.12 PK/PD Analyses with Implications Relevant for Safety (See Section VI.A.5.7.4) (performed by the Sponsor and confirmed by the Division's Biopharmaceutics Reviewer)**

**VI.C.12.1 Accumulation**

During SEN-3614, treatment of acromegalic patients with pegvisomant 20 mg/day for 12 weeks resulted in mean serum pegvisomant concentrations of 27,000 ng/mL - which still appeared to be increasing slightly at that time. However, during the open label extension studies, (SEN-3613A and 3615), after patients had been titrated to a maintenance dose of pegvisomant, monthly fasting serum levels of pegvisomant were very stable - even in patients requiring 20-40 mg/day. See Biopharmaceutics Review for further comment in this regard.

**VI.C.12.2 Drug-Drug (and Drug-Disease) Interactions**

None of the pegvisomant clinical trials were designed to evaluate drug-drug and drug-disease interactions.

A separate population PK analysis revealed that concomitant treatment with lipid-lowering drugs was found to decrease pegvisomant clearance by -30% (compared with patients not taking these drugs). The clinical significance of this observation is unknown.

**VI.C.13 Preclinical Data Pertinent to Human Safety**

Results and observations from preclinical toxicology studies which may be relevant to human safety appear below:

- Six month rat toxicology study (SEN-118):
  - As discussed in Section 9.12 above, the daily administration of 3-30 mg/kg of pegvisomant for 6 months resulted in significant histologic tubulopathy (at Week 26, but not Week 13) associated with proteinuria in female rats only; these changes were reversible after discontinuation of the 3 mg/kg dose only (a crude NOAEL according to the Division's Pharmacology Reviewer).
  - In addition, an increase in liver weight associated with hepatocellular vacuolization (but not associated with elevated LTs) was observed after treatment with pegvisomant 10 and 30 mg/kg in female rats only.
  - Furthermore, skin thickening associated with chronic active inflammation histologically was commonly seen at the injection sites in male and female rats.

- Six month monkey toxicology study (SEN-109) (weekly dosing makes this study much less meaningful):
  - Injection site reactions (as well as an increase in body fat) were noted after all doses in male and female monkeys.
- One month monkey toxicology study (SEN-108) (daily dosing):
  - Injection site reactions were noted once again after all doses.
- Immunogenicity data:
  - Antibody formation studies were weakly positive in transgenic mice (SEN-122) and Rhesus monkeys (SEN-102).
  - During the 6 month rat toxicology study (SEN-118), no pegvisomant-related antibodies were identified.
- Reproductive studies
  - The administration of pegvisomant at doses  $\leq 10$  mg/kg/day resulted in no maternal toxicity, and at doses  $\leq 3$  mg/kg/day produced no fetal toxicity.

These preclinical studies suggest that longterm SC administration of pegvisomant to humans may well be complicated by injection site reactions (which in fact were observed more frequently in the pegvisomant-treated patients compared with the placebo-treated subjects - see Section VI.C.6.3.2 and Table 21). More than likely these injection site reactions are a consequence of drug-induced inflammation  $\pm$  lipohypertrophy (patient 3613A-0600-602 in fact withdrew because of biopsy-proven lipohypertrophy - see Section VI.C.6.2).

In addition, the tubulopathy/proteinuria observed in female rats suggest the potential for pegvisomant (?PEG?)-induced renal toxicity in humans. To date, evidence of renal dysfunction has not been observed during the pegvisomant trials (see Section VI.C.11).

#### VI.C.14 ISS - Conclusions

- The overall safety profile of pegvisomant during the clinical trials was satisfactory.
- Acromegaly is an orphan disease for which presently available therapies are inadequate for a substantial number of patients. Under these circumstances, a safety database consisting of 160 acromegalics, 84 of whom were exposed to pegvisomant for  $>1$  year, would appear to be sufficient.
- The possibility of hepatotoxicity was the most important safety concern which became apparent during the pegvisomant drug development program. The absence of simultaneous elevations of transaminase levels  $\geq 3$ X ULN and TBIL is reassuring (see Section II.C.1.3 in Summary of Clinical Findings in EXECUTIVE SUMMARY).

- Injection site reactions were the adverse effects uncovered during the clinical trials most likely directly related to pegvisomant administration.
- Treatment with pegvisomant results in a significant incidence of low titer, non-neutralizing anti-human GH antibodies. Anti-human GH antibodies did not appear to play a role in the lack of IGF-I normalization in 1) the 3 patients (out of 38) during SEN-3613A, or 2) the 1 patient (out of 10) with anti-pegvisomant antibodies (off study drug). The presence of anti-human GH antibodies (on-study) in the 10/39 patients with positive anti-pegvisomant antibodies (off study drug) possibly supports the use of anti-human GH antibodies as a surrogate for anti-pegvisomant antibodies in patients receiving active therapy with pegvisomant.
- Overtreatment with pegvisomant resulting in IGF-I levels less than the age-adjusted reference range (e.g., a state of "effective" GH deficiency) was unusual.
- 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 over time, suggest that the increase in serum GH concentration observed in acromegalic patients treated with pegvisomant is physiologically related to pegvisomant-induced IGF-I suppression.
- The 2 patients with significant acromegalic tumor growth during the pegvisomant trials 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.
- After treatment with pegvisomant, acromegalic patients with diabetes mellitus may require a reduction in the need for antihyperglycemic therapy.
- After exposure to pegvisomant, clinically significant changes in renal function did not occur. It appears that 1) new-onset proteinuria after the initiation of pegvisomant therapy does not result in progressive/persistent proteinuria during longterm exposure, and 2) extended exposure to pegvisomant does not exacerbate preexisting proteinuria. Note: Insert on casts/cells.

See the EXECUTIVE SUMMARY for further discussion of conclusions (Section II), and recommendations (Section I.B) regarding safety issues relevant to this NDA - in-particular 1) exposure; 2) abnormal LTs; 3) injection site reactions; 4) immunogenicity; 5) pegvisomant-induced "effective" GH deficiency; 6) GH elevations; 7) change in GH-secreting pituitary adenoma volume on serial MRI scans; 8) possible decreased requirement for antidiabetic therapy in acromegalics with diabetes mellitus; and 9) potential renal safety issues related to pegylation.

## VI.D ISE

### VI.D.1 SEN-3614

SEN-3614 was a randomized, placebo controlled, double blind, fixed duration (12 weeks) study which compared the efficacy of 3 doses of pegvisomant (10, 15 and 20 mg/day - all preceded by an 80 mg loading dose), and placebo, in the treatment of acromegaly. Patients were required to have a baseline IGF-I level  $\geq 3X$  ULN of an age-adjusted range after washout from previous therapy (e.g., SAs) in order to be included in this clinical trial. All 3 doses of pegvisomant produced substantial, dose-dependent reductions in baseline serum IGF-I concentrations which were significantly different from the minimal changes observed after the administration of placebo at each post-treatment time point. 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).

Please refer to Section VI.A for a comprehensive review of efficacy for this clinical trial, and to the Summary of Efficacy in the EXECUTIVE SUMMARY. Comparative references to the efficacy results of SEN-3614 will be made in the brief discussions of efficacy for SEN-3613A, SEN-3615, SEN-3611 and SEN-3613 below.

### VI.D.2 SEN-3613A

#### VI.D.2.1 Study Design, Inclusion Criteria, Dosing, Efficacy Parameters and Statistical Methods

SEN-3613A was an open label, dose-titration, extension study designed to assess the longterm efficacy of daily pegvisomant therapy in acromegaly. Patients completing SEN-3611 (a randomized, placebo controlled, 6 week trial which compared the efficacy of 2 weekly doses of pegvisomant, and placebo, in the treatment of acromegaly) and/or SEN-3613 (an open-label, dose-titration, extension study designed to assess the longterm efficacy of weekly pegvisomant in acromegaly - which immediately followed SEN-3611) were eligible to enroll in SEN-3613A.

Daily dosing was chosen because 1) the efficacy observed with weekly dosing during SEN-3611 was not substantial, and 2) PK modeling indicated that trough concentrations of pegvisomant would be increased by ~20% if daily dosing was employed. At the first visit in SEN-3613A, an 80 mg SC loading dose of pegvisomant was administered (in order to achieve the steady state more rapidly); 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 (the maximum dose allowed per protocol was 30 mg/day).

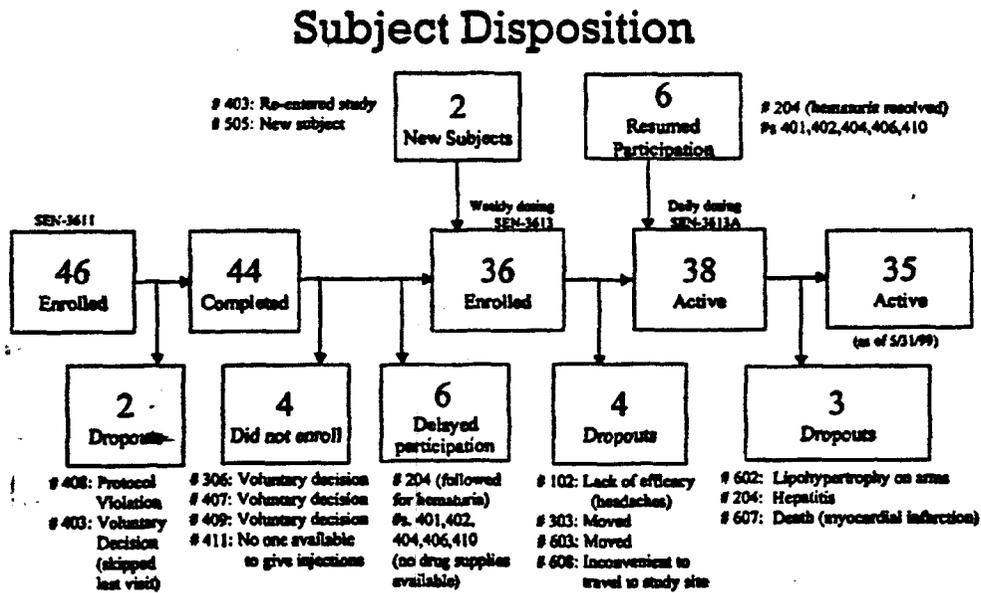
As in SEN-3614 and SEN-3611, the primary efficacy endpoints were the percent reduction in and percent normalization of IGF-I levels. Secondary measures included changes in ring size, and the symptoms and signs of acromegaly scores. Formal statistical analyses were not conducted; however, descriptive statistics were tabulated.

## VI.D.2.2 Results

### VI.D.2.2.1 Disposition

As depicted in Figure 7, 31 patients entered SEN-3613A after completing SEN-3611 and participating in SEN-3613, 1 patient after participating in SEN-3613, and 6 patients after completing SEN-3611. As of the time of data cutoff, 3 patients (#204-hepatitis, #602-lipohypertrophy, #607-death from presumed myocardial infarction) had withdrawn from SEN-3613A (these patients have previously been discussed at length in the ISS).

Figure 8. ISE - SEN-3611 Through SEN-3613



## VI.D.2.2.2 Duration of Therapy

The mean duration of therapy/exposure during SEN-3613A was 55.5 weeks (range 9.9 to 64.3 weeks).

## VI.D.2.2.3 Efficacy Results

### VI.D.2.2.3.1 Primary Efficacy Endpoints

#### VI.D.2.2.3.1.1 Percent Reduction in IGF-I Levels

As seen in Table 34, when all 38 patients<sup>a</sup> enrolled in SEN-3613A are considered, the mean values of IGF-I decreased from 916.5 ng/mL (baseline level prior to SEN-3611) to 522.5 ng/mL prior to the start of SEN-3613A (a 43% decrease reflecting prior weekly pegvisomant therapy), and to 268.3 ng/mL at the data cutoff date (a 71% decrease). During the ~1 year mean duration of daily pegvisomant therapy in SEN-3613A, IGF-I values decreased 49% further. The mean IGF-I level at data cutoff expressed as a MULN was <1 (0.65).

Of further note, mean IGF-I levels decreased by 60% in the 6 patients who enrolled in SEN-3613A (directly from SEN-3611) after a long period without any form of pegvisomant therapy.

Table 34. ISE - Mean IGF-I Concentrations and Mean IGF-I Levels Expressed as MULN (SEN-3611 Through SEN-3613A)

	IGF-I Concentration (Multiple of ULN)		
	Baseline SEN-3611 or Pretreatment	First Visit SEN-3613A	Data Cutoff Visit SEN-3613A
Continuing Subjects (N=32)	900.4 ng/mL (2.27)	445.5 ng/mL (1.13)	249.0 ng/mL (0.61)
New SEN-3613A Subjects (N=6)	1002.5 ng/mL (2.41)	920.5 ng/mL (2.30)	371.5 ng/mL (0.91)
SEN-3613A Subjects (N=38)	916.5 ng/mL (2.30)	522.5 ng/mL (1.3)	268.0 ng/mL (0.65)

<sup>a</sup>Continuing subjects are those who also participated in SEN-3613; new subjects are those who did not participate in SEN-3613 (Subjects 204, 401, 402, 404, 406, and 410).

#### VI.D.2.2.3.1.2 Percent Normalization of IGF-I Levels

As seen in Table 35, during the ~1 year mean duration of daily pegvisomant therapy in SEN-3613A, 35/38 (92.1%) patients manifested normal IGF-I levels (Note: 27/38 (71.1%) patients achieved a normal IGF-I level after a mean duration of therapy of ~12 weeks). The 3 patients who did not

attain normal IGF-I levels had substantial (~60%) reductions in their baseline levels of IGF-I (patient 3613A-204: 945 down to 392 ng/mL; patient 3613A-305: 1255 down to 548 ng/mL; patient 3613A-401: 1450 down to 570 ng/mL; ULN was 360 ng/mL for 3 patients). Seventeen of these 35 patients (48.6%) had previously achieved a normal IGF-I concentration as a consequence of weekly dosing during SEN-3613 (mean duration of therapy -23 weeks; 7/17 patients required pegvisomant 80 mg/week). On the other hand, an additional 18/35 patients (51.4%) required daily therapy with pegvisomant during SEN-3613A to normalize their IGF-I levels (9/18 required pegvisomant 20 mg/day). Table 36 summarizes the incidence of IGF-I normalization by dose level during daily dosing only, regardless of whether IGF-I had previously normalized on weekly dosing. During daily dosing, the majority of patients (20/38; 52.6%) achieved/maintained or maintained normal IGF-I concentrations after therapy with pegvisomant 10 mg/day. Interestingly, this observed incidence of IGF-I normalization (52.6%) was almost identical to the incidence of IGF-I normalization seen after the administration of the same dose of pegvisomant (53.8%) during the placebo controlled SEN-3614 study, demonstrating a similar magnitude of drug effect across protocols and patients!

In an attempt to assess the durability of pegvisomant-induced IGF-I reductions, an additional analysis was performed. The number of visits where the IGF-I value was  $\leq$ ULN of the age-adjusted reference range subsequent to the visit where a normal value was first observed during SEN-3613A (in the 35 patients who manifested normal IGF-I concentrations during SEN-3613A) were totaled. IGF-I normalization was maintained at 403/437 (92%) visits. This indicates that pegvisomant exerts a sustained and consistent effect on the control of IGF-I levels. In fact, 25/35 (71.4%) patients demonstrated 100% durability of effect. (Note: According to the Sponsor, after a mean duration of therapy of -82.6 weeks (as of 31 May00), pegvisomant's durability of effect remained >90%; at this time, these results are unsubstantiated.) In addition, only 2/35 (5.7%) patients required an increase in the dose of pegvisomant to maintain IGF-I normalization - indicating durability of dosing as well.

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**Table 35. ISE -Incidence of IGF-I Normalization by Daily and Weekly Dosing (SEN-3611 Through SEN-3613A)**

	All Subjects (n=38)	
<b>Subjects Whose IGF-I Levels Became Normal</b>		
No	2	5.3%
Yes*	36	94.7%
<b>Total</b>	<b>38</b>	
<b>Dose at Which Subjects IGF-I Levels First Became Normal**</b>		
Placebo	1	2.6%
30 mg/wk	2	5.3%
40 mg/wk	2	5.3%
50 mg/wk	1	2.6%
60 mg/wk	3	7.9%
70 mg/wk	1	2.6%
80 mg/wk	7	18.4%
10 mg/day	3	7.9%
15 mg/day	3	7.9%
20 mg/day	9	23.7%
25 mg/day	2	5.3%
30 mg/day	1	2.6%
Unknown***	1	2.6%
<b>Total Subjects</b>	<b>38</b>	

\*Because Subject #305 had only 1 IGF-I value in the normal range and because that value was not within the normal range for her age at the time the value was reported, it is considered that the number of subjects with normal IGF-I concentrations during SEN-3613A was 35 (92.1%).

\*\*Includes subjects whose IGF-I concentrations became normal prior to daily dosing.

\*\*\*Subject's 108's IGF-I became normal; however, he overdosed on study drug so the weekly dose when IGF-I became normal is unknown

**Table 36. ISE - Incidence of IGF-I Normalization Daily Dosing Only (SEN-3611 Through SEN-3613A)**

	All Subjects (n=38)
<b>Subjects Whose IGF-I Levels Become Normal</b>	
No	2    5.3%
Yes	36   94.7%
Total	38
<b>Daily Dose Which Subjects IGF-I Levels First Become Normal</b>	
10 mg/day	20   52.6%
15 mg/day	4    10.5%
20 mg/day	9    23.7%
25 mg/day	2    5.3%
30 mg/day	1    2.6%
Total Subjects	38

#### VI.D.2.2.3.2 Secondary Efficacy Parameters

Both the mean total acromegaly symptoms and signs score, and mean ring size, decreased moderately but progressively between the beginning of SEN-3611 and data cutoff for SEN-3613A. See Tables 37 and 38. Similar changes were seen in the levels of free IGF-I, ALS and IGFBP-3 (data not shown).

**Table 37. ISE - Mean Total Scores for Signs and Symptoms of Acromegaly (SEN-3611 Through SEN-3613A)**

	Total Signs and Symptoms Score		
	Baseline SEN-3611 or Pretreatment	First Visit SEN-3613A	Data Cutoff Visit SEN-3613A
Continuing Subjects (N=32)	7.3	6.4	6.6
New SEN-3613A Subjects (N=6)	6.5	8.7	2.4
SEN-3613A Subjects (N=38)	7.2	6.7	5.9

\* Scores are based on a 40-point scale, where lower scores indicate better response.

Continuing subjects are those who also participated in SEN-3613; new subjects are those who did not participate in SEN-3613 (Subjects 204, 401, 402, 404, 406, and 410).

**Table 38. ISE - Mean Ring Size (SEN-3611 Through SEN-3613A)**

	Ring Size (mm)		
	Baseline SEN-3611 or Pretreatment	First Visit SEN-3613A	Data Cutoff Visit SEN-3613A
Continuing Subjects (N=32)	79.5	76.4	74.3
New SEN-3613A Subjects (N=6)	80.2	78.2	78.5
SEN-3613A Subjects (N=38)	79.6	76.8	75.0

Continuing subjects are those who also participated in SEN-3613; new subjects are those who did not participate in SEN-3613 (Subjects 204, 401, 402, 404, 406, and 410).

### VI.D.3 SEN-3615

#### VI.D.3.1 Study Design, Inclusion Criteria, Dosing, Efficacy Parameters and Statistical Methods

SEN-3615 was an open label, dose-titration, extension study designed to assess the longterm efficacy of daily pegvisomant therapy in acromegaly. Patients completing SEN-3614, and de novo patients, were eligible to enroll in SEN-3615.

At the first visit in SEN-3615, an 80 mg SC loading dose of pegvisomant was administered to patients who had received placebo during SEN-3614 and de novo enrollees (but not to patients who had received any dose of pegvisomant during SEN-3614) (in order to achieve

the steady state more rapidly); 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 (the maximum dose allowed per protocol was 30 mg/day).

As in SEN-3614 and SEN-3611, the primary efficacy endpoints were the percent reduction in and percent normalization of IGF-I levels. Secondary measures included changes in ring size and the symptoms and signs of acromegaly scores. Formal statistical analyses were not conducted; however, descriptive statistics were tabulated.

## VI.D.3.2 Results

### VI.D.3.2.1 Disposition

At the time of data cutoff (30AP99), 101 patients had enrolled in SEN-3615 (98 patients were SEN-3614 completers, 2 were de novo patients, and 1 patient was allowed to enroll even though he had been discontinued from SEN-3614 because of apparent pegvisomant-induced transaminitis). As of 30AP99, 4 patients had withdrawn prematurely (only 1 because of an adverse event; #1707 - headaches).

### VI.D.3.2.2 Duration of Therapy

The mean duration of therapy/exposure during SEN-3615 was only ~12 weeks (range 0.14 to 26.1 weeks).

### VI.D.3.2.3 Efficacy Results

#### VI.D.3.2.3.1 Primary Efficacy Endpoints

##### VI.D.3.2.3.1.1 Percent Reduction in IGF-I Levels

As seen in Table 39, when the 94 patients enrolled in SEN-3615 with on-study data available are considered, the mean values of IGF-I decreased from 705.4 ng/mL (baseline level prior to SEN-3614) to 540.4 ng/mL prior to the start of SEN-3615 (an unimpressive 23% decrease - more than likely - a reflection of the fact that patients receiving placebo during SEN-3614 were included), and to 372.4 ng/mL at the data cutoff date (a 47% decrease). During the ~12 week mean duration of daily pegvisomant therapy in SEN-3615, IGF-I values decreased 31% further. The mean IGF-I level at data cutoff expressed as a MULN was 1.

**Table 39. ISE - Mean IGF-I Concentrations, Percent Change from Baseline, and Mean IGF-I Levels Expressed as MULN (SEN-3614 Through SEN-3615)**

IGF-I Results	3614 Baseline	3615 Baseline	3615 Last Visit Cut-off
<b>Actual IGF-I Results (ng/mL)</b>			
N	101	101	94
Mean	705.4	640.4	372.4
SE	30.98	37.06	18.82
SD	311.36	372.35	180.61
Median	638.0	440.0	340.0
Min			
Max			
<b>Percent Change from Baseline</b>			
N	101	101	94
Mean	705.4	-24.1	-44.1
SE	30.98	3.47	2.44
SD	311.36	34.82	23.65
Median	638.0	-18.1	-48.0
Min			
Max			
<b>Multiple of IGF-I from ULM</b>			
N	101	101	94
Mean	1.8	1.4	1.0
SE	0.07	0.08	0.05
SD	0.71	0.87	0.44
Median	1.7	1.2	0.9
Min			
Max			

**VI.D.3.2.3.1.2 Percent Normalization of IGF-I Levels**

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. The most likely explanation relates to the ~12 week mean duration of treatment during SEN-3615 necessitated by the data cutoff date (e.g., there was insufficient time to up-titrate the dose of pegvisomant in that adjustments based on serum IGF-I levels were made every 8 weeks). (Note: According to the Sponsor, after a mean duration of therapy of ~41.6 weeks (as of 31 May00), the rate of IGF-I normalization during SEN-3615 increased to >90% (100/108), and the durability of effect was ~90%; at this time, these results are unsubstantiated.)

Table 40 summarizes the incidence of IGF-I normalization by dose level during daily dosing in SEN-3615, regardless of whether IGF-I had previously normalized during daily dosing in SEN-3614 (in fact, 37/66 [56%] patients who manifested normal IGF-I levels during SEN-3615 had normal values at the SEN-3615 baseline visit which coincided with completion of SEN-3614).

In any case, the majority of patients (54/94; 57.4%) achieved/maintained or maintained normal IGF-I concentrations after therapy with pegvisomant 10 mg/day. Interestingly, as was the case

during SEN-3613A, this observed incidence of IGF-I normalization (57.4%) was almost identical to the incidence of IGF-I normalization seen after the administration of the same 10 mg dose of pegvisomant (53.8%) during the placebo controlled SEN-3614 study, demonstrating once again a similar magnitude of drug effect across protocols and patients!

Of the 26 patients who were treated with placebo during SEN-3614, or new to study participation, and who had on-study IGF-I data available for review, 19 (73%) achieved normal IGF-I concentrations (treatment with pegvisomant 10 mg/day normalized IGF-I in 15/19).

**Table 40. ISE - Incidence of IGF-I Normalization by Daily Dosing (SEN-3614 Through SEN-3615)**

	All Subjects (n=94)
<b>Subjects Whose IGF-I Levels Became Normal</b>	
No	28 29.8%
Yes	66 70.2%
Total	94
<b>Dose Which Subjects IGF-I Levels First Became Normal</b>	
10 mg/day	54 57.4%
15 mg/day	10 10.6%
20 mg/day	1 1.1%
25 mg/day	1 1.1%
Total Subjects	94

#### VI.D.3.2.3.2 Secondary Efficacy Parameters

The mean total acromegaly symptoms and signs score, mean ring size, and mean levels of free IGF-I, ALS and IGFBP-3 decreased moderately but progressively between the beginning of SEN-3614 and data cutoff for SEN-3615 (data not shown).

## **VI.D.4 SEN-3611**

### **VI.D.4.1 Study Design, Inclusion Criteria, Dosing, Efficacy Parameters and Statistical Methods**

SEN-3611 was a randomized, placebo controlled, double blind, fixed duration (6 week) study designed to compare the short term efficacy of 2 weekly doses of pegvisomant (30 mg/week and 80 mg/week), and placebo, in the treatment of acromegaly. Inclusion criteria were similar to SEN-3614 previously described in detail in Section .

As in SEN-3614, SEN-3613A and SEN-3615, the primary efficacy endpoints were the percent reduction in and percent normalization of IGF-I levels. Secondary measures included changes in ring size and the symptoms and signs of acromegaly scores. Formal statistical analyses were conducted using repeated measures ANOVA.

### **VI.D.4.2 Results**

#### **VI.D.4.2.1 Duration of Therapy**

The mean duration of therapy in SEN-3611 was 6 weeks.

#### **VI.D.4.2.2 Efficacy Results**

##### **VI.D.4.2.2.1 Primary Efficacy Endpoints**

###### **VI.D.4.2.2.1.1 Percent Reduction in IGF-I Levels**

Treatment with pegvisomant 30 mg/week for 6 weeks resulted in a 16% reduction in baseline serum IGF-I levels; treatment with 80 mg/week produced a 31% decrease. Both of these decrements were statistically significant compared with effects of placebo. See Tables 41 and 42.

###### **VI.D.4.2.2.1.2 Percent Normalization of IGF-I Levels**

IGF-I levels normalized in 12.5% of patients treated with pegvisomant 30 mg/week, and 26.7% of acromegalic patients treated with pegvisomant 80 mg/week. See Table 43.

**Table 41. ISE - Percent Change of IGF-I from Baseline (SEN-3611)**

Percent Change From Baseline	Placebo (n=15)	30 mg B2036-PEG (n=16)	80 mg B2036-PEG (n=15)	Total Subjects (N=46)
Visit 9 (Day 42 or Final Visit)				
N	14	16	14	44
Mean	-0.4	-15.7	-31.3	-15.8
SE	4.82	4.76	6.68	3.60
SD	18.03	19.05	25.00	23.86
Median	0.1	-14.0	-33.8	-12.6
Min				
Max				

**Table 42. ISE - IGF-I Efficacy Parameters: P-values for Pairwise Treatment Comparisons (SEN-3611)**

Parameter	Pla vs. 80mg	Pla vs. 30mg	30mg vs. 80mg
Percent change from baseline in IGF-I (Primary Efficacy Analysis)	0.0008	0.0426	0.2182
Actual post-baseline IGF-I values, with baseline IGF-I values as covariate <sup>1</sup> (p-value = 0.0001)	0.0006	0.0899	0.1143
Multiple of ULN for IGF-I post-baseline	0.0140	0.0941	0.4983
Multiple of ULN for IGF-I post-baseline, with baseline IGF-I values as covariate (p-value = 0.0001)	0.0021	0.0239	0.4703

P-values for the pairwise comparisons are from a repeated-measures analysis of variance model.

<sup>1</sup> Confirmatory (supportive) analysis to primary efficacy analysis.

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**Table 43. ISE - Incidence of IGF-I Normalization Post-Baseline (SEN-3611)**

	Placebo (n=15)	30 mg B2036-PEG (n=16)	80 mg B2036-PEG (n=15)	Total Subjects (N=46)
Subjects Whose IGF-I Levels Become Normal at Anytime Post-Treatment				
Yes	1 6.7%	2 12.5%	4 26.7%	7 15.2%
Total	15	16	15	46

#### VI.D.4.2.2.2 Secondary Efficacy Parameters

The mean total acromegaly symptoms and signs score, mean ring size, and mean levels of free IGF-I, ALS and IGFBP-3 did not change during this clinical trial.

#### VI.D.5 SEN-3613

SEN-3613 was an open label, dose titration, extension study designed to assess the longterm efficacy of weekly pegvisomant therapy in acromegaly. Patients completing SEN-3611 were eligible to enroll in SEN-3613. Patients were begun on pegvisomant 30 mg/week, and then up-titrated based on serial IGF-I levels (maximum dose of 80 mg/week). Seventeen patients (~50%) achieved a normal IGF-I level at some point during the study (most often after being treated with pegvisomant 80 mg/week). The mean duration of pegvisomant therapy was ~23 weeks - before the study was prematurely terminated, and most patients were enrolled in the daily dose titration extension study, SEN-3613A.

#### VI.E ISE - 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\*\*.

\*During SEN-3613A, the treatment of acromegalic patients for ~1 year with daily pegvisomant (following a sustained period of weekly pegvisomant therapy) resulted in a substantial increase in the number of patients with normalization of IGF-I levels (e.g., 17/38 [44.7%] up to

35/38 [92.1%]). The 3 patients who did not attain normal IGF-I levels had substantial (~60%) reductions in their baseline levels of IGF-I.

\*\*During SEN-3615, the treatment of acromegalic patients for ~12 weeks with daily pegvisomant (following a 12 week course of daily pegvisomant therapy during SEN-3614) also resulted in a substantial increase in the number of patients with normalization of IGF-I levels (e.g., 37/94 [39.4%] up to 66/94 [70.2%]). (Note: The disparity in the rates of IGF-I normalization observed in SEN-3613A [92.1%] and SEN-3615 [70.2%] more than likely was a consequence of insufficient time to up-titrate the dose of pegvisomant because of the shorter ~12 week mean duration of treatment in SEN-3615 (necessitated by the data cutoff date).

- 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.
- The durability of dosing observed after longterm pegvisomant therapy was very satisfactory as well. During SEN-3613A, only 2/35 (5.7%) patients required up-titration of the dose of pegvisomant to maintain IGF-I levels in the age-referenced normal range.

VII. Assessment of Dosing Regimen - See Sections I.B.3 and II.D in the EXECUTIVE SUMMARY.

VIII. Use in Special Populations - See Section II.E in the EXECUTIVE SUMMARY.

## IX. Conclusions

See Summary of Clinical Findings (Section II) in the EXECUTIVE SUMMARY, and Sections VI.C.14 and VI.E in the ISS and ISE, respectively, in the CLINICAL REVIEW, for conclusions related to important efficacy and safety issues.

## X. Recommendations

See Section I.B in the EXECUTIVE SUMMARY for recommendations related to important efficacy and safety issues (including labeling recommendations).

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

## XI. Risk/Benefit Analysis

See Section I.A.1 in the EXECUTIVE SUMMARY.

## XII. 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.

/S/ 4/25/01

Robert S. Perlstein MD, FACP, FACE  
Medical Review Officer

CC: Original NDA 21-106 - HFD-510; Original : \_\_\_\_\_ - HFD-510;  
HFD-510 RPerlstein, SMalozowski, DOrloff, JJenkins, RShore, FAlavi,  
JBrown, LPian, CKing

/S/ 4/25/01

Saul Malozowski MD, PhD  
Team Leader

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Saul Malozowski  
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MEDICAL OFFICER

David Orloff  
6/8/01 11:56:38 AM  
MEDICAL OFFICER

To: NDA 21-106  
From: Robert S. Perlstein MD, Medical Officer  
CC: Saul Malozowski MD, Team Leader  
Crystal King, Project Manager  
Date: 05/08/01  
Re: Review of Safety Update

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The Safety Update for NDA 21-106 was submitted on 23 February 2001 by the Sponsor, Sensus Drug Development Corporation, Austin, TX. The Safety Update reported safety data for the open label extension studies, SEN-3613A and SEN-3615, between 30 April 1999/31 May 1999 and 31 May 2000. An analysis of this safety data can be found in the Medical Officer's NDA review, incorporated into the Integrated Summary of Safety (ISS) (pages 63-103).

*/S/*  
Robert Perlstein MD, FACP, FACE  
Medical Officer  
*/S/*

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Saul Malozowski MD, PhD  
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CC: Original NDA 21-106; HFD-510 NDA 21-106  
Original IND \_\_\_\_\_ HFD-510 IND \_\_\_\_\_  
HFD-510 RPerlstein, SMalozowski, CKing

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