

### *Conclusions*

No new safety signals were identified during the period covered by this 120-day safety update. The adverse event profile observed in the studies utilizing lanreotide acetate at dose strengths of 60, 90, or 120 mg was consistent with that summarized in NDA 22-074.

## **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

Adverse events of special interest to the somatostatin analogs include the following:

### **7.3.1 Local Tolerability**

- See Section 7.1.5.5 Identifying common and drug-related adverse events
- See Section 7.1.17 Postmarketing Experience

Lanreotide Acetate is a depot formulation injected via a deep s.c. route and some local reactions are expected. In the three pooled studies of lanreotide acetate in healthy subjects (Studies 149, 038 and 047), injection site induration was reported as a TEAE in 17.8% (19/107) of subjects. There were three AEs reported which led to withdrawal. In the pooled lanreotide acetate studies in acromegalic patients, most local reactions at the injection site occurred on the day of injection (median time between last injection before event occurrence and event onset 0.0 days, range 0 to 4 days). The median time between first lanreotide acetate administration and event onset was 74.5 days (range 0 to 319 days), indicating that local reactions continued to occur throughout treatment.

For most injection site AEs, there was an increasing incidence at higher dose strengths at time of AE onset.

### **7.3.2 Gastrointestinal Effects**

- See Section 7.1.5.5 Identifying common and drug-related adverse events
- See Section 7.1.17 Postmarketing Experience

Lanreotide has pharmacological effects on the GI function and so adverse effects affecting the GI tract are anticipated. Gastrointestinal AEs are more commonly reported soon after the start of treatment. GI AEs were reported within 7 days by more than half of the 188 patients where data of injection and date of onset were available in the pooled lanreotide acetate studies. The reduction in new reports with time may be due to a decrease of AEs over time or a reduction in reporting by patients.

Postmarketing data indicate that disorders related to the gastrointestinal tract were the most frequent reactions reported with a total of 178 reactions, of which 79 were serious. The adverse effect profile from the postmarketing data is consistent with data from the clinical studies. The GI adverse effect profile with somatostatin analogs is well known. No new signals have become apparent from the data.

### **7.3.3 Gallbladder and Pancreas Effects**

- See Section 7.1.5.5 Identifying common and drug-related adverse events
- See Section 7.1.17 Postmarketing Experience

Gallbladder ultrasound examination was performed at multiple timepoints for the majority of studies in acromegalic patients due to the known increased incidence of cholelithiasis in acromegalic patients and the expected effects on the gallbladder predicted by the pharmacology of SSAs. In the pooled lanreotide acetate studies, cholecystitis and cholelithiasis AEs were reported by 20% (85/416) patients and were considered related to study drug in all but one patient. Gallbladder AEs occurred throughout the treatment period, between 0 and 425 days after first lanreotide acetate administration. The assessments of the gallbladder and pancreas in clinical studies of lanreotide acetate and other formulations showed evidence consistent with the known propensity of SSAs to reduce gallbladder motility. The occurrence of cholelithiasis may be related to dose and time on treatment. Few patients developed acute symptoms requiring cholecystectomy. Cases of pancreatitis occurred in patients rarely but were serious. Although increases in LFTs were noted they were mostly nonserious. LFT increases reported as serious were usually related to reported clinical events.

Postmarketing data confirmed cholelithiasis as the most commonly occurring AE related to the gallbladder. There were also postmarketing cases of pancreatitis in non-acromegalic indications, which were less frequent, but included one fatal case that was considered related to study drug.

Overall, the occurrence of new gallstones or sludge did not exceed the expected rate for this known side effect of somatostatin analog treatment. Because of the possible effects of lanreotide on the gallbladder patients may need to be monitored periodically.

#### 7.3.4 Glycoregulation

- See Section 7.1.5.5 Identifying common and drug-related adverse events
- See Section 7.1.17 Postmarketing Experience

The overall picture of glycoregulation observed with lanreotide acetate in patients with acromegaly was suggestive of some degree of reduction in glucose tolerance with treatment. Similar results were seen with lanreotide MPF in patients with acromegaly. Lanreotide treatment may result in an increased incidence of hyperglycemia (with elevated HbA1c) in acromegalic patients. Hypoglycemia was also reported.

The postmarketing data were consistent with clinical trial findings. Lanreotide, as known for other SSA treatment, alters the balance between insulin and glucagon, which may result in hypoglycemia or hyperglycemia. For this reason, it is recommended that blood glucose levels are monitored when lanreotide treatment is initiated, or when the dose strength is altered, and that antidiabetic treatment be adjusted accordingly.

#### 7.3.5 Thyroid Function

- See Section 7.1.5.5 Identifying common and drug-related adverse events
- See Section 7.1.17 Postmarketing Experience

In the clinical trials with lanreotide, thyroid function was rarely investigated as a defined objective. On review of the AE data, there were few TEAEs of hyper- or hypothyroidism. Two patients withdrew due to pituitary or thyroid –related reasons and one of these had malignant thyroid cancer, (considered to be unrelated by the investigator). Very small numbers of PMS reports relating to thyroid or pituitary function have been received since launch in 1995. Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, though clinical hypothyroidism is rare (<1%). Thyroid function tests are recommended where clinically indicated.

#### 7.3.6 Cardiac Function (sinus bradycardia, hypertension)

- See Section 7.1.5.5 Identifying common and drug-related adverse events
- See Section 7.1.17 Postmarketing Experience

The most common overall cardiac adverse events observed in three pooled Somatuline Cardiac Studies (Studies 721, 717 and 076) in patients with acromegaly were sinus bradycardia (12/217, 5.5%), bradycardia (6/217, 2.8%) and hypertension (12/217, 5.5%). In 416 acromegalic patients treated with Somatuline in the seven pooled studies, the incidence was sinus bradycardia (13/416, 3%) and hypertension (20/416, 5%). In studies 081 and 717, where patients with elevated GH and IGF-1 levels were either naive to somatostatin analog therapy or had undergone a 3 month washout, the incidence was sinus bradycardia (12/170, 7%) and hypertension (11/170, 5%). During the double-blind placebo-controlled portion of Study 717 (weeks 0 to 4) bradycardia was reported in 8% of the lanreotide patients as compared to 0% of the placebo-treated patients.

In the post-marketing database, cardiac adverse reactions reported in more than one patient being treated for acromegaly were bradycardia and sinus bradycardia, palpitations, hypertension, and edema. Among these cardiac adverse reactions, several were serious including bradycardia, sinus bradycardia, palpitations and edema.

#### 7.3.7 Anemia

- See Section 7.1.5.5 Identifying common and drug-related adverse events
- See Section 7.1.17 Postmarketing Experience

In Study 717, anemia was reported in 13 patients (12%) during the three study phases. During the double-blind placebo-controlled phase (weeks 0 to 4), anemia was reported in 7% of the lanreotide patients as compared to 0% of the placebo-treated patients. In 416 acromegalic patients treated with Somatuline in the seven pooled studies, the incidence of anemia was (14/416, 3.4%). In studies 081 and 717, where patients with elevated GH and IGF-1 levels were either naive to somatostatin analog therapy or had undergone a 3 month washout, the incidence of anemia was (12/170, 7.1%).

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

#### 7.4.1.1 Pooled data vs. individual study data

This clinical reviewer analyzed the safety of the Phase 3 studies by examining the overall data pooled from the seven Phase 3 studies, whenever applicable. These studies not only contributed the major proportion of the experience with lanreotide at the dose proposed for marketing, but was adequately controlled by 3 doses of lanreotide and by placebo (in Study 717 only). The pooling of the data allows for more robust analyses of safety. The particular benefit is the ability to compare incidences of common AEs, or AEs that occur more frequently in patients with acromegaly. The seven pivotal studies for safety and efficacy were also reviewed individually to confirm that the results were consistent with the pooled study results.

#### 7.4.1.2 Combining data

Data were combined across similar studies in the pooled datasets according to treatment group and/or dose whenever appropriate. This was described in the individual review sections.

### 7.4.2 Explorations for Predictive Factors

This clinical reviewer explored for predictive factors among demographic variables, dose, and time to event. Demographic factors such as gender, age and race do not appear to prevent any groups of patients from safe treatment with lanreotide. In special populations, such as renally-impaired, hepatically-impaired and elderly subjects, the pharmacokinetic profile of lanreotide is altered, with an increased half-life in all cases. Transient increases in blood pressure were seen in renally-impaired patients and in one elderly patient after either an i.v. bolus injection or a short i.v. infusion of lanreotide IRF. Dose adjustments are likely necessary in the moderate to severe hepatically impaired and moderate to severe renally impaired population groups, as there were limited number of subjects studied with hepatic or renal impairment and we cannot rule out clinically significant differences in safety data between these groups. Renal function declines with age so it would be prudent to start older subjects at a lower dose and titrate cautiously. Starting dose adjustments in these populations are discussed in Section 7.4.2.3 and 7.4.2.4, below.

#### 7.4.2.1 Explorations for dose dependency for adverse findings

The sponsor's proposed dose and regimen for patients with acromegaly is lanreotide acetate 90 mg given via the deep subcutaneous route at 4 week intervals for 3 months. After 3 months dosage may be adjusted based on GH and IGF-1 levels and clinical symptoms to 60 or 120 mg administered at 4 week intervals, or the patient may remain at the 90 mg dose. The majority of

studies utilized a dose titration schema similar to the proposed dose and regimen making an assessment of AEs by dose of lanreotide acetate difficult. However, the effect of lanreotide acetate at fixed dose strengths of 60, 90 and 120 mg administered every 28 days was evaluated in a randomized setting in two studies conducted in patients with acromegaly: Studies 717 and 076. In Study 717, the effects of single dose strengths of 60, 90 and 120 mg also were compared to a single dose of placebo in a randomized, double-blind setting. The most commonly reported treatment-emergent adverse events during the double-blind, placebo-controlled phase and during the double/single-blind phase of Study 717 are displayed in Table 7.4.2.1.1 and Table 7.4.2.1.2, respectively. At preferred term level, the incidence of diarrhea and flatulence increased with dose strength of lanreotide acetate (diarrhea 11.1%; 25.9%; 37.9%, 60, 90 and 120 mg respectively) and (flatulence 0%, 7.4%; 10.3%, 60, 90 and 120 mg respectively).

**Table 7.4.2.1.1 Most Common Adverse Events (Incidence  $\geq$ 5.0% in any lanreotide treatment group) in Double-blind, placebo-controlled, single-dose period of lanreotide Acetate Study 717**

MedDRA SOC HLT PT	Lanreotide Autogel (double blind period)								Placebo	
	60 mg (N=27)		90 mg (N=27)		120 mg (N=29)		Overall (N=83)		(N=25)	
	N	%	N	%	N	%	N	%	N	%
<b>Patients with &gt;1 TEAE</b>	<b>8</b>	<b>29.6</b>	<b>17</b>	<b>63.0</b>	<b>19</b>	<b>65.5</b>	<b>44</b>	<b>53.0</b>	<b>6</b>	<b>24.0</b>
Gastrointestinal disorders	4	14.8	12	44.4	14	48.3	30	36.1	0	0
Diarrhoea (excl infective)	3	11.1	7	25.9	11	37.9	21	25.3	0	0
Diarrhoea	3	11.1	7	25.9	11	37.9	21	25.3	0	0
Faeces abnormal	0	0	3	11.1	2	6.9	5	6.0	0	0
Loose stools	0	0	3	11.1	2	6.9	5	6.0	0	0
Flatulence, bloating and distension	0	0	2	7.4	3	10.3	5	6.0	0	0
Flatulence	0	0	2	7.4	3	10.3	5	6.0	0	0
Gastrointestinal and abdominal pains (excl oral and throat)	1	3.7	1	3.7	2	6.9	4	4.8	0	0
Investigations	3	11.1	3	11.1	1	3.4	7	8.4	1	4.0
Physical examination procedures	3	11.1	3	11.1	1	3.4	7	8.4	1	4.0
Weight decreased	2	7.4	3	11.1	1	3.4	6	7.2	0	0
General disorders and administration site conditions	2	7.4	2	7.4	2	6.9	6	7.2	1	4.0
Infection and infusion site reactions	1	3.7	1	3.7	2	6.9	4	4.8	0	0
Injection site swelling	0	0	0	0	2	6.9	2	2.4	0	0
Nervous system disorders	0	0	1	3.7	2	6.9	3	3.6	2	8.0
Headaches NEC	0	0	0	0	2	6.9	2	2.4	1	4.0
Headache	0	0	0	0	2	6.9	2	2.4	1	4.0
Psychiatric disorders	0	0	0	0	2	6.9	2	2.4	1	4.0

Source: Sponsor's Appendix 4 - Statistical Table AE.1.9.1

**Table 7.4.2.1.2 Most Common Adverse Events (Incidence ≥5.0% Overall): Fixed Dose Period of Lanreotide Acetate Study 717**

MedDRA SOC <i>HLT</i> PT	Lanreotide Autogel (fixed dose period)							
	60 mg (N=34)		90 mg (N=36)		120 mg (N=37)		Overall (N=107)	
	N	%	N	%	N	%	N	%
<b>Patients with &gt;1 TEAE</b>	<b>26</b>	<b>76.5</b>	<b>30</b>	<b>83.3</b>	<b>33</b>	<b>89.2</b>	<b>89</b>	<b>83.2</b>
<b>Gastrointestinal disorders</b>	12	35.3	19	52.8	27	73.0	58	54.2
<i>Diarrhoea (excl infective)</i>	7	20.6	10	27.8	18	48.6	35	32.7
Diarrhoea	7	20.6	10	27.8	18	48.6	35	32.7
<i>Gastrointestinal and abdominal pains (excl oral and throat)</i>	1	2.9	4	11.1	5	13.5	10	9.3
Abdominal pain	1	2.9	3	8.3	4	10.8	8	7.5
<i>Faeces abnormal</i>	2	5.9	2	5.6	5	13.5	9	8.4
Loose stools	2	5.9	1	2.8	5	13.5	8	7.5
<i>Nausea and vomiting symptoms</i>	2	5.9	1	2.8	5	13.5	8	7.5
<i>Flatulence, bloating and distension</i>	1	2.9	2	5.6	4	10.8	7	6.5
Flatulence	1	2.9	2	5.6	3	8.1	6	5.6
<i>Gastrointestinal signs and symptoms NEC</i>	3	8.8	2	5.6	1	2.7	6	5.6
Abdominal discomfort	3	8.8	2	5.6	1	2.7	6	5.6
<b>General disorders and administration site conditions</b>	8	23.5	6	16.7	11	29.7	25	23.4
<i>Injection and infusion site reactions</i>	4	11.8	3	8.3	6	16.2	13	12.1
Injection site pain	3	8.8	2	5.6	3	8.1	8	7.5
<i>Asthenic conditions</i>	3	8.8	3	8.3	1	2.7	7	6.5
<b>Hepatobiliary disorders</b>	11	32.4	8	22.2	4	10.8	23	21.5
<i>Cholecystitis and cholelithiasis</i>	7	20.6	7	19.4	3	8.1	17	15.9
Cholelithiasis	7	20.6	7	19.4	3	8.1	17	15.9
<b>Investigations</b>	10	29.4	4	11.1	9	24.3	23	21.5
<i>Carbohydrate tolerance analyses (incl diabetes)</i>	2	5.9	2	5.6	2	5.4	6	5.6
<b>Cardiac disorders</b>	8	23.5	5	13.9	8	21.6	21	19.6
<i>Supraventricular arrhythmias</i>	6	17.6	3	8.3	2	5.4	11	10.3
Sinus bradycardia	4	11.8	3	8.3	2	5.4	9	8.4
<b>Musculoskeletal and connective tissue disorders</b>	3	8.8	8	22.2	5	13.5	16	15.0
<i>Joint related signs and symptoms</i>	2	5.9	5	13.9	2	5.4	9	8.4
Arthralgia	2	5.9	4	11.1	2	5.4	8	7.5
<b>Musculoskeletal and connective tissue signs and symptoms NEC</b>	1	2.9	4	11.1	1	2.7	6	5.6
<b>Nervous system disorders</b>	6	17.6	3	8.3	7	18.9	16	15.0
<b>Skin and subcutaneous tissue disorders</b>	4	11.8	4	11.1	3	8.1	11	10.3
<b>Infections and infestations</b>	4	11.8	3	8.3	3	8.1	10	9.3
<b>Vascular disorders</b>	4	11.8	3	8.3	3	8.1	10	9.3
<i>Vascular hypertensive disorders NEC</i>	2	5.9	2	5.6	2	5.4	6	5.6
Hypertension	2	5.9	2	5.6	2	5.4	6	5.6
<b>Metabolism and nutrition disorders</b>	2	5.9	4	11.1	2	5.4	8	7.5
<b>Psychiatric Disorders</b>	3	8.8	2	5.6	3	8.1	8	7.5
<b>Blood and lymphatic system disorders</b>	2	5.9	3	8.3	2	5.4	7	6.5
<i>Anaemias NEC</i>	2	5.9	3	8.3	2	5.4	7	6.5
Anaemia	2	5.9	3	8.3	2	5.4	7	6.5
<b>Respiratory, thoracic and mediastinal disorders</b>	2	5.9	2	5.6	3	8.1	7	6.5

Source: Sponsor's Appendix 4 - Statistical Table AE.1.9.2

During the fixed dose period of the study, the percentage of patients who reported at least one TEAE increased with increasing dose strength (76.5%; 83.3%, and 89.2% in the 60, 90 and 120 mg groups, respectively). This relationship is mainly derived from the SOC Gastrointestinal disorders (35.3%; 52.8%; and 73.0% in the 60, 90 and 120 mg groups, respectively) in which the PTs diarrhea, abdominal pain, and flatulence also show an increase with increasing dose strength. Further, the incidence of injection site mass was highest among patients who received 120 mg lanreotide acetate compared to patients who received 60 or 90 mg. None of the other commonly reported events, including loose stools, injection site pain, cholelithiasis, sinus bradycardia, arthralgia, hypotension and anemia showed an increased incidence with higher dose strengths.

In Study 076, in which patients were randomly assigned to fixed dose strengths of 60, 90 and 120 mg lanreotide acetate administered every 28 days for 4 doses, the only commonly reported adverse event which showed an increased incidence with dose of was abdominal pain reported in 0/6, 1/6 (17%) and 2/6 (33%) patients receiving 60, 90 and 120 mg, respectively. However, the small sample size within each dose group makes it difficult to assess incidence of adverse events by dose. Other commonly reported events in this study included diarrhea (50%, 33%, 50% in the 60, 90 and 120 mg groups, respectively), flatulence (33%, 17%, 50%, respectively) and nausea (33%, 17%, 17%, respectively).

#### 7.4.2.2 Explorations for time dependency for adverse findings

In the lanreotide clinical program, it was difficult to examine time from first ever lanreotide treatment to onset of adverse events in any meaningful way since many patients had already received lanreotide or octreotide treatment prior to study entry. It was mainly possible to assess the type of AEs occurring during the long term studies and compare them to those in shorter studies. It was possible to compare 709 to its long term extension, 710, from the original study data. The most commonly reported AEs during long term treatment were the same as during short-term treatment. As expected, most adverse events had a higher incidence over the extended treatment period compared to the short treatment period, both overall and for individual preferred terms, due to the increased opportunity for adverse events to occur. There were no adverse events that showed a consistent increase between short-term and long term observation in these studies. There was no evidence that long term treatment with lanreotide acetate lead to a higher incidence of antibodies.

#### 7.4.2.3 Explorations for drug-demographic interactions

Summary information is provided here. Refer to Section 7.1.5.6 for further details.

##### 7.4.2.3.1 Gender

No specific studies have been conducted to examine gender differences. However, there were a number of specific AEs where reporting was different between males and females. More males

reported diarrhea and cholelithiasis whereas more females reported nausea, constipation and arthralgia.

#### 7.4.2.3.2 Age

GH-secreting pituitary adenomas are extremely rare in children and constitute a separate clinical entity of pituitary gigantism. Experience with lanreotide acetate in the pediatric population is limited and the sponsor has applied for a pediatric waiver.

Study 012ELD, an open comparative, parallel group study, was carried out to compare the PK profile of lanreotide in healthy elderly subjects (six male and six female subjects aged 65 to 76 years) and healthy young subjects (13 male subjects aged 20 to 33 years). The PK analysis showed that lanreotide had a longer half-life ( $T_{1/2}$ ) in elderly subjects but that there was no difference between the groups with respect to clearance values.

For the most commonly occurring TEAEs in the pooled analysis (diarrhea, abdominal pain and cholelithiasis) there was no apparent trend for increasing incidence with age. For other TEAEs there was an increased incidence in patients over 65 years of age, however, many of these were symptoms that are more common in the older age group.

#### 7.4.2.3.3 Race

Two studies have been conducted to investigate the PK of lanreotide in Japanese subjects. The sponsor states these showed PK equivalence between Japanese and Caucasian subjects (studies E-55-52030-146 and 2-55-52030-162). No other studies have been conducted to investigate the PK profile of lanreotide in other ethnic groups. In the pooled Lanreotide acetate studies there were 22 non-Caucasian subjects and 394 Caucasians subjects. The number of non-Caucasian subjects was small but the pattern of TEAEs seen in the non-Caucasian population was consistent with that seen in the overall safety analysis.

#### 7.4.2.4 Explorations for drug-disease interactions

Summary information is provided here. Refer to Section 7.1.5.6 for further details.

##### 7.4.2.4.1 Diabetes Status

The percentage of diabetic and nondiabetic patients who reported  $\geq 1$  TEAE was similar: 89% (117/131) and 84% (239/285), respectively. GI disorders were reported by a higher percentage of diabetic patients than nondiabetic patients (63% vs 54%), and the higher incidence in diabetic patients was reflected in many of the individual AEs in this SOC, including diarrhea, abdominal pain, nausea, vomiting, constipation and flatulence. As expected, there was a difference between the two groups for carbohydrate tolerance analyses (13% vs 4%) and diabetes mellitus (9% vs 0.4%). There was also a higher incidence of arthralgia (11.5% vs 5%) in diabetic patients.

##### 7.4.2.4.2 Renal Impairment

There were three renally impaired patients in the pooled set of lanreotide acetate studies in acromegaly. These three patients reported a total of 23 TEAEs. One patient, a 73-year-old female, was withdrawn from Study 710 after experiencing an SAE of cerebral ischemia, considered by the investigator to be unrelated to study treatment. This patient also reported other TEAEs, including gastrointestinal events, hot flush and abnormal laboratory test results. The second patient, a 62-year-old female, experienced diarrhea, cholelithiasis and abnormal laboratory test results including increased LFTs. The third patient, a 53-year-old male, experienced conjunctivitis which was unlikely to be related to lanreotide.

PK Studies were previously conducted under the — submission. Subjects with severe renal insufficiency showed an approximate 2-fold decrease in total serum clearance of lanreotide, with a consequent increase in half-life and AUC. Clinical studies with Somatuline did not include sufficient numbers of subjects with renal impairment. Therefore, a starting dose of 60 mg is recommended in patients with moderate or severe renal impairment. The dose strength should be re-evaluated after 3 months and titrated to optimal clinical and hormonal control based upon individual response.

#### 7.4.2.4.3 Hepatic Insufficiency

There was generally an increased incidence of TEAEs in the 23 patients with impaired hepatic function compared to the overall population. The 23 patients designated hepatically-impaired in the ISS comprise 13 patients in Study E-28-52030-709, six patients in Study E-28-52030-717, four patients in Study 2-47-52030-721 and three patients in Study E-54-52030-081. None of these studies made all of the assessments required (e.g. bilirubin, albumin, ascites) to enable calculation of Child-Pugh scores. GI disorders (including diarrhea, abdominal pain, nausea, vomiting, constipation and flatulence) were reported by more patients with impaired hepatic function than patients with no impaired hepatic function (65% vs. 56%). Liver function elevations were more common in hepatically impaired patients. The incidence of cholelithiasis was similar between groups although other hepatobiliary disorders were more common in patients with hepatic impairment. Renal and urinary disorders were also more common in patients with documented hepatic impairment at 30.4% (7/23) compared to 6.6% (26/393). Only 2 subjects with CHILD-PUGH classification C were evaluated in the PK studies. Therefore, a starting dose of 60 mg is recommended in patients with moderate or severe hepatic impairment. The dose strength should be re-evaluated after 3 months and titrated to optimal clinical and hormonal control based upon individual response.

#### 7.4.2.5 Explorations for drug-drug interactions

Study 038, a PK interaction study in healthy subjects, explored the potential for PK interactions of lanreotide with cyclosporine, and also with other lipophilic substances using vitamin K as a model. This study reported a PK interaction between cyclosporine and lanreotide (with a 19% decrease in relative bioavailability of cyclosporine), but no significant interaction was observed between lanreotide and vitamin K. Therefore, concurrent administration of lanreotide acetate and cyclosporine may necessitate adjustment of cyclosporine dosage to maintain therapeutic levels.

Lanreotide alters the balance between insulin and glucagon, which may result in hypoglycemia or hyperglycemia. In acromegalic patients treated with lanreotide (pooled analysis), hyperglycemia was reported as an adverse event in 1.2% of patients (between 0% and 16% in individual studies) and hypoglycemia in 2.2% of patients. Due to this class effect on glycoregulation, the sponsor recommends that blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose strength is altered, and antidiabetic treatment be adjusted accordingly.

There is also a potential pharmacodynamic interaction between lanreotide and orally administered drugs. Lanreotide's GI effects may hinder absorption of some co-administered drugs, modifying their efficacy.

There is a potential additive effect of bradycardia-inducing drugs, such as beta-blockers, with lanreotide. Bradycardia was reported in acromegalic patients treated with lanreotide in 3.1% of patients overall (pooled analysis; N=416). However, in patients not treated with SSAs at baseline, the incidence of bradycardia was 7.1% of patients (Studies 081 and 717; n=170). The pooled analysis showed that 18.5% of patients were taking beta-blocking agents. This higher incidence of bradycardia with initiation of lanreotide treatment indicates dose adjustment of concomitant medications that affect heart rate may be needed.

One paper has shown that the bioavailability of the dopaminergic agonist bromocriptine was increased by approximately 40% when administered concurrently with octreotide, probably caused by altered absorption or first pass metabolism.<sup>26</sup> A similar interaction with bromocriptine may occur for lanreotide.

Several papers<sup>27,28</sup> have discussed the possibility of lanreotide modulation of cytochrome P450 activity, either directly or through modulation of GH concentrations. A secondary effect of this would be the potential for altered drug metabolism in patients treated with lanreotide acetate. Patients may need to have dose levels adjusted for concomitant medications.

### 7.4.3 Causality Determination

Determination of causality must take into account various factors to different extents: the relative frequency of an adverse event compared to the control group, the timing of the event and the likelihood that such event would be allowed to manifest itself in that period of exposure, the investigator opinion after analysis of confounding circumstances and the biologic plausibility based on the mechanism of action. The most likely adverse events caused by lanreotide in the clinical studies presented in this application are injection site reactions, gastrointestinal events (diarrhea, abdominal pain, flatulence, and nausea), cholelithiasis, glycoregulation (hypoglycemia, hyperglycemia, diabetes) and sinus bradycardia. Alopecia, anemia and hypertension may also be related to lanreotide therapy. The incidence of injection site reactions, diarrhea, abdominal pain and flatulence increased with lanreotide dose in some but not all studies.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

As per the applicant's proposed package insert:

"Patients should begin treatment with Somatuline Autogel 90 mg given via the deep subcutaneous route, at 4 week intervals for 3 months.

After 3 months dosage may be adapted as follows:

- GH  $>1$  to  $\leq 2.5$  ng/mL, IGF-1 normal and clinical symptoms controlled: maintain Somatuline Autogel dosage at 90 mg every 4 weeks.
- GH  $> 2.5$  ng/mL, IGF-1 elevated and/or clinical symptoms uncontrolled, increase Somatuline Autogel dosage to 120 mg every 4 weeks.
- GH  $\leq 1$  ng/mL, IGF-1 normal and clinical symptoms controlled: reduce Somatuline Autogel dosage to 60 mg every 4 weeks.

Thereafter, the dose should be adjusted according to the response of the patient as judged by a reduction in serum GH and /or IGF-1 levels; and/or changes in symptoms of acromegaly.

Somatuline Autogel should be injected via the deep subcutaneous route in the superior external quadrant of the buttock."

The sponsor's proposed dose and regimen for patients with acromegaly is justified. Serum concentrations of lanreotide approached the median values sufficient to provide hormonal control of acromegaly after a single 90 or 120 mg injection of lanreotide acetate in Study 076. These results were supported by the minimum serum lanreotide levels obtained in Study 717. Therefore, the 90 mg dose is a logical minimal effective starting dose strength based upon both 1) lower annual cumulative GH levels as compared to a 60 mg starting dose strength, and 2) serum levels of lanreotide sufficient to approach hormonal control of acromegaly after the first injection. The dose strength prescribed should be evaluated after 3 months and titrated to optimal clinical and hormonal control based upon individual response. It is not necessary to alter the starting dose in elderly patients, as subgroup analysis did not show any significant difference in response to treatment with regard to age, gender, BMI, bodyweight or race.

Subjects with severe renal or hepatic insufficiency and the elderly showed an increase in half-life and AUC. Clinical studies with Somatuline did not include sufficient numbers of subjects with renal impairment or severe hepatic impairment. Therefore, I recommend a starting dose of 60 mg in patients with moderate to severe renal impairment or moderate to severe hepatic impairment. The dose strength should be re-evaluated after 3 months and cautiously titrated to optimal clinical and hormonal control based upon individual response.

## 8.2 Drug-Drug Interactions

Please see Section 7.4.2.5.

### Cyclosporine

Study 038, a PK interaction study in healthy subjects, reported a PK interaction between cyclosporine and lanreotide with a 19% decrease in relative bioavailability of cyclosporine. Therefore, concurrent administration of lanreotide acetate and cyclosporine may necessitate adjustment of cyclosporine dosage to maintain therapeutic levels.

### Antidiabetic Treatment

Lanreotide alters the balance between insulin and glucagon, which may result in hypoglycemia or hyperglycemia. Due to this class effect on glycoregulation, it is recommended that blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose strength is altered, and antidiabetic treatment be adjusted accordingly.

### Bradycardia-inducing Drugs

There is a potential additive effect of bradycardia-inducing drugs, such as beta-blockers, with lanreotide. Dose adjustment of concomitant medications that affect heart rate may be needed.

## 8.3 Special Populations

The clinical studies are representative of the intended patient population by age, gender, BMI and acromegaly history. Please refer to Sections 6.1.4.6 and 7.1.5.6 for details.

In the 2 pivotal efficacy studies, Study 717 and 081, 48% (82/170) were female; 24% (41/170) were 65 years or older; 39% (41/104) had a BMI of 26 or greater; and 15% (26/170) had a baseline GH $\geq$ 10 ng/mL. The majority of subjects were Caucasian. Patients in Study 717 were 84% Caucasian, 11% Asian, 4% Black and 2% American Hispanic. Data for ethnicity were not collected in Study 081.

- After treatment with lanreotide acetate, the incidence of patients with mean GH $\leq$ 2.5 ng/mL with normalized IGF-1 was similar in females (42.7%; 95% CI: 31.8, 54.1) and males (37.5%; 95% CI: 27.4, 48.5).
- The greatest percentage of responders was seen in the oldest group of patients ( $\geq$ 75 years), with 64% (7/11) of patients having mean GH $\leq$ 2.5 ng/mL with normalized IGF-1 after treatment compared to 30.0% (9/30) in the 65 to 74 age group, 41% (44/108) in the 40 to 64 age group, and 38% (8/21) in the <40 age group.
- Based on BMI, 38% (12/32) of subjects with a BMI <26 kg/m<sup>2</sup> had a mean GH $\leq$ 2.5 ng/mL and normalized IGF-1 which increased to 42% (22/52) at BMI 26 to 32 and 45% (9/20) at BMI >32. However, the confidence intervals were wide and overlapped significantly making it unlikely that there is any meaningful difference in response rate with regard to body mass index.
- There was a higher percentage of responders (i.e., patients with GH $\leq$ 2.5 ng/mL and normalized IGF-1) among patients with lower GH concentrations (mean GH <10 ng/mL) at baseline (44.8% responders; 95% CI: 35.0, 54.8), compared with patients with higher

GH concentrations (mean GH  $\geq 10$  ng/mL) at baseline (32.3% responders; 95% CI: 21.2, 45.1).

- There did not appear to be any difference in the percentage of responders between the Caucasian (44.4% responders; 95% CI: 44.7, 66.0) and Asian (36.4% responders; 95% CI: 10.9, 69.2) populations. Since less than 4% of patients were Black and less than 2% were American Hispanic, there were too few patients to make meaningful comparisons for these two groups.

In the 7 pooled safety studies, (717, 081, 721, 076, 087, 709, and 710), 51% (211/416) were female; 17% (72/416) were 65 years or older; only 5% (22/416) were Non-Caucasian; and 31% (131/416) were diabetic.

- The most commonly reported TEAE, diarrhea, was reported by a larger percentage of males (41%) than females (34%). Loose stools were also reported by a larger percentage of males (8%) than females (3%). However, some other GI disorders, including nausea and constipation, were each reported by a larger percentage of females (8-10% more than males). Cholelithiasis was reported by a larger percentage of males (26%) than females (15%).
- For the GI disorders of nausea, vomiting, constipation, flatulence, loose stools and hiatus hernia, there was an increasing incidence with age to 74 years. However, for diarrhea and abdominal pain, the highest incidence was in the 40-65 years and  $< 40$  years groups, respectively. For liver function analyses, a similar percentage of patients (15 and 17%) was reported in the 40-65 years and the  $\geq 75$  years groups, respectively. For injection site reactions (including injection site pain and mass), asthenic conditions (including fatigue) and pain and discomfort (including chest pain) the highest incidence occurred in the  $\geq 75$  years group. In summary, for the most commonly occurring TEAEs in the pooled analysis, diarrhea, abdominal pain and cholelithiasis, there was no apparent trend for increasing incidence with age. However, for other TEAEs, there was an increased incidence in the higher age groups (66-74 years and  $\geq 75$  years), although interpretation of the data is difficult due to the imbalance in the number of patients per age group and extent of exposure.
- The most commonly occurring TEAEs in non-Caucasian patients were GI disorders, reported by 15 (68%) patients with the highest incidence recorded for diarrhea (41%) and loose stools (23%). The pattern of TEAEs seen in the small non-Caucasian population is consistent with the profile seen in the overall safety analysis.
- GI disorders (including diarrhea, abdominal pain, nausea, vomiting, constipation and flatulence) were reported by a higher percentage of diabetic patients than nondiabetic patients (63% versus 54%). As expected, there was a difference between the two groups for carbohydrate tolerance analyses (13% vs. 4%) and diabetes mellitus (9% vs. 0.4%). There was also a higher incidence of arthralgia (11.5% vs. 5%).

Special dosing considerations based on race, gender, weight or concomitant illness other than renal and hepatic impairment does not appear to be necessary for Lanreotide acetate. The starting dose should be decreased in subjects with moderate to severe renal or hepatic impairment.

## 8.4 Pediatrics

GH-secreting pituitary adenomas are extremely rare in children and constitute a separate clinical entity of pituitary gigantism. Experience with lanreotide acetate in the pediatric population is limited and the sponsor has applied for a pediatric waiver, which in this reviewer's opinion is appropriate and should be granted.

## 8.5 Advisory Committee Meeting

The Division of Metabolic and Endocrine Products felt that consultation with the Endocrinology and Metabolic Advisory Committee would not be necessary for the following reasons:

- Although lanreotide is a new molecular entity, it is a somatostatin analog whose mechanism of action is similar to currently marketed octreotide acetate, Sandostatin and Sandostatin LAR (approved 1992 and 1998, respectively), whose safety and efficacy profiles have been well established in the intended population.
- The review of data from clinical studies did not raise specific questions on aspects of safety or efficacy for the population of acromegalics as a whole or for specific subsets.

## 8.6 Literature Review

A literature review was conducted and relevant findings were summarized in Section 7.2.2.3 and in specific discussion of issues throughout this document.

## 8.7 Postmarketing Risk Management Plan

The applicant should continue to monitor the safety of lanreotide in ongoing nonclinical studies, clinical trials and through routine pharmacovigilance.

### AEs of special interest

The AEs of special interest include injection site reactions, selected gastrointestinal adverse events, cholelithiasis, glycoregulation, sinus bradycardia, hypertension, anemia, and alopecia. The selected laboratory findings of interest are hematocrit/hemoglobin and hyperglycemia. The above should be followed by routine post-marketing surveillance and by monitoring these AEs of special interest in ongoing and planned clinical trials.

### Unanticipated Safety Signals

Data from clinical trials cannot always predict rare AEs which may only become evident after being used in a larger number of patients with a greater range of co-morbid conditions. Unanticipated safety signals will be monitored through routine pharmacovigilance.

## 8.8 Other Relevant Materials

None

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

This NDA contains reports of clinical studies which demonstrate substantial evidence of improved GH and IGF-1 control in patients with acromegaly treated with lanreotide acetate. Review of the safety profile did not identify risks associated with lanreotide acetate therapy to offset its efficacy profile. Treatment with lanreotide acetate did not demonstrate a meaningful difference in the risk of developing new or worsening valvular regurgitation or significant regurgitation compared to octreotide. The safety profile for lanreotide acetate was similar to that of the octreotide-containing drug products for the same indication. I recommend a reduction in the starting dose to 60 mg in patients with moderate to severe renal impairment or moderate to severe hepatic impairment.

### 9.2 Recommendation on Regulatory Action

I recommend approval of Somatuline (lanreotide acetate) for the first indication sought, "for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option" but not for the

### 9.3 Recommendation on Postmarketing Actions

None

#### 9.3.1 Risk Management Activity

See Section 8.7.

#### 9.3.2 Required Phase 4 Commitments

None

#### 9.3.3 Other Phase 4 Requests

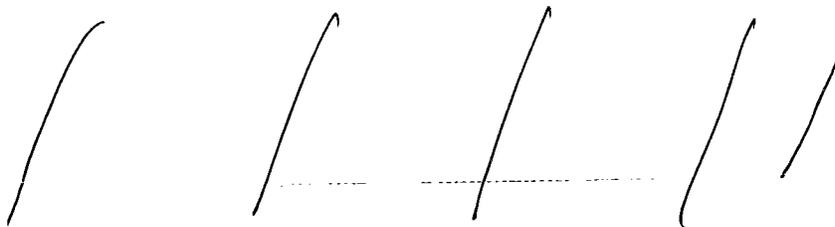
None

## 9.4 Labeling Review

A consult was issued to the Division of Medication Errors and Technical Support (DMETS) for assessment of the proprietary name, "Somatuline Autogel", regarding potential name confusion with other proprietary or established drug names<sup>29</sup>. Since Somatuline Autogel is available in foreign markets, DMETS conducted an AERS search to determine if there were any reported errors involving this product. The search did not identify any errors relating to nomenclature, dosing, packaging, or administration. In reviewing the proprietary name, Somatuline Autogel, the primary concerns relating to potential look-alike and sound-alike confusion with Somatuline Autogel, are with Somatropin, Famotidine, and Loratadine. Since there are no additional Somatuline products in the U.S. marketplace from which to differentiate Somatuline Autogel, DMETS expects that the modifier 'Autogel' may be omitted in an order for this product. Additionally, DMETS has concerns about the inclusion of the modifier in an order, in that it may be misinterpreted as a second medication. DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. One participant from the outpatient written study and two from the verbal study omitted the modifier, Autogel. Thus, DMETS has no objection to the use of the proprietary name, Somatuline. However, DMETS object to the use of any modifier with this proprietary name as the modifier 'Autogel' is misleading and may be confusing to healthcare practitioners.

In the review of the insert labeling of Somatuline Autogel, DMETS has identified the following areas of improvement which may minimize user error.

1. According to the DOSAGE FORMS AND STRENGTHS Section of the package insert labeling, the strength of Lanreotide is based on the active moiety and not the acetate salt. However, the manner in which this information is presented throughout the labeling is inconsistent. It appears that the milligram amount pertains to the base and not the amount of salt; however the sponsor includes the salt in the presentation of the established name. DMETS recommends revising the labeling so that it is consistent throughout the labeling.
2. DMETS notes the labeling includes trailing zeroes. The use of trailing zeroes has led to medication errors. Because of these errors, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g., trailing zeros such as 1.0 mg/0.5 mg). Thus, DMETS recommends that trailing zeroes be removed from all labels and labeling.
3. The DOSAGE FORMS AND STRENGTHS section includes



Clinical Review  
Eileen M. Craig, MD  
NDA 22-074, Submission 000  
Somatuline® Autogel® (lanreotide acetate) Injection

4. The HOW SUPPLIED section refers to a '...syringe fitted with a needle covered with a natural rubber sheath'. DMETS suggests that the gauge of the needle is included as each person's amount of subcutaneous tissue is different and may require a readjustment in the size of the needle used for the injection.

DDMAC finds the proprietary name, Somatuline Autogel, acceptable from a promotional perspective.

Please refer to Section 10.2, Line-by-Line Labeling Review for the detailed labeling review.

#### 9.5 Comments to Applicant

None

**APPEARS THIS WAY  
ON ORIGINAL**

## **10 APPENDICES**

### **10.1 Review of Individual Study Reports**

#### **10.1.1 Study Title: E28-52030-717 (Study 717)**

Phase II, multi-center, randomized, double-blind study in acromegalic patients evaluating the efficacy and safety of a single deep subcutaneous administration of lanreotide acetate (60, 90, or 120 mg) versus placebo followed by a single-blind fixed dose phase evaluating the pharmacokinetic, pharmacodynamic, efficacy and safety profile of multiple deep subcutaneous administrations of lanreotide acetate (60, 90, & 120 mg) ending in open label dose titration phase

#### **Investigators:**

Thirty principal investigators participated in the study. The co-coordinating investigator was Shlomo Melmed, MD, professor in endocrinology at the Pituitary Center, Suite 490 West 8635 West Third St., Los Angeles, CA, 90048 USA.

#### **Study center(s):**

Thirty centers from 8 countries [United States (11), France (5), Germany (3), United Kingdom (3), Czech Republic (3), Netherlands (2), Hungary (2), and Hong-Kong (1) participated in the study from 2 May 2000 to 3 January 2003.

**Study period:** 02 May 2000 to 03 January 2003

**Phase of Development:** Phase II

**Publications Based on the Study:** None

#### **Primary Objectives:**

To demonstrate that lanreotide acetate was more active on growth hormone (GH) levels in patients with acromegaly than placebo 4 weeks after a single injection.

#### **Secondary Objectives:**

- 1.) To demonstrate that lanreotide acetate was more active on insulin-like growth factor 1 (IGF-1) levels in patients with acromegaly than placebo 4 weeks after a single injection.
- 2.) To show the effect of repeated injections of lanreotide acetate on GH levels over time.
- 3.) To show the effect of repeated injections of lanreotide acetate on IGF-1 levels over time.
- 4.) To document the evolution of acromegaly symptoms between baseline, week 4, week 16 and at the end of the study.
- 5.) To document the safety of lanreotide acetate in terms of:

- Physical examination [including electrocardiogram (ECG), echocardiogram, blood pressure, heart rate and weight] at Weeks 4 and 16 and at the end of the study (echocardiogram was not assessed at Week 4).
  - Standard hematology and chemistry laboratories at Weeks 4 and 16, and at the end of the study.
  - Gallbladder lithiasis at Week 16 and at the end of the study.
  - Tumor status at Week 16 and at the end of study.
  - Adverse events at all visits.
  - Blood levels of antibodies to lanreotide acetate at Weeks 4, 16, 36 and at the end of the study.
- 6.) To document the pharmacokinetic profile and the pharmacodynamic effect of lanreotide acetate in patients with acromegaly on GH, IGF-1 and lanreotide blood levels over time.

**Design:**

This was a phase II, multi-center, randomized study conducted in patients with acromegaly who may or may not have been previously treated by surgery, radiotherapy, somatostatin analogs or dopamine agonists. Patients were randomized into one of 6 treatment groups: lanreotide acetate 60 mg, lanreotide acetate 90 mg, lanreotide acetate 120 mg, placebo 60 mg, placebo 90 mg, or placebo 120 mg. The ratio of active medication to placebo was 3:1 (i.e., 24 active: 8 placebo per dose group).

The study consisted of 4 distinct phases:

- Wash-out phase (Week -12 to Week 0). This phase was required only for patients who were previously treated with a somatostatin analog or a dopaminergic agonist.
- Double-blind, placebo-controlled phase (Week 0 to Week 4); single injection of lanreotide acetate 60, 90, or 120 mg or placebo based on random assignment.
- Single-blind, fixed-dose phase (Week 4 to Week 20); 4 injections of lanreotide acetate 60, 90 or 120 mg based on dose group as assigned during double-blind phase.
- Open-label dose titration phase (Week 20 to Week 52); 8 injections of lanreotide acetate at a dose based on dose titration schema. Two dose adjustments could be made based on biochemical efficacy (i.e., GH and IGF-1 levels).

**Patient Population:**

Patients 18 years of age or older with documentation of a diagnosis of active acromegaly based on one of the following definitions:

- The patient had never received somatostatin analog nor dopaminergic agonist or had previously received this medication but had stopped more than 3 months before visit 1 and had a mean GH level > 5 ng/mL at visit 1.
- The patient was receiving treatment with a somatostatin analog (other than lanreotide acetate) or a dopaminergic agonist at visit 1, had a mean GH > 3 ng/mL at visit 2 (or visit 2a) and had at least a 100% increase in mean GH levels between visit 1 and visit 2 (or visit 2a).

Main exclusion criteria included receipt of radiotherapy for acromegaly within 3 years or pituitary surgery within 3 months prior to visit 1; prior receipt of lanreotide acetate or GH antagonist; anticipated need for pituitary surgery (adenomectomy) or radiotherapy during the

study period; known hypersensitivity to any of the test materials or related compounds; clinically significant renal or hepatic abnormalities.

**Treatment Groups:**

Patients were randomized at entry into the double-blind treatment phase (Week 0, visit 3) into one of the following dose groups:

- Lanreotide acetate 60 mg (24 patients) or placebo (8 patients),
- Lanreotide acetate 90 mg (24 patients) or placebo (8 patients),
- Lanreotide acetate 120 mg (24 patients) or placebo (8 patients),

The ratio of active medication to placebo was 3:1 (i.e., 24 active: 8 placebo per dose group). The randomization scheme was implemented through the use of randomized blocks of patients; block size was 12.

**Duration of Treatment:**

A total of 108 patients received at least one dose of study drug during the 4-week double-blind placebo-controlled phase, including 27, 27, 29 and 25 patients in the 60, 90, and 120 mg lanreotide treatment groups and placebo group, respectively. A total of 107 of these 108 patients went on to receive treatment during the 16-week single-blind fixed-dose phase, including 34, 36 and 37 patients in the 60, 90 and 120 mg lanreotide treatment groups, respectively. One-hundred-five (105) patients received treatment in the 32-week open-label dose-titration phase, including 21, 15 and 69 patients whose last dose received was 60, 90 and 120 mg lanreotide acetate, respectively.

A total of 107 patients received at least one injection of lanreotide acetate during this study including 34 patients (32%) who received lanreotide acetate 60 mg, 36 (34%) who received lanreotide acetate 90 mg, and 37 (35%) who received lanreotide acetate 120 mg.

**Table 10.1.1.1 Total Exposure to Lanreotide Acetate during All Three Studies Phases (Double-blind, Single-blind and Open-label) (Safety Population, Double/Single-blind + Open-label Phases)**

Statistic	Cumulative lanreotide dose (mg)	Average monthly lanreotide dose (mg) <sup>1</sup>	Duration of active treatment (days) <sup>2</sup>
N	107	107	107
Median	1140.0	98.6	364.0
Mean ± SD	1196.4 ± 301.6	96.4 ± 20.4	348.0 ± 48.7
Minimum, Maximum	270, 1560	58.8, 121.3	86, 400

<sup>1</sup> [Cumulative lanreotide dose/duration of active treatment] × 28.  
<sup>2</sup> [Date of last lanreotide dose – date of first lanreotide dose] + 28.  
 Sponsor's Table 43, Module 5, Vol 53, pg 122

**Endpoints:**

Primary Efficacy Parameter:

Proportion of patients with a >50% decrease in mean GH from baseline to Week 4.

*Reviewer comment: More relevant co-primary endpoint of clinical relevance would be (1) % of patients achieving and maintaining normal IGF-1 levels (for sex and age) and (2) % of patients achieving and maintaining Growth Hormone (GH) levels < 1 ng/mL following an oral glucose load (measure GH during a 2-hr period after a standard 75-g oral glucose load) (preferable criteria for GH) or GH level < 2.5 ng/mL.*

**Efficacy:**

- Mean serum GH levels determined from serial measurements<sup>1</sup> obtained at screening, at Weeks 4, 13, 14, 15, 16, 32 and 52, and in the event of early withdrawal.
- A single fasting serum IGF-1 level was obtained at screening, at Weeks 4, 13, 14, 15, 16, 32 and 52, and in the event of early withdrawal.
- Acromegaly symptoms, including headache, perspiration (night sweats), fatigue, swelling of extremities, joint pain, impotence (male) and oligomenorrhea (female) assessed as absent, mild, moderate or severe by the investigator at screening and Weeks 0, 4, 16, 32, 52 and in the event of early withdrawal.

**Pharmacokinetics:**

Lanreotide serum levels obtained prior to receipt of study drug at Weeks 0, 4, 16, 36 and 52, and at weeks 13, 14 and 15 corresponding to 1, 2 and 3 weeks after the 4th injection.

Estimation of the population PK/PD relationship using lanreotide serum concentration and GH levels as a response.

**Safety:**

Adverse events<sup>2</sup>, clinical laboratory tests, physical examinations, vital signs (blood pressure and heart rate), ECG, echocardiography, anti-lanreotide antibodies, ultrasound of gallbladder, pituitary (magnetic resonance imaging (MRI) or computed tomography (CT) scan, and concomitant medications.

**Statistical Analyses:**

The primary efficacy analysis was based on the intent to treat (ITT) population. Supportive secondary efficacy analyses were based on the per protocol (PP) population. Study populations were defined by treatment phase. The ITT population for the double-blind phase included all randomized patients who received at least one dose of lanreotide or placebo and the ITT population for the single-blind and open-label phases was comprised of all randomized patients who received at least one dose of lanreotide. The PP population included all randomized patients who received at least one dose of the study medication (lanreotide or placebo) and who did not have major protocol deviations.

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<sup>1</sup> A series of 7 serum samples where the first sample was obtained after an 8-hour fast between 08:00 and 09:00 in the morning and the last sample was obtained between 11:00 and 12:00 in the morning (just prior to the injection of lanreotide autogel, when applicable).

<sup>2</sup> At each visit, information was solicited from patients with regard to any symptoms or unexpected occurrences since the previous visit. The information was gathered using non-leading questions (e.g., "Do you feel different in any way since starting the new treatment/the last assessment?").

Categorical variables are presented using number of patients and percent; continuous variables are presented using number of patients, mean, standard deviation (SD), median, minimum and maximum. All statistical tests were 2-sided at the 5% level of significance.

The primary efficacy parameter is the proportion of patients with a >50% decrease in mean GH from baseline to Week 4. The primary comparisons were lanreotide acetate 60 mg versus placebo, lanreotide acetate 90 mg versus placebo and lanreotide acetate 120 mg versus placebo, 4 weeks after a single injection. A secondary comparison of interest was the pooled lanreotide acetate group (60 mg, 90 mg, and 120 mg) versus placebo, 4 weeks after a single injection. No overall test of treatment effect was performed. Treatment groups were compared using Fisher's exact test with permutation resampling. In addition, the treatment difference estimated by the odds ratio is provided in each tabulation. A 95% confidence interval (CI) of the treatment difference was calculated using Mantel-Haenszel methodology.

Secondary efficacy endpoints included the proportion of patients with a decrease in mean GH from baseline >50% at Weeks 16, 32, 52 and the last value available post-baseline (LVA), analyzed using pairwise comparisons among the lanreotide groups; the proportion of patients with mean GH  $\leq 2.5$  ng/mL; the proportion of patients with normalized IGF-1; the proportion of patients with mean GH  $\leq 2.5$  ng/mL and normalized IGF-1; and changes from Baseline in acromegaly symptoms. For the latter 4 secondary endpoints, the comparisons of interest were the pairwise comparisons of lanreotide dose groups versus placebo at Week 4, and the among lanreotide dose groups at Weeks 16, 32, 52 and LVA.

Safety data are reported in summary tables using only descriptive statistics. No formal statistical tests were performed on these data. All safety tabulations are based on the safety population comprised of all patients who received at least one dose of study drug. Adverse events were coded using the World Health Organization Adverse Reaction Terminology (WHOART) dictionary (October, 1997). Tabulations of adverse events were performed for treatment-emergent adverse events (TEAE) defined as any event that occurred during the active phase of the study (until 56 days after the last injection) provided the event was not present prior to first injection (placebo or lanreotide), or if it was present, the intensity had increased during the active phase of the study.

#### Data Sets Analyzed:

Of the 107 patients included in the ITT population for the double/single-blind study phase, 18 patients (17%) did not fulfill the criteria to be included in the PP population for this phase. A total of 3 (9%), 9 (25%) and 6 (16%) patients were excluded from the lanreotide acetate 60 mg, 90 mg and 120 mg dose groups, respectively. The table below presents the reasons for exclusion across all study phases; results are displayed by last dose of lanreotide administered during the study.

**Table 10.1.1.2. Reasons for Exclusion from the Per Protocol Population in the Double/Single-blind and Open-label Study Phases by Last Dose Administered**

Study Phase Reason for Exclusion	Lanreotide Autogel:			Total
	60 mg	90 mg	120 mg	
Double/Single-blind + Open-label Phases <sup>1</sup> ITT population	21 (100%)	17 (100%)	69 (100%)	107 (100%)
Total excluded	5 (24%)	8 (47%)	18 (26%)	31 (29%)
GH assessment at V14 and/or V19 <21 or >35 days after previous injection	0	4 (25%)	7 (10%)	11 (10%)
< 25 or >31 days between injection at V3 and GH assessment at V4	2 (10%)	1 (6%)	7 (10%)	10 (9%)
At least one interval ≥35 days between injections 5 to 13	2 (10%)	1 (6%)	4 (6%)	7 (7%)
Dose not adjusted per protocol	1 (5%)	1 (6%)	5 (7%)	7 (7%)
At least one interval ≥35 days between injections 2 to 5	1 (5%)	1 (6%)	2 (3%)	4 (4%)
Received dopamine agonist after study entry	0	1 (6%)	1 (1%)	2 (2%)
No efficacy assessment at V10	0	2 (13%)	0	2 (1%)
Did not receive entire dose all injections	0	0	2 (3%)	2 (2%)
GH assessment at V10 >35 days after previous injection	0	0	1 (1%)	1 (<1%)
No GH at Visit 1	1 (5%)	0	0	1 (<1%)

Note: percents are based on the total number of patients included in the ITT population within a treatment group during the study phase. Patients may have had more than one reason for exclusion and may therefore appear in more than one category.

<sup>1</sup> Patients are grouped by the last dose level administered during the open-label phase.

Sponsor's Table 7, Module 5, Vol 53, pg. 73.

An overview of the analysis patient populations is provided in Table 10.1.1.3 for the double-blind, double/single-blind, and all 3 study phases. A total of 94 (87%) of 108 patients were included in the PP population for the double-blind phase, 89 (83%) of 107 patients were included in the PP population for the double/single-blind phase and 76 (71%) of 107 patients were included in the PP population for all 3 study phases.

**Table 10.1.1.3. Data Sets Analyzed**

Study Phase Patient Population	Lanreotide Autogel:			Placebo	Total
	60 mg	90 mg	120 mg		
Double-blind Study Phase <sup>1</sup>					
ITT population	27 (100%)	27 (100%)	29 (100%)	25 (100%)	108 (100%)
PP population	26 (96%)	22 (81%)	25 (86%)	21 (84%)	94 (87%)
Safety population	27 (100%)	27 (100%)	29 (100%)	25 (100%)	108 (100%)
Double/Single-blind Study Phases <sup>1</sup>					
ITT population	34 (100%)	36 (100%)	37 (100%)	--	107 (100%)
PP population	31 (91%)	27 (75%)	31 (84%)	--	89 (83%)
Safety population	34 (100%)	36 (100%)	37 (100%)	--	107 (100%)
Double/Single-blind + Open-label Study Phases <sup>2</sup>					
ITT population	21 (100%)	17 (100%)	69 (100%)	--	107 (100%)
PP population	16 (76%)	9 (53%)	51 (74%)	--	76 (71%)
Safety population	21 (100%)	17 (100%)	69 (100%)	--	107 (100%)

Note: percents are based on the total number of patients included in the ITT population within a treatment group during the study phase. For the double/single-blind & open-label phases patients are grouped by the last dose received.

<sup>1</sup> Patients are grouped based on randomization.

<sup>2</sup> Patients are grouped by the last dose level administered during the open-label phase.

Sponsor's Table 8, Module 5, Vol 53, pg. 74

**Protocol Amendments:**

The original study protocol, dated 11 February 2000, was amended 5 times.

<b>Amendment No., Date</b>	<b>Primary Changes Implemented:</b>
No. 1, 28 February 2000	Echocardiography was deleted from the Week 4 assessment.
No. 2, 23 March 2000	Added an exclusion criterion for patients who had received prior GH antagonist. Modified the dose adjustment rules to include both GH and IGF-1 levels.
No. 3, 7 August 2000	Expanded the time period between visits 2 and 2a from 2 weeks to 2 to 6 weeks; therefore visit 1 could occur up to 12 weeks prior to visit 3 (week 0 visit). Moved the medical history and physical examination from visit 3 to visit 1.
No. 4, 26 September 2001	Only modifications made to informed consent form providing further clarification of possible risks and discomforts.
No. 5, 5 November 2001	Modified the Pharmacovigilance contacts for emergency reports.

One additional change in protocol procedures was implemented by the sponsor. In addition to the local assessment of ECG and echocardiograms conducted by the study site and presented in this report, ECG and echocardiograms are to be read and analyzed by a central laboratory.

**Results:**

**Patient Demographics**

The 108 patients included in the ITT (and safety) population for the double-blind phase comprised 47% (51) males and 53% (57) females; 84% (91) of patients were Caucasian, 10% (11) were Asian, 4% (4) were Black and 2% (2) were American Hispanic. Median and mean age were similar across the 4 treatment groups; median age was 54 years across all 108 patients with a range of 19 to 84 years. Most patients [73 (68%) of 108] were 40 to 65 years of age; 20 patients (19%) were over 65 years of age at study entry. Across all 108 patients, males were slightly younger (median of 52 and 58 years for males and females, respectively). Mean and median height and weight were similar across the treatment groups; median height and weight were 172 cm and 82 kg, respectively, across all patients with data available.

**Table 10.1.1.4 Demographic Characteristics by Dose as Randomized (ITT and Safety Populations, Double-blind Phase)**

Demographic Characteristic	Lanreotide Autogel:			Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)		
Age (years)					
Median	54.0	58.0	55.0	51.0	54.0
Mean ± SD	52.2 ± 16.6	54.5 ± 14.2	55.6 ± 12.1	51.4 ± 12.7	53.5 ± 13.9
Min, Max	19, 84	27, 77	24, 78	27, 73	19, 84
Height (cm) <sup>1</sup>					
Median	171.5	165.1	172.7	174.0	172.0
Mean ± SD	170.8 ± 8.8	168.1 ± 8.4	171.3 ± 9.4	172.7 ± 11.5	170.7 ± 9.6
Min, Max	147.3, 197.0	157.0, 190.0	152.0, 184.0	152.0, 195.6	147.3, 197.0
Weight (kg) <sup>2</sup>					
Median	79.1	82.0	82.3	92.7	82.0
Mean ± SD	80.1 ± 15.7	81.5 ± 14.1	87.1 ± 19.7	86.4 ± 16.6	83.8 ± 16.7
Min, Max	41.0, 128.0	50.0, 115.0	50.5, 135.5	56.0, 123.0	41.0, 135.5
Sex					
Male	13 (48%)	9 (33%)	16 (55%)	13 (52%)	51 (47%)
Female	14 (52%)	18 (67%)	13 (45%)	12 (48%)	57 (53%)
Race					
Caucasian	22 (81%)	24 (89%)	25 (86%)	20 (80%)	91 (84%)
Asian	2 (7%)	2 (7%)	3 (10%)	4 (16%)	11 (10%)
Black	1 (4%)	1 (4%)	1 (3%)	1 (4%)	4 (4%)
American Hispanic	2 (7%)	0	0	0	2 (2%)

<sup>1</sup> Two patients, one each in the lanreotide acetate 60 mg and placebo groups, did not have height assessed.

<sup>2</sup> One patient in the lanreotide acetate 60 mg group did not have weight assessed.

Sponsor's Table 9, Module 5, Vol 53, pg. 76.

Across all 108 patients, median and mean (±SD) duration since diagnosis were 3.4 and 6.5 (± 8.2) years, respectively, with a range of 0 to 42 years. A total of 59 (55%) of the 108 patients had undergone prior surgery and 12 (11%) had undergone prior radiation therapy for treatment of their acromegaly.

Half (54, 50%) of the 108 patients had never received medical therapy for the treatment of acromegaly or had stopped treatment 3 or more months prior to study entry; 31 patients (29%) were receiving octreotide, 21 (19%) were receiving lanreotide, and 4 (4%) were receiving a dopaminergic agent for the treatment of acromegaly at visit 1 and underwent wash-out of therapy prior to study entry.

**Table 10.1.1.5. Time since Diagnosis and Previous Treatment for Acromegaly by Dose as Randomized (ITT and Safety Populations, Double-blind Phase)**

Disease Characteristic	Lanreotide Autogel:			Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)		
<b>Time since diagnosis (years)</b>					
Median	1.9	2.5	5.0	4.7	3.4
Mean ± SD	5.5 ± 9.0	6.4 ± 9.6	7.4 ± 7.5	6.5 ± 6.7	6.5 ± 8.2
Minimum, Maximum	0.1, 40.0	0.1, 42.0	0.0, 25.2	0.0, 20.8	0.0, 42.0
<b>Previous acromegaly treatment<sup>1</sup></b>					
Surgery	15 (56%)	15 (56%)	15 (52%)	14 (56%)	59 (55%)
Radiotherapy	3 (11%)	4 (15%)	2 (7%)	3 (12%)	12 (11%)
<b>Acromegaly treatment at Visit 1<sup>1</sup></b>					
No treatment or treatment stopped ≥ 3 months ago	18 (67%)	13 (48%)	13 (45%)	10 (40%)	54 (50%)
Lanreotide 30 mg (q 12-16 days)	2 (7%)	1 (4%)	2 (7%)	3 (12%)	8 (7%)
Lanreotide 30 mg (q 9-11 days)	1 (4%)	0	2 (7%)	1 (4%)	4 (4%)
Lanreotide 30 mg (q 6-8 days)	2 (7%)	5 (19%)	1 (3%)	1 (4%)	9 (8%)
Octreotide long-acting	4 (15%)	6 (22%)	9 (31%)	8 (32%)	27 (25%)
Octreotide short-acting	0	2 (7%)	1 (3%)	1 (4%)	4 (4%)
Dopaminergic agonist	1 (4%)	1 (4%)	1 (3%)	1 (4%)	4 (4%)

Note: percents are based on the total number of patients included in the ITT population within a treatment group.

<sup>1</sup> Patients may have checked more than one option.

Sponsor's Table 10, Module 5, Vol 53, pg. 77

A total of 96 (89%) of the 108 patients had at least one ongoing medical condition at study entry, including 93%, 93%, 79% and 92% of patients in the 60, 90, and 120 mg lanreotide groups and the placebo group, respectively. The most common ongoing medical conditions at study entry, typical of a patient population with acromegaly, were hypertension (41%), diabetes mellitus (25%), other anterior pituitary disorders (17%), hypothyroidism (13%), and sleep apnea (10%). There were 20 reports of ongoing medical conditions related to the gallbladder or biliary tract in 18 patients: calculus of gallbladder without mention of cholecystitis or obstruction (9 patients, 8%), other specified disorders of the biliary tract (5 patients, 5%; all reports of dilatation of the common bile duct), unspecified disorder of the gallbladder (5 patients, 5%; 4 reports of sludge and one report of mild gallbladder disease), and cholesterolosis of gallbladder (1 patient, 1%). For calculus of gallbladder without cholecystitis or obstruction, 3 (11%), 2(7%), 3(10%), and 1(4%) of the 60 mg, 90 mg, 120 mg, and placebo group, respectively, experienced this at study entry. Aortic valve disorders were present at study entry in 0, 5(19%), 0, 2(8%) of the 60 mg, 90 mg, 120 mg, and placebo group, respectively. All other ongoing conditions were reported in < 10% of the 108 patients.

The proportion of patients with normal IGF-1 at baseline were 15%, 11%, 3% and 8% in the 60, 90 and 120mg lanreotide groups, and placebo respectively. Across the lanreotide treatment groups, a lower proportion of patients in the 120 mg treatment group had normal IGF-1 at baseline compared to the other lanreotide groups. However, none of the 108 patients enrolled and treated in this study had mean GH ≤ 2.5 ng/mL AND normalized IGF-1 (age-adjusted) at study baseline.

### Patient Disposition

A total of 220 patients were screened for study enrollment: One-hundred-nine patients were screen failures and 111 patients were randomized to receive lanreotide acetate 60, 90, or 120 mg, or placebo. Three of the 111 randomized patients did not receive any study medication (Patients 701.0019, 705.0002 and 734.0011 because of protocol deviation, consent withdrawn and protocol deviation, respectively). Thus, a total of 112 of the 220 screened patients were not injected with the study medication. The primary reasons why 62 out of the 112 patients did not receive study medication was failure to meet the inclusion criteria requiring patients who had received treatment with a somatostatin analog (other than lanreotide acetate) or a dopaminergic agonist at visit 1 to have a mean GH > 3 ng/mL at visit 2a (or visit 2) and have at least a 100% increase in mean GH levels between visit 1 and visit 2a (or visit 2 and did not attend visit 2a).

A summary of patient disposition during the study, including all study phases, is provided in the Table below:

Table 10.1.1.6. Summary of Patient Disposition

Disposition:	Lanreotide Autogel:			Placebo	Total
	60 mg	90 mg	120 mg		
Injected in the Double-blind Phase <sup>1</sup>	27 (25%)	27 (25%)	29 (27%)	25 (23%)	108 (100%)
Completed the Double-blind Phase	27 (25%)	27 (25%)	29 (27%)	24 (22%)	107 (99%)
Withdrawn during Double-blind	0	0	0	1 (1%)	1 (1%)
Reason: Adverse Event	0	0	0	1 (1%)	1 (1%)
Injected in the Single-blind Phase <sup>1</sup>	34 (32%)	36 (34%)	37 (35%)	NA	107 (100%)
Completed the Single-blind Phase	34 (32%)	34 (32%)	37 (35%)	NA	105 (98%)
Withdrawn during Single-blind	0	2 (2%)	0	NA	2 (2%)
Reason: Adverse Event	0	2 (2%)	0	NA	2 (2%)
Injected in the Open-label Phase <sup>2</sup>	21 (20%)	15 (14%)	69 (66%)	NA	105 (100%)
Completed the Open-label Phase	21 (20%)	13 (12%)	65 (62%)	NA	99 (94%)
Withdrawn during Open-label	0	2 (2%)	4 (4%)	NA	6 (6%)
Reason: Lack of Efficacy	0	1 (1%)	3 (3%)	NA	4 (4%)
Reason: Adverse Event	0	1 (1%)	1 (1%)	NA	2 (2%)

Note: percents are based on the total number of patients injected during the study phase.

NA = not applicable

<sup>1</sup> Patients are grouped based on randomization.

<sup>2</sup> Patients are grouped by the last dose level administered during the open-label phase.

Sponsor's Table 5, Module 5, Vol 53, pg. 68

A total of 108 patients received at least one injection of lanreotide or placebo during the double-blind study phase; 69 (64%) of these 108 patients were enrolled in Europe (64 patients) or Hong-Kong (5 patients) with 39 patients (36%) enrolled in the US. One patient, Patient 711.0004 in the placebo group, withdrew from the study during the double-blind phase due to the occurrence of an adverse event (headache) that was ongoing from the screening phase (i.e., was not treatment-emergent).

A total of 107 patients entered the single-blind study phase. Two patients, both in the lanreotide acetate 90 mg group (Patients 703.0001 and 715.0001), withdrew from the study during the single-blind phase. Patient 703.0001 withdrew after receiving 4 injections of study medication

primarily due to femur fracture and other associated events and Patient 715.0001 withdrew after receiving 3 injections due to thyroid carcinoma.

All 105 patients who completed the single-blind phase, including 34, 34 and 37 patients who received 60, 90 and 120 mg lanreotide acetate during that phase, entered and received dosing in the open-label titration phase of the study. During this study phase, patient dosing could be titrated based on response to treatment. Dose titrations could occur at Week 20 (visit 11) and Week 36 (visit 15) based on the previous visit's assessment of GH and IGF-1 levels. A total of 99 (94%) of the 105 patients included in the open-label phase completed the study. Six patients withdrew from this study phase prematurely due to lack of efficacy (4 patients) or adverse event (2 patients). Patient 707.0005 in the 90 mg group and Patients 711.0008, 713.0006 and 724.0003 in the 120 mg group discontinued due to lack of efficacy. Adverse event was the primary cause of treatment termination for Patient 713-0008 in the 90 mg group (albuminuria, diabetic nephropathy and peripheral edema) and Patient 701.0015 in the 120 mg group (growth of a pre-existing meningioma).

Patient Exposure to Study Drug

In the open-label titration phase of the study, the majority of the 34 patients who received 60 mg in the single-blind phase were titrated to 120 mg (17 patients, 50%) or to 90 mg (5 patients, 15%); 12 (35%) of these 34 patients were receiving 60 mg at the end of the open-label phase. As well, the majority of the 34 patients who received 90 mg in the single-blind phase had their dose titrated to 120 mg (20 patients, 59%); 7 patients (21%) continued to receive 90 mg and 7 patients (21%) had their dose reduced to 60 mg by the end of the open-label phase. Doses higher than 120 mg were not permitted during the study. The majority of the 37 patients who were receiving 120 mg in the single-blind phase continued to receive this dose (32 patients, 86%); 3 patients (8%) had their dose reduced to 90 mg and 2 (5%) to 60 mg. Overall a total of 12 (11%) of the 105 patients had their dose decreased, 42 (40%) had their dose increased and 51 patients (49%) remained on the same dose at the end of the study. Thus, the final dose administered in the open-label phase of the study was 60 mg for 21 (20%) of the 105 patients, 90 mg for 15 patients (14%) and 120 mg for 69 patients (66%). Patients were designated by 'dose group' as last dose received in the open-label phase.

Total exposure, including dose and duration of treatment, for all 107 lanreotide-treated patients across all 3 study phases is provided in the Table below:

**Table 10.1.1.7 Total Exposure to Lanreotide Acetate During All Three Studies Phases (Double-blind, Single-blind and Open-label) (Safety Population, Double/Single-blind + Open-label Phases)**

Statistic	Cumulative lanreotide dose (mg)	Average monthly lanreotide dose (mg) <sup>1</sup>	Duration of active treatment (days) <sup>2</sup>
N	107	107	107
Median	1140.0	98.6	364.0
Mean ± SD	1196.4 ± 301.6	96.4 ± 20.4	348.0 ± 48.7
Minimum, Maximum	270, 1560	58.8, 121.3	86, 400

1 [Cumulative lanreotide dose/duration of active treatment] × 28.

2 [Date of last lanreotide dose – date of first lanreotide dose] + 28.

Sponsor's Table 43, Module 5, Vol 53, pg. 122

### Treatment Compliance

All 108 patients included in the ITT population for the double-blind study phase received a single-dose of study medication at Week 0 (visit 3) as randomly assigned including 83 patients who received lanreotide and 25 who received placebo. One patient in the placebo group withdrew from the study during the double-blind phase and did not attend the Week 4 visit (visit 4). The remaining 107 patients attended the Week 4 visit (start of single-blind study phase) and received the 2<sup>nd</sup> injection of study medication; all 107 patients received lanreotide at that time as randomly assigned. One-hundred-five of the 107 patients who entered the single-blind study phase received 2 additional injections of study medication at Week 8 (visit 5) and Week 12 (visit 6) as planned.

A total of 105 patients received dosing at Week 16 including 104 patients who received dosing as planned and one patient (Patient 712.0002) who was randomized to receive 120 mg but received 60 mg in error. Of the 108 subjects who were injected at the start of the 4-week double-blind study, 99 (92%) completed all 3 phases (Double-Blind, Single Blind, and Open Label).

### Concomitant Medication Use

Somatostatin analogues (other than the study drug) and dopaminergic agonists were not permitted during the study; administration of cyclosporin also was not allowed. A summary of the most commonly administered medications administered during the double-blind and single-blind study phase are provided in the table below.

**Table 10.1.1.8. Classes of Prior and Concomitant Medications administered to  $\geq 10\%$  of Patients during the Double-blind and Single-blind Phases by Dose as Randomized (ITT and Safety Populations, Double-blind Phase)**

Classes of Medications	Lanreotide Autogel:			Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)		
Received any medication	23 (85%)	25 (93%)	25 (86%)	21 (84%)	94 (87%)
ACE inhibitors	8 (30%)	4 (15%)	10 (34%)	3 (12%)	25 (23%)
Thyroid hormones	5 (19%)	8 (30%)	4 (14%)	3 (12%)	20 (19%)
Anilides	3 (11%)	8 (30%)	4 (14%)	2 (8%)	17 (16%)
Benzodiazepine derivatives	5 (19%)	6 (22%)	3 (10%)	3 (12%)	17 (16%)
Glucocorticoids	5 (19%)	6 (22%)	3 (10%)	3 (12%)	17 (16%)
Dihydropyridine derivatives	5 (19%)	3 (11%)	6 (21%)	2 (8%)	16 (15%)
Propionic acid derivatives	5 (19%)	2 (7%)	6 (21%)	3 (12%)	16 (15%)
Beta-blocking agents, selective	5 (19%)	4 (15%)	3 (10%)	3 (12%)	15 (14%)
Sulfonamides, urea derivatives	2 (7%)	2 (7%)	4 (14%)	4 (16%)	12 (11%)
3-oxoandrost-4 derivatives	3 (11%)	4 (15%)	2 (7%)	2 (8%)	11 (10%)
Platelet aggregation inhibitors excluding heparin	5 (19%)	4 (15%)	2 (7%)	0	11 (10%)
Sulfonamides	5 (19%)	2 (7%)	2 (7%)	2 (8%)	11 (10%)

Sponsor's Table 14, Module 5, Vol 53, pg. 83

### Primary Efficacy Outcomes

Analysis of Results for the Double-blind Phase, ITT Population:

A statistically significantly higher proportion of patients in each of the 3 lanreotide treatment groups had a >50% decrease in mean GH from baseline (defined as the last value available before drug administration) to Week 4 (i.e., after a single injection) as compared to the placebo group ( $p < 0.001$ ). As well, a statistically significantly higher proportion of patients in the combined lanreotide treatment groups had a >50% decrease in mean GH from baseline to Week 4 as compared to the placebo group ( $p < 0.001$ ).

**Table 10.1.1.9 Proportion of Patients with a Decrease in Mean GH of >50% from Baseline to Week 4 (ITT Population) Treatment Group Response p-value**

Treatment Group	Response	p-value
Lanreotide 60 mg (N = 27)	14/27 (52%)	<0.001 <sup>1</sup>
Lanreotide 90 mg (N = 27)	12/27 (44%)	<0.001 <sup>1</sup>
Lanreotide 120 mg (N = 29)	26/29 (90%)	<0.001 <sup>1</sup>
Lanreotide overall (N = 83)	52/83 (63%)	<0.001 <sup>2</sup>
Placebo (N = 25)	0/25 (0%)	

Note: missing values are included as non-responses in this tabulation.

<sup>1</sup> Adjusted p-value for comparison with placebo using Fisher's exact test with permutation resampling.

<sup>2</sup> Unadjusted p-value for comparison with placebo using Fisher's exact test.

Sponsor's table, pg 16, Vol 53, Module 5

Results for the primary endpoint for the PP population confirmed those obtained in the ITT population. A total of 46 (63%) of the 73 lanreotide-treated patients included in the PP population had a >50% decrease in mean GH from baseline to Week 4 including 50%, 50% and 88% of patients in the 60, 90 and 120 mg groups, respectively. The proportion of lanreotide-treated patients with a >50% decrease in mean GH to Week 4 was similar between the 2 regions: US (19 of 32, 59%) and Europe/Hong Kong (33 of 51, 65%). The highest response rates in both regions were observed in the 120 mg group (90% for US and 89% for Europe/Hong Kong).

### Secondary Efficacy Outcomes

Double-blind Phase: Week 4

GH  $\leq$  2.5 ng/mL

Similar to the results for the primary efficacy analyses, a statistically significantly higher proportion of patients in each of the 3 active treatment groups had mean GH  $\leq$  2.5 ng/mL at Week 4 compared to the placebo group ( $p \leq 0.019$ ). As well, a statistically significantly higher proportion of patients in the combined lanreotide treatment groups had mean GH  $\leq$  2.5 ng/mL at Week 4 compared to the placebo group ( $p < 0.001$ ). A total of 28 (34%) of the 83 lanreotide-treated patients had mean GH  $\leq$  2.5 ng/mL at Week 4, including 19% (5/27), 30% (8/27), and 52% (15/29) of patients in the 60, 90 and 120 mg treatment groups, respectively. None of the 25 patients in the placebo group had mean GH  $\leq$  2.5 ng/mL at Week 4. Similar results were noted for analysis of the Week 4 results for the ITT population excluding missing values and for the PP population. Over all lanreotide-treated patients, a total of 38% (12 of 32) and 31% (16 of 51) of patients in the US and Europe/Hong Kong, respectively, had mean GH  $\leq$  2.5 ng/mL at the Week 4 evaluation.

**Table 10.1.1.10 Proportion of Patients with Mean GH  $\leq$  2.5 ng/mL at Week 4 by Dose as Randomized (ITT Population, Double-blind Phase)**

Treatment Group	Response	Odds Ratio	95% CI	p-value <sup>1</sup>
Lanreotide 60 mg (N = 27)	5/27 (19%)	5.868	0.628, 54.781	0.019
Lanreotide 90 mg (N = 27)	8/27 (30%)	11.008	1.274, 95.098	0.005
Lanreotide 120 mg (N = 29)	15/29 (52%)	29.503	3.452, 252.137	<0.001
Lanreotide overall (N = 83)	28/83 (34%)	12.649	1.619, 98.852	<0.001
Placebo (N = 25)	0/25 (0%)	NA	NA	NA

Note: missing values are included as non-responses in this tabulation; NA = not applicable; The odds ratio represents the increase in odds of a favorable response for each specific treatment group relative to placebo based on the logit approximation.

<sup>1</sup> P-value for comparing each lanreotide dose group against placebo using a Cochran-Mantel-Haenszel test.

Sponsor's table 19, pg 91, Vol 53, Module 5

#### Mean GH Over Time on Study

Mean GH decreased from baseline to Week 4 in all lanreotide treatment groups; mean ( $\pm$  SD) decreases of  $44.9 \pm 31.0\%$ ,  $40.9 \pm 38.5\%$  and  $70.2 \pm 22.0\%$  were noted in the 60, 90 and 120 mg treatment groups, respectively. A mean increase of  $55.5 \pm 171.6\%$  was noted for the placebo group. All pairwise comparisons of percent change from baseline to Week 4 for mean GH between each lanreotide treatment group and placebo were significant ( $p < 0.001$ ).

#### Normalized IGF-1 (Age-adjusted)

It is important to note that the normal values for age-adjusted IGF-1 were not consistent from study to study. The table below provides the age-adjusted normals for Study 717 which is different than that used for Study 081.

**Table 10.1.1.11 Age-Adjusted IGF-1 Normal Values for Study E-28-52030-717**

Age	Low* (ng/ml)	High* (ng/ml)
16-24	182	780
25-39	114	492
40-54	90	360
>55	71	290

\* Normal ranges were the same for males and females

Consistent results were also noted for the analysis of the proportion of patients with normalized IGF-1 at Week 4. A statistically significantly higher proportion of lanreotide-treated patients (25%, 21 of 83) had normalized IGF-1 as compared to placebo patients (4%, 1 of 25) ( $p = 0.021$ ). Across the lanreotide treatment groups the proportions of patients with normalized IGF-1 were 30%, 30% and 17% for the 60, 90 and 120 mg groups, respectively. Pair-wise comparisons for this parameter between the 60 mg group vs. placebo and the 90 mg group vs. placebo were statistically significant. However, the pair-wise comparison between the 120 mg group and placebo was not statistically significant. It is important to note the proportion of patients with

normal IGF-1 at baseline were 15%, 11%, 3% and 8% in the 60, 90 and 120mg lanreotide groups, and placebo respectively. Similar results were noted for the ITT population when patients with missing data were excluded from the analysis and for the PP population. There were no significant differences between the 2 regions US and Europe/Hong Kong. At Week 4, 25% of lanreotide-treated patients in both the US and Europe/Hong Kong had normalized IGF-1.

**Table 10.1.1.12. Proportion of Patients with Normalized IGF-1 (Age-adjusted) at Week 4 by Dose as Randomized (ITT Population, Double-blind Phase)**

Treatment Group	Response	Odds Ratio	95% CI	p-value <sup>1</sup>
Lanreotide 60 mg (N = 27)	8/27 (30%)	7.149	1.136, 44.997	0.015
Lanreotide 90 mg (N = 27)	8/27 (30%)	6.690	1.050, 42.626	0.019
Lanreotide 120 mg (N = 29)	5/29 (17%)	3.680	0.554, 24.448	0.113
Lanreotide overall (N = 83)	21/83 (25%)	5.602	1.002, 31.320	0.021
Placebo (N = 25)	1/25 (4%)	NA	NA	NA

Note: missing values are included as non-responses in this tabulation; NA = not applicable; The odds ratio represents the increase in odds of a favorable response for each specific treatment group relative to placebo based on the logit approximation.

<sup>1</sup> P-value for comparing each lanreotide dose group against placebo using a Cochran-Mantel-Haenszel test. Sponsor's Table 22, Module 5, Vol 53, pg. 94

#### Mean IGF-1 Over Time on Study

Mean IGF-1 decreased from baseline to Week 4 in all lanreotide treatment groups; mean ( $\pm$  SD) percent decreases were  $19.7 \pm 33.1\%$ ,  $23.3 \pm 26.5\%$  and  $38.6 \pm 19.2\%$  for the 60, 90 and 120 mg treatment groups, respectively. A mean increase of  $7.2 \pm 19.5\%$  was noted in the placebo group. All pairwise comparisons of change from baseline to Week 4 for mean IGF-1 between each lanreotide treatment group and placebo were significant ( $p < 0.001$ ).

#### Mean GH $\leq$ 2.5 ng/mL AND Normalized IGF-1 (Age-adjusted)

The table below presents the proportion of patients in the ITT population with mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 (age-adjusted) at Week 4 including patients with missing data as non-responders. A significantly higher proportion of lanreotide-treated patients (13 of 83, 16%) had mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 at Week 4 as compared to placebo (0 of 25) ( $p = 0.033$ ). Across the lanreotide treatment groups, pairwise comparisons for the 120 mg and 90 mg groups vs. placebo were statistically significant for this parameter but the comparison of the 60 mg group vs. placebo was not significant. Similar results were noted for the ITT population when patients with missing data were excluded from the analysis and for the PP population.

**Table 10.1.1.13. Proportion of Patients with Mean GH  $\leq$  2.5 ng/mL and Normalized IGF-1 (Age-adjusted) at Week 4 by Dose as Randomized (ITT Population, Double-blind Phase)**

Treatment Group	Response	Odds Ratio	95% CI	p-value <sup>1</sup>
Lanreotide 60 mg (N = 27)	3/27 (11%)	3.838	0.394, 37.368	0.088
Lanreotide 90 mg (N = 27)	5/27 (19%)	6.276	0.695, 56.676	0.027
Lanreotide 120 mg (N = 29)	5/29 (17%)	5.471	0.587, 50.962	0.028
Lanreotide overall (N = 83)	13/83 (16%)	4.553	0.561, 36.946	0.033
Placebo (N = 25)	0/25 (0%)	NA	NA	NA

Note: missing values are included as non-responses in this tabulation; NA = not applicable; The odds ratio represents the increase in odds of a favorable response for each specific treatment group relative to placebo based on the logit approximation.

<sup>1</sup> P-value for comparing each lanreotide dose group against placebo using a Cochran-Mantel-Haenszel test.

Sponsor's Table 25, Module 5, Vol 53, pg. 96

### Acromegaly Symptoms

A higher proportion of patients treated with lanreotide showed improvements from baseline to Week 4 in headache (22% vs. 13%) and fatigue (30% vs. 13%) as compared to patients who received placebo during the double-blind phase. A higher proportion of females in the placebo group showed improvement in the symptoms of oligomenorrhea (1, 33%) as compared to lanreotide-treated patients (2, 10%). Twenty-five (30%) of lanreotide-treated and 9 (38%) of placebo-treated patients showed improvement in perspiration; twenty-five (30%) of lanreotide-treated and 8 (33%) of placebo-treated patients showed improvement in swelling of extremities; twenty-seven (33%) of lanreotide-treated and 8 (33%) of placebo-treated patients showed improvement in joint pain; and one (3%) of lanreotide-treated and 1 (8%) of placebo-treated patients showed improvement in impotence between baseline and Week 4.

### Analysis of Results for the Double/Single-blind Phases, ITT Population:

#### Decrease in mean GH of >50% from baseline

At Week 16, 72% of all 107 lanreotide-treated patients had a decrease from baseline in mean GH of >50% including 68% (23/34), 64% (23/36) and 84% (31/37) of patients in the 60, 90 and 120 mg lanreotide treatment groups, respectively. The differences between the treatment groups were not significant for the comparison of the 120 mg and 60 mg groups ( $p = 0.116$ ) or between the 90 mg and 60 mg groups ( $p = 0.742$ ), and was close to the nominal significance level for the comparison of the 120 mg and 90 mg groups ( $p = 0.056$ ). Results for this analysis were similar for the 2 regions; 71% and 72% of patients in the US and Europe/Hong Kong, respectively, had a mean decrease of >50% in GH between baseline and Week 16. Response rates were 67%, 69% and 77% for the 60, 90 and 120 mg treatment groups, respectively, in the US and 68%, 61% and 88%, respectively, in Europe/Hong Kong. Analysis of results from the PP population and the IIT population (excluding data from patients with missing week 16 results) revealed similar response rates.

#### GH $\leq$ 2.5 ng/mL

A total of 52 (49%) of the 107 lanreotide-treated patients had a GH level  $\leq$  2.5 ng/mL at Week 16 including 44%, 44% and 57% of patients in the 60, 90 and 120 mg treatment groups, respectively. No statistically significant differences were noted for any of the pairwise comparisons among the 3 active treatment groups ( $p \geq 0.279$ ) for this analysis. Similar results were noted for analysis of the Week 16 results for the ITT population excluding missing values and for the PP population. At Week 16, significant differences were noted between the regions

for the proportion of patients with mean GH  $\leq$  2.5 ng/mL across the treatment groups. In the US, the odds of responding to 90 mg were 4.8 times greater than that of responding to 60 mg. However, in Europe/Hong Kong the odds were reversed with the odds of responding to 60 mg 2.3 times greater than that of responding to 90 mg. As well, the odds ratios were reversed between the 2 regions for the comparison of the 120 mg and 60 mg treatment groups (greater than 1.0 for US, less than 1.0 for Europe/Hong Kong). It is unclear if the differences noted in this analysis between the 2 regions are due to the small samples sizes or to some unknown difference between the 2 populations.

**Table 10.1.1.14. Proportion of Patients with Mean GH  $\leq$  2.5 ng/mL at Week 16 by Dose as Randomized (ITT Population, Double/Single-blind Phase)**

Treatment Group	Response	Compared to:	Odds Ratio	95% CI	p-value <sup>1</sup>
Lanreotide 60 mg (N = 34)	15/34 (44%)	90 mg	1.013	0.407, 2.518	0.978
Lanreotide 90 mg (N = 36)	16/36 (44%)	120 mg	1.699	0.657, 4.392	0.279
Lanreotide 120 mg (N = 37)	21/37 (57%)	60 mg	1.620	0.649, 4.041	0.294
Lanreotide overall (N = 107)	52/107 (49%)	NA	NA	NA	NA

Note: missing values are included as non-responses in this tabulation; NA = not applicable; The odds ratio represents the increase in odds of a favorable response for each specific treatment group based on the Mantel-Haenszel estimation; odds ratios based on the higher dose to lower dose comparisons.

<sup>1</sup> P-value for the pairwise comparison among the lanreotide groups (60 vs. 90 mg, 90 vs. 120 mg and 120 vs. 60 mg) using a Cochran Mantel-Haenszel test, stratified by region (US vs. Europe + Hong Kong).

Sponsor's Table 20, Module 5, Vol 53, pg. 92

#### Mean GH Over Time on Study

Overall, mean GH decreased  $62.3 \pm 36.6\%$  from baseline to Week 16 among all lanreotide-treated patients; this change from baseline was statistically significant ( $p < 0.001$ ). Mean decreases of  $53.0 \pm 42.2\%$ ,  $61.0 \pm 32.3\%$  and  $72.1 \pm 33.0\%$  were noted for the 60, 90 and 120 mg treatment groups, respectively. The differences in the percent decrease from baseline were not statistically significant for comparison of the 60 and 90 mg groups or for comparison of the 90 and 120 mg groups. However, percent decrease from baseline to Week 16 in the 120 mg group was significantly greater compared to the 60 mg group ( $p = 0.022$ ). The mean decreases in GH observed at Week 16 support the persistent efficacy of all 3 dose levels of lanreotide, and suggests a trend for a dose-effect relationship on mean serum GH levels.

#### Normalized IGF-1 (Age-adjusted)

Overall, 58 (54%) of the 107 lanreotide-treated patients had normalization of IGF-1 at Week 16 including 56%, 53% and 54% of patients in the 60, 90 and 120 mg treatment groups, respectively. There were no statistically significant differences between the lanreotide treatment groups for this analysis ( $p \geq 0.799$ ). Similar results were noted for the ITT population when patients with missing data were excluded from the analysis and for the PP population. At Week 16, 55% and 54% of lanreotide-treated patients in the US and Europe/Hong Kong had normalized IGF-1.

**Table 10.1.1.15. Proportion of Patients with Normalized IGF-1 (Age-adjusted) at Week 16 by Dose as Randomized (ITT Population, Double/Single-blind Phase)**

Treatment Group	Response	Compared to:	Odds Ratio	95% CI	p-value <sup>1</sup>
Lanreotide 60 mg (N = 34)	19/34 (56%)	90 mg	0.886	0.350, 2.244	0.799
Lanreotide 90 mg (N = 36)	19/36 (53%)	120 mg	1.059	0.419, 2.675	0.905
Lanreotide 120 mg (N = 37)	20/37 (54%)	60 mg	0.930	0.369, 2.347	0.878
Lanreotide overall (N = 107)	58/107 (54%)	NA	NA	NA	NA

Note: missing values are included as non-responses in this tabulation; NA = not applicable; The odds ratio represents the increase in odds of a favorable response for each specific treatment group based on the Mantel-Haenszel estimation; odds ratios based on the higher dose to lower dose comparisons.

<sup>1</sup> P-value for the pairwise comparison among the lanreotide groups (60 vs. 90 mg, 90 vs. 120 mg and 120 vs. 60 mg) using a Cochran Mantel-Haenszel test, stratified by region (US vs. Europe + Hong Kong).

Sponsor's Table 23, Module 5, Vol 53, pg. 95

#### Mean IGF-1 Over Time on Study

Overall, mean IGF-1 decreased  $44.5 \pm 29.6\%$  from baseline to Week 16 among all lanreotide-treated patients; this change from baseline was statistically significant ( $p < 0.001$ ). The mean percent decrease observed in the 120 mg treatment group ( $54.4 \pm 19.4\%$ ) was significantly higher than that observed in the 60 mg group ( $32.3 \pm 38.0\%$ ) ( $p = 0.002$ ) but not significantly different from the 90 mg group ( $46.0 \pm 25.5\%$ ) ( $p = 0.232$ ). The difference between the 60 and 90 mg treatment groups for change from baseline to Week 16 in mean IGF-1 was close to the nominal significance level ( $p = 0.054$ ). Similar to the results for GH levels, these results suggest a trend for a dose-effect relationship on IGF-1 levels.

#### Mean GH $\leq$ 2.5 ng/mL AND Normalized IGF-1 (Age-adjusted)

Overall, a total of 41 (38%) of the 107 lanreotide-treated patients had mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 at Week 16 including 38%, 42% and 35% of patients in the 60, 90 and 120 mg treatment groups, respectively. The differences in these responses rates were not statistically significant for any of the pairwise comparisons ( $p \geq 0.576$ ). Similar results were noted for the ITT population when patients with missing data were excluded from the analysis and for the PP population.

**Table 10.1.1.16. Proportion of Patients with Mean GH  $\leq$  2.5 ng/mL and Normalized IGF-1 (Age-adjusted) at Week 16 by Dose as Randomized (ITT Population, Double/Single-blind Phase)**

Treatment Group	Response	Compare to:	Odds Ratio	95% CI	p-value <sup>1</sup>
Lanreotide 60 mg (N = 34)	13/34 (38%)	90 mg	1.142	0.451, 2.895	0.776
Lanreotide 90 mg (N = 36)	15/36 (42%)	120 mg	0.761	0.293, 1.973	0.576
Lanreotide 120 mg (N = 37)	13/37 (35%)	60 mg	0.876	0.335, 2.290	0.788
Lanreotide overall (N = 107)	41/107 (38%)	NA	NA	NA	NA

Note: missing values are included as non-responses in this tabulation; NA = not applicable; The odds ratio represents the increase in odds of a favorable response for each specific treatment group based on the Mantel-Haenszel estimation; odds ratios based on the higher dose to lower dose comparisons.

<sup>1</sup> P-value for the pairwise comparison among the lanreotide groups (60 vs. 90 mg, 90 vs. 120 mg and 120 vs. 60 mg) using a Cochran Mantel-Haenszel test, stratified by region (US vs. Europe + Hong Kong).

Sponsor's Table 26, Module 5, Vol 53, pg. 97

### Acromegaly Symptoms

Analysis of change from baseline in acromegaly symptoms revealed that the majority of patients in all treatment groups had stable symptoms or improvement between baseline and Week 16. Improvements associated with treatment were observed for perspiration (45% of patients improved), swelling of extremities (43% improved), joint pain (37% improved), fatigue (36% improved), and headache (27% improved). Improvements in impotence or oligomenorrhea were observed in 4% and 18% of patients, respectively. No apparent trend was noted for improvement in symptoms with increasing lanreotide dose. Worsening of headache, perspiration, fatigue, swelling of extremities and joint pain was observed in 8% or fewer of all patients over the 16 weeks. The proportion of patients with worsening of perspiration, fatigue and swelling of extremities increased with lanreotide dose.

### Analysis of Results for the Double/Single-blind + Open-label Phase, ITT Population: Decrease in mean GH of >50% from baseline

At entry into the dose-titration portion of the study (i.e., the open-label phase, Week 16), a total of 77 (73%) of 105 patients with data available had a decrease in mean GH of >50% from baseline. The proportion of patients with this level of response increased to 80% (82 of 103 patients) by Week 32 and to 82% (80 of 98 patients) by Week 52.

### GH ≤ 2.5 ng/mL

A total of 52 (50%) of 105 patients with data available had mean GH of ≤ 2.5 ng/mL at entry into the open-label phase (Week 16). The proportion of patients with this level of response increased to 57% (59 of 103 patients) by Week 32 and was maintained at 54% (53 of 98 patients) at Week 52. Evaluation of last value available on study revealed that 55 (51%) of the 107 patients had mean GH ≤ 2.5 ng/mL by the end of the study, including 95% (20 of 21 patients), 82% (14 of 17 patients) and 30% (21 of 69 patients) of patients whose last dose administered was 60, 90 or 120 mg, respectively. Similar results were noted for the PP population. At the end of the study a total of 39 (51%) of the 76 patients had mean GH ≤ 2.5 ng/mL, including 94% (15 of 16), 89% (8 of 9) and 31% (16 of 51) of patients whose last dose was 60, 90 or 120 mg of lanreotide acetate, respectively.

**Table 10.1.1.17. Proportion of Patients with Mean GH ≤ 2.5 ng/mL at Weeks 16, 32, 52 and LVA by Last Dose Administered (Missing Values Excluded) (ITT Population, Double/Single-blind Phase + Open-label Phase)**

Treatment Group	Week 16	Week 32	Week 52	LVA
Lanreotide 60 mg (N = 21)	21/21 (100%)	21/21 (100%)	20/21 (95%)	20/21 (95%)
Lanreotide 90 mg (N = 17)	12/15 (80%)	12/15 (80%)	12/13 (92%)	14/17 (82%)
Lanreotide 120 mg (N = 69)	19/69 (28%)	26/67 (39%)	21/64 (33%)	21/69 (30%)
Lanreotide overall (N = 107)	52/105 (50%)	59/103 (57%)	53/98 (54%)	55/107 (51%)

Note: Patients are grouped by the last dose level administered during the open-label phase; the denominator for percent is based on the number of patients available at each visit; missing values are excluded.  
 Sponsor's Table 21, Module 5, Vol 53, pg. 93

**Mean GH Over Time on Study**

Over all 107 lanreotide-treated patients included in the ITT population for the open-label phase, mean ( $\pm$ SD) percent decrease from baseline in mean serum GH was 62.3% ( $\pm$  36.6), 65.5% ( $\pm$  36.9) and 67.1% ( $\pm$  32.0) at Weeks 16, 32 and 52, respectively. All of these decreases from baseline were significant ( $p < 0.001$ ). Mean decreases from baseline were noted at Weeks 16, 32 and 52 in mean serum GH concentrations for all dose groups based on last dose administered during the study.

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**Table 10.1.1.18. Mean ( $\pm$  SD) GH at Baseline† and Mean Percent Decrease to Weeks 16, 32 and 52, and LVA by Last Dose Administered (ITT Population, Double/Single-blind + Open-label Phases)**

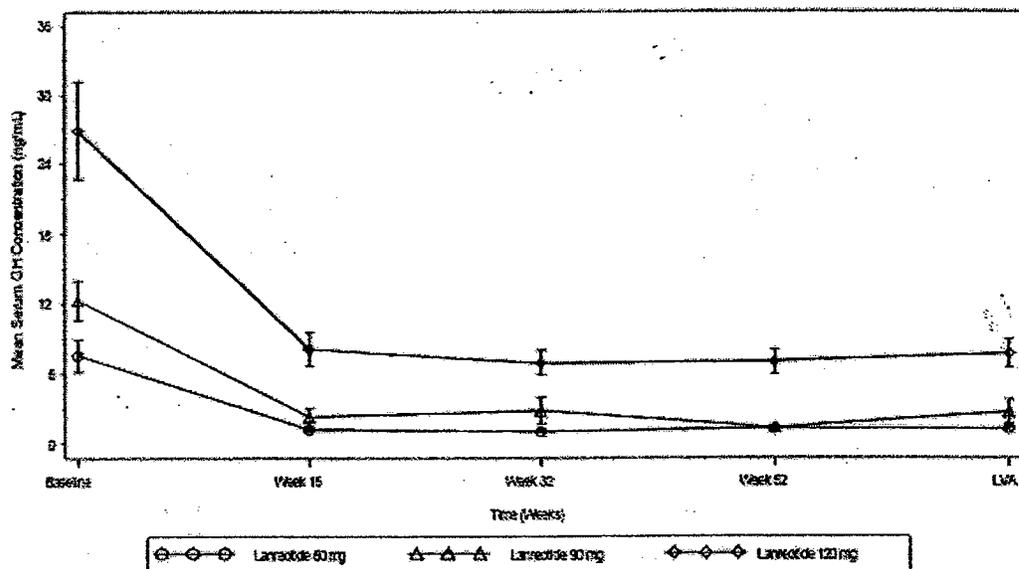
Treatment Group	GH (ng/mL)				
	Baseline	Percent Decrease to:			
		Week 16	Week 32	Week 52	LVA
Lanreotide 60 mg (N = 21)	7.6 $\pm$ 6.3	78.0 $\pm$ 15.9	81.0 $\pm$ 13.3	76.3 $\pm$ 17.7	76.3 $\pm$ 17.7
Lanreotide 90 mg (N = 17)	12.3 $\pm$ 7.0	73.6 $\pm$ 38.0	68.3 $\pm$ 50.3	85.4 $\pm$ 10.4	68.5 $\pm$ 49.0
Lanreotide 120 mg (N = 69)	26.9 $\pm$ 35.2	55.1 $\pm$ 38.9	60.0 $\pm$ 37.4	60.4 $\pm$ 36.2	57.2 $\pm$ 39.2
Lanreotide overall (N = 107)	20.8 $\pm$ 29.7	62.3 $\pm$ 36.6*	65.5 $\pm$ 36.9*	67.1 $\pm$ 32.0*	62.7 $\pm$ 38.4*

\*  $P < 0.001$  for comparison of the change from baseline in all lanreotide-treated patients.

Sponsor's Table 30, Module 5, Vol 53, pg. 102

† The baseline GH concentrations were similar across the treatment groups at the start of the study. Median and mean ( $\pm$  SD) serum GH level at baseline for the double-blind study phase were 9.9 and 19.8 ( $\pm$  29.3) ng/mL, respectively, across all 108 patients; the median varied across the treatment groups from 8.6 ng/mL in the lanreotide acetate 120 mg group to 11.5 ng/mL in the lanreotide acetate 60 mg group. However, Table 10.1.1.18. shows the baseline for the groups as they were redistributed by the end of the study. By study end, more patients were in the 120 mg group and this group had higher baseline GH and IGF values than the patients in the 60 mg group at the end of the study.

**Figure 10.1.1.1. Mean ( $\pm$  SEM) for Mean Serum GH Levels (ng/mL) at Weeks 16, 32 and 52, and LVA by Last Dose Administered (ITT Population, Double/Single-blind + Open-label Phases)**



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Sponsor's Figure 9, Module 5, Vol 53, pg. 102

#### Normalized IGF-1 (Age-adjusted)

At baseline, a total of 9 (8%) of the 107 ITT patients had normalized IGF-1. At entry into the open-label phase (Week 16), a total of 58 (55%) of 105 patients with data available had normalized IGF-1. The proportion of patients with this level of response was maintained at 55% (57 of 103 patients) at week 32 and was increased to 59% (58 of 98 patients) at week 52. Evaluation of the last value available on study revealed that 57% of patients (61 of 107 patients) had normalized (age-adjusted) IGF-1 by the end of the study, including 95% (20 of 21 patients), 71% (12 of 17 patients) and 42% (29 of 69 patients) of patients whose last dose administered was 60, 90 or 120 mg, respectively.

**Table 10.1.19. Proportion of Patients with Normalized IGF-1 (Age-adjusted) at Weeks 16, 32, 52 and LVA by Last Dose Administered (Missing Values Excluded) (ITT Population, Double/Single-blind Phase + Open-label Phase)**

Treatment Group	Week 16	Week 32	Week 52	LVA
Lanreotide 60 mg (N = 21)	21/21 (100%)	21/21 (100%)	20/21 (95%)	20/21 (95%)
Lanreotide 90 mg (N = 17)	12/15 (80%)	13/15 (87%)	11/13 (85%)	12/17 (71%)
Lanreotide 120 mg (N = 69)	25/69 (36%)	23/67 (34%)	27/64 (42%)	29/69 (42%)
Lanreotide overall (N = 107)	58/105 (55%)	57/103 (55%)	58/98 (59%)	61/107 (57%)

Note: Patients are grouped by the last dose level administered during the open-label phase; the denominator for percent is based on the number of patients available at each visit; missing values are excluded.

Sponsor's Table 24, Module 5, Vol 53, pg. 95

#### Mean IGF-1 Over Time on Study

Over all 107 lanreotide-treated patients included in the ITT population for the open-label phase, mean ( $\pm$  SD) percent decrease from baseline in mean serum IGF-1 was 44.5% ( $\pm$  29.6%), 48.0%

(± 27.1) and 48.9% (± 28.6) at Weeks 16, 32 and 52, respectively. All of these decreases from baseline were significant ( $p < 0.001$ ).

Mean GH  $\leq$  2.5 ng/mL AND Normalized IGF-1 (Age-adjusted)

At entry into the dose-titration portion of the study (i.e., Week 16, the open-label phase), a total of 41 (39%) of 105 patients with data available had mean GH  $\leq$  2.5 ng/mL and normalized IGF-1. The proportion of patients with this level of response was increased to 45% (46 of 103 patients) at Week 32 and decreased to 43% (42 of 98 patients) at Week 52. Analysis of last value available on study revealed that 43 (41%) of the 106 patients with data available had mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 by the end of the study, including 90% (19 of 21 patients), 65% (11 of 17 patients) and 19% (13 of 68 patients) of patients whose last dose administered was 60, 90 or 120 mg, respectively. Similar results were noted for the PP population.

**Table 10.1.1.20. Proportion of Patients with Mean GH  $\leq$  2.5 ng/mL and Normalized IGF-1 (Age-adjusted) at Weeks 16, 32, 52 and LVA by Last Dose Administered (Missing Values Excluded) (ITT Population, Double/Single-blind Phase + Open-label Phase)**

Treatment Group	Week 16	Week 32	Week 52	LVA
Lanreotide 60 mg (N = 21)	21/21 (100%)	21/21 (100%)	19/21 (90%)	19/21 (90%)
Lanreotide 90 mg (N = 17)	11/15 (73%)	11/15 (73%)	10/13 (77%)	11/17 (65%)
Lanreotide 120 mg (N = 69)	9/69 (13%)	14/67 (21%)	13/64 (20%)	13/68 (19%)
Lanreotide overall (N = 107)	41/105 (39%)	46/103 (45%)	42/98 (43%)	43/106 (41%)

Note: Patients are grouped by the last dose level administered during the open-label phase; the denominator for percent is based on the number of patients available at each visit; missing values are excluded.  
 Sponsor's Table 27, Module 5, Vol 53, pg. 98

*Reviewer Comment: The sponsor's efficacy analysis uses the GH and IGF-1 values from Weeks 16, 32, 52 and LVA by Last Dose Administered. In contrast, the Sandostatin LAR NDA used the average of the serum GH and IGF-1 obtained over the entire treatment period. The Sandostatin NDA 21-008 describes 2 clinical trials of ~2 years in duration and 1 trial one year in duration with monthly levels of GH and IGF-1. It is reasonable to average all post-baseline GH and IGF-1 levels to reflect the efficacy of the drug to hormonally control the disease over the entire treatment period. However, in Study 717 the dose was fixed until Week 16 when dose titration was allowed based on the patient's GH and IGF-1 level. GH and IGF-1 levels were not measured monthly, as in the Sandostatin trials, but at Weeks 4, 13, 14, 15, 16, 32 and 52. This reviewer does not believe an analysis using average values during the duration of this trial is necessary due to the fixed dose for the first 16 weeks followed by dose titration based on patient response for the remainder of the trial. Furthermore, 41/105 (39%) of the subjects at Week 16, 46/103 (45%) of the subjects at Week 32, and 42/98 (43%) of the subjects at Week 52 had achieved a Mean GH  $\leq$  2.5 ng/mL and Normalized IGF-1, suggesting that efficacy was reasonably maintained during the trial. The sponsor was asked to provide the data for the additional weeks (Week #4, 13, 14, and 15 to ensure that the effect was consistent. The results are described below:*

Table 10.1.1.21. Average GH and IGF-1 Values over the course of study E-28-52030-717

Week	Visit	Average GH Value at Visit (N)	Average IGF-1 Value at Visit (N)	GH<2.5 ng/mL n/N (%)	IGF-1 normal n/N (%)	GH<2.5 ng/mL + IGF-1 normal n/N (%)
4	4	11.307 (107)	576.96 (107)	28/107 (26.17)	22/107 (20.56)	13/107 (12.15)
13	7	5.04 (104)	380.53 (104)	55/104 (52.88)	61/104 (58.65)	44/104 (42.31)
14	8	5.23 (104)	387.73 (104)	55/104 (52.88)	57/104 (54.80)	42/104 (40.38)
15	9	6.04 (102)	394.91 (101)	55/102 (53.92)	58/101 (57.42)	44/101 (43.56)
16	10	5.93 (105)	406.98 (105)	52/105 (49.52)	58/105 (55.24)	41/105 (39.05)
32	14	5.16 (103)	383.60 (102)	59/103 (57.28)	57/102 (55.88)	46/102 (45.10)
52	19	5.05 (98)	367.76 (98)	53/98 (54.08)	59/98 (60.20)	43/98 (43.88)

- Average GH, average IGF-1, GH<2.5 and IGF-1 normal denominator is patients who have had an assessment  
 - GH<2.5 with IGF-1 denominator is the number of patients who have had both assessments

Efficacy results in terms of treatment-naïve and non-treatment-naïve patient populations: The sponsor was asked by this reviewer to present the efficacy results separately for treatment-naïve and non-treatment-naïve populations (as requested in the 6 July 2004 pre-NDA meeting for lanreotide acetate). The sponsor reanalyzed the data for Study 717 separately for the three populations as defined in the clinical protocol: treatment "Naïve" (Naïve); not treated within three months prior to study entry; and previously treated (non-treatment naïve). These populations are further defined below:

- Naïve - not previously treated with somatostatin or SSA but may have had surgery and/or radiotherapy and/or other medication;
- Not treated within the 3 months prior to study entry - any previous treatment with somatostatin or SSA was to be stopped within 3 months of study entry to provide successful washout/active disease at study baseline;
- Previously Treated - previous treatment with somatostatin or SSA that was confirmed ongoing at baseline (Visit 1).

Due to the relatively small number of patients in these subpopulations reanalyses of the study 717 efficacy data by region (e.g. US, EU, Hong Kong), as performed for the overall population of patients in the clinical study report, were not done.

For the primary endpoint in study 717, the proportion of patients with a greater than 50% decrease in mean GH from baseline, the results were similar in all patient subpopulations.

Similar results were seen for a median reduction in mean GH. For all other efficacy parameters, there was a general trend towards a higher response rate within the previously treated population compared to the naive (not previously treated with somatostatin or SSA but may have had surgery and/or radiotherapy and/or other medication) patient group.

**Table 10.1.1.22 Revised Efficacy Data for Study 717: All Doses from Last Value Available (LVA) by Previous Somatostatin Analog History**

Endpoint	Measurement	Naive	Not treated within 3 months	Previously treated
<b>GH[a]</b>				
>30% reduction	%	13/15 (86.7)	25/39 (64.1)	42/51 (82.4)
≤5.0 ng/mL	n/N (% of patients)	8/15 (53.3)	23/39 (59.0)	43/51 (84.3)
≤2.5 ng/mL	n/N (% of patients)	5/15 (33.3)	15/39 (38.5)	35/51 (68.6)
≤1.0 ng/mL[b]	n/N (% of patients)	0/15 (0)	6/39 (15.4)	11/51 (21.6)
Median GH	ng/mL	3.29	3.17	1.91
Median % change in GH [c]	%	68.6	78.0	74.9
<b>IGF-1</b>				
Normal	n/N (% of patients)	6/15 (40.0)	19/39 (48.7)	36/51 (70.6)
Median IGF-1	ng/mL	450.0	392.0	259.0
Median % change in IGF-1 [b]	%	44.8	52.5	58.6
<b>IGF-1 normal + mean GH ≤2.5 ng/mL</b>	n/N (% of patients)	3/15 (20.0)	13/39 (33.0)	28/51 (54.9)

(a) GH is reported as a mean of at least five GH values (ng/mL)  
 (b) Not part of original 717 efficacy analyses, added for comparison across pivotal efficacy studies  
 (c) % change reduction from baseline

Table 10.1.1.23 illustrates mean GH levels by treatment group and previous somatostatin analog history.

**Table 10.1.1.23 Mean GH levels by Treatment Group and Previous Somatostatin Analog History**

		Naive			Not Treated Within 3 months			Previously Treated		
		≤5 ng/ml	≤2.5 ng/ml	≤1 ng/ml	≤5 ng/ml	≤2.5 ng/ml	≤1 ng/ml	≤5 ng/ml	≤2.5 ng/ml	≤1 ng/ml
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline	Placebo	0/3 (0)	0/3 (0)	0/3 (0)	0/7 (0)	0/7 (0)	0/7 (0)	7/14 (50.0)	0/14 (0)	0/14 (0)
	Lanreotide	0/12 (0)	0/12 (0)	0/12 (0)	0/32 (0)	0/32 (0)	0/32 (0)	17/38 (44.7)	0/38 (0)	0/38 (0)
Week 4	Placebo	0/3 (0)	0/3 (0)	0/3 (0)	1/7 (14.3)	0/7 (0)	0/7 (0)	2/14 (14.3)	0/14 (0)	0/14 (0)
	Lanreotide	5/12 (41.7)	4/12 (33.3)	1/12 (8.3)	14/32 (43.8)	7/32 (21.9)	2/32 (6.3)	29/38 (76.3)	17/38 (44.7)	1/38 (2.6)
Week 16	Lanreotide	8/15 (53.3)	7/15 (46.7)	2/15 (13.3)	21/39 (53.8)	13/39 (33.3)	1/39 (2.6)	42/51 (82.4)	32/51 (62.7)	12/51 (23.5)
Week 32	Lanreotide	10/15 (66.7)	7/15 (46.7)	3/15 (20.0)	25/39 (64.1)	17/39 (43.6)	3/39 (7.7)	41/49 (83.7)	35/49 (71.4)	12/49 (24.5)
Week 52	Lanreotide	7/14 (50.0)	4/14 (28.6)	0/14 (0)	23/36 (63.9)	15/36 (41.7)	6/36 (16.7)	41/48 (85.4)	34/48 (70.8)	11/48 (22.9)
LVA	Lanreotide	8/15 (53.3)	5/15 (33.3)	0/15 (0)	23/39 (59.0)	15/39 (38.5)	6/39 (15.4)	43/51 (84.3)	35/51 (68.6)	11/51 (21.6)

Table 10.1.1.24 illustrates IGF-1 normal by treatment group and previous somatostatin analog history.

**Table 10.1.1.24 IGF-1 Normal by Treatment Group and Previous Somatostatin Analog History**

		Naive (n/N) (%)		Not Treated Within 3 months (n/N) (%)		Previously Treated (n/N) (%)	
Baseline	Placebo	0/3	(0)	1/7	(14.3)	0/14	(0)
	Lanreotide	0/12	(0)	2/32	(6.3)	6/38	(15.8)
Week 4	Placebo	0/3	(0)	0/7	(0)	0/14	(0)
	Lanreotide	1/12	(8.3)	5/32	(15.6)	15/38	(39.5)
Week 16	Lanreotide	7/15	(46.7)	14/39	(35.9)	36/51	(70.6)
Week 32	Lanreotide	5/15	(33.3)	17/39	(43.6)	34/49	(69.4)
Week 52	Lanreotide	5/14	(35.7)	19/36	(52.8)	34/48	(70.8)
LVA	Lanreotide	6/15	(40.0)	19/39	(48.7)	36/51	(70.6)

Table 10.1.1.25 illustrates IGF-1 normal with mean GH level  $\leq 2.5$  by treatment group and previous somatostatin analog history.

Table 10.1.1.25 IGF-1 normal with Mean GH level  $\leq 2.5$  by Treatment Group and Previous Somatostatin Analog History

		Naive (n/N) (%)		Not Treated Within 3 months (n/N) (%)		Previously Treated (n/N) (%)	
Baseline	Placebo	0/0	(N/A)	0/0	(N/A)	0/0	(N/A)
	Lanreotide	0/0	(N/A)	0/0	(N/A)	0/0	(N/A)
Week 4	Placebo	0/0	(N/A)	0/0	(N/A)	0/0	(N/A)
	Lanreotide	1/4	(25.0)	4/7	(57.1)	8/17	(47.1)
Week 16	Lanreotide	6/7	(85.7)	8/13	(61.5)	27/32	(84.4)
Week 32	Lanreotide	4/7	(57.1)	13/17	(76.5)	29/35	(82.9)
Week 52	Lanreotide	2/4	(50.0)	13/15	(86.7)	28/34	(82.4)
LVA	Lanreotide	3/5	(60.0)	13/15	(86.7)	28/35	(80.0)

#### Acromegaly Symptoms

The table below presents change from baseline in the symptoms of acromegaly to Weeks 16, 32 and 52 and to the last value available during the study for all lanreotide-treated patients.

Table 10.1.1.26. Change from Baseline to Weeks 16, 32, 52 and LVA in Acromegaly Symptoms Across All Lanreotide-Treated Patients (ITT Population, Double/Single-blind + Open-label Phases)

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Symptom	Change to:			
	Week 16 (N = 105)	Week 32 (N = 103)	Week 52 (N = 99)	LVA (N = 106)
Headache				
Improved	28 (27%)	29 (28%)	30 (30%)	37 (35%)
Stable	70 (67%)	64 (62%)	57 (58%)	57 (54%)
Worsened	7 (7%)	10 (10%)	12 (12%)	12 (11%)
Perspiration				
Improved	47 (45%)	49 (48%)	45 (45%)	46 (43%)
Stable	51 (49%)	48 (47%)	48 (48%)	50 (47%)
Worsened	7 (7%)	6 (6%)	6 (6%)	10 (9%)
Fatigue				
Improved	38 (36%)	35 (34%)	34 (34%)	34 (32%)
Stable	59 (56%)	52 (50%)	55 (56%)	61 (58%)
Worsened	8 (8%)	16 (16%)	10 (10%)	11 (10%)
Swelling of extremities				
Improved	45 (43%)	48 (47%)	47 (47%)	50 (47%)
Stable	52 (50%)	50 (49%)	47 (47%)	50 (47%)
Worsened	8 (8%)	5 (5%)	5 (5%)	6 (6%)
Joint pain				
Improved	39 (37%)	39 (38%)	40 (40%)	43 (41%)
Stable	58 (55%)	49 (48%)	47 (47%)	50 (47%)
Worsened	8 (8%)	15 (15%)	12 (12%)	13 (12%)
Impotence <sup>1</sup>				
Improved	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Stable	43 (90%)	42 (89%)	39 (85%)	40 (85%)
Worsened	3 (6%)	4 (9%)	5 (11%)	5 (11%)
Oligomenorrhea <sup>2</sup>				
Improved	4 (18%)	3 (14%)	3 (16%)	3 (14%)
Stable	16 (73%)	16 (76%)	16 (84%)	19 (86%)
Worsened	2 (9%)	2 (10%)	0	0

1 Reported for males in the ITT population with data available: N = 48, 47, 46 and 47 for weeks 16, 32, 52 and LVA, respectively.

2 Reported for females in the ITT population with data available: N = 22, 21, 19 and 22 for weeks 16, 32, 52 and LVA, respectively.

Sponsor's Table 36, Module 5, Vol 53, pg. 111

### Efficacy Conclusions:

- GH  $\leq$  2.5 ng/mL and normalized IGF-1

A total of 13 out of 83, (16%) of lanreotide-treated patients had a mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 at Week 4. A total of 41 (38%) of the 107 lanreotide-treated patients had mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 at Week 16 including 38%, 42% and 35% of patients in the 60, 90 and 120 mg treatment groups, respectively. Analysis of the last value available on study showed 41% of patients had both mean serum GH level  $\leq$  2.5 ng/mL and normalized (age-adjusted) IGF-1 at the end of the study.

- Acromegaly Symptoms  
Symptoms of acromegaly improved between baseline and Week 16 including

45%, 43%, 37%, 36% and 27% of patients with improvement in perspiration, swelling of extremities, joint pain, fatigue and headaches, respectively. Fewer patients showed improvements in impotence or oligomenorrhea. No apparent trend was noted for improvement in acromegaly symptoms with increasing lanreotide dose. By the end of the study (LVA), the acromegaly symptoms of headache, perspiration, fatigue, swelling of extremities, and joint pain had improved from baseline or were stable in 88% to 94% of patients.

- In the majority of eligible patients, the last dose of lanreotide administered during the dose titration phase was titrated to a higher level, including 42 (62%) of 68 patients who had received 60 or 90 mg during the double/single-blind phase. Very few patients were titrated to a lower dose by the end of the study [12 (17%) of 71 patients who had received 90 or 120 mg during the double/single-blind phase].

#### Safety Data:

##### *Deaths*

There were no deaths reported during the study.

##### *Serious Adverse Events*

A total of 18 (17%) of the 107 patients experienced at least one serious adverse event during lanreotide treatment including 4 (9%) of 46 patients during treatment with 60 mg, 8 (12%) of 66 patients during treatment with 90 mg and 8 (11%) of 74 patients during treatment with 120 mg. One (4%) patient (732.0003) experienced a serious adverse event of hepatic neoplasm during treatment with placebo in the double-blind phase. The most commonly reported type of event was neoplasm reported in 7 patients overall, including one patient during placebo treatment and 6 during treatment with lanreotide (3 each during treatment with 90 and 120 mg) (see table below for details). Other commonly reported serious events during lanreotide treatment were pathological fracture and depression aggravated, each reported in 2 patients. Other SAEs included anemia and atrial fibrillation (Pt. 731.0006); deep venous thrombosis; congestive heart failure; pancreatitis; diabetic nephropathy; complete bowel obstruction (this pt., #701.0032, also had an SAE of aggravated depression); complete heart block requiring pacemaker in a patient with history of CHF, RBBB, and bradycardia (701.0001); myocardial infarction; and aggravated hypertension with hypoglycemia. One serious event, pancreatitis associated with gallbladder lithiasis migration, was judged to be related to study treatment by the investigator. Patient 717.0002, randomized to receive 60 mg lanreotide, experienced pancreatitis of moderate intensity during open-label treatment with 60 mg at Week 29. The event was assessed as probably related to treatment with lanreotide and the patient recovered within ~3 weeks following cholecystectomy for gallbladder lithiasis. This is the only subject (717.0002) that required a cholecystectomy during the course of Study 717.

**Table 10.1.1.27. Patient Listing of Neoplasms Reported as Serious Adverse Events during the Study (Safety Population, Double/Single-blind and Open-label Phases)**

Pt ID	Verbatim/Preferred Term	Severity	Relation-ship	Action on Study Drug	Outcome	Onset of AE/ Study Day	Duration	Treatment Required
<b>Placebo group</b>								
732.0003	Solitary nodule within the liver, suspicious for focal nodular hyperplasia/hepatic neoplasm <sup>1</sup>	NA	None	Not applicable	Not yet recovered	0 (Week 0)	Ongoing	No
<b>90 mg group</b>								
701.0030	Metastatic adenocarcinoma of right lung (originally small (R) pleural effusion on final visit ultrasound)/adenocarcinoma NOS	Severe	None	Not applicable	Not yet recovered	419 (Wk 59)	Ongoing	Yes
713.0006	Pituitary adenoma for acromegaly /pituitary neoplasm benign	NA	None	Not applicable	Recovered without sequelae	136 (Wk 19)	77 days	Yes
715.0001	Thyroid carcinoma/thyroid neoplasm malignant	Severe	None	Discontinued	Not yet recovered	72 (Wk 10)	Ongoing	No
<b>120 mg group</b>								
701.0015	Growth of pre-existing meningioma causing status epilepticus and requiring craniotomy and resection/brain neoplasm NOS	Severe	None	Discontinued	Recovered with sequelae	145 (Wk 20)	14 days	Yes
713.0005	Trans-rhinoseptal pituitary surgery for pituitary adenoma/pituitary neoplasm benign	Moderate	None	Not applicable	Recovered without sequelae	373 (Wk 53)	9 days	No
732.0007	Operation for left ovarian dermoid cyst/teratoma benign	NA	None	Continued	Recovered without sequelae	325 (Wk 46)	8 days	No

NA = not available

1 Event was reported during the double-blind period. Pt was on placebo when solid liver nodule was diagnosed. Sponsor's Table 51, Module 5, Vol 53, pg. 144

*Adverse Events that Led to study Withdrawal*

*Placebo-Controlled Double-Blind Phase (Week 0-4)*

None of the patients withdrew from the double-blind study phase due to treatment-emergent adverse events. Patient 711.0004, randomized to receive placebo during the double-blind phase, withdrew from the study 3 days after receiving an injection of placebo due to a severe headache that had started 3 days prior to the placebo injection and was considered a non-treatment-emergent headache. This patient did not enter the single-blind study phase.

*Single-Blind Phase (Week 4-16)*

Two patients withdrew from the single-blind study phase due to treatment-emergent adverse events; both patients were in the 90 mg lanreotide treatment group:

1. Patient 703.0001 fell and fractured her left femur and experienced rib pain secondary to the fall on Study Day 102 (Week 14); the patient was hospitalized for treatment of the fracture. At that time the patient was diagnosed with mild leukocytosis, cardiomegaly, and hypercalcemia, as well as a probable hiatal hernia. She underwent surgery for the fracture and post-operatively developed pain at the incision, constipation and a urinary tract infection. She was discontinued from the study due to these events. The patient had received 4 injections of lanreotide acetate 90 mg prior to discontinuation.
2. Patient 715.0001 was diagnosed with thyroid carcinoma on Study Day 72 (Week 10); he was discontinued from the study at that time due to this event. The patient had received 3 injections of lanreotide acetate 90 mg prior to discontinuation.

*Open-Label Phase (Week 16-52)*

Two additional patients withdrew from the study during the open-label phase including one patient during treatment with 90 mg and one during treatment with 120 mg:

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3. Patient 713.0008, with a history of diabetes mellitus and diabetic polyneuritis, developed diabetic nephropathy at Week 23 during treatment with 90 mg. Peripheral edema and albuminuria were present. At the time of discontinuation from the study this patient had received one injection of placebo and 9 lanreotide injections including 4 at 60 mg and 5 at 90 mg.
4. Patient 701.0015 required a craniotomy and resection of a pre-existing parietal meningioma that progressed during the study causing status epilepticus. The growth of the brain neoplasm led to discontinuation from the study. At the time of discontinuation from the study this patient had received 6 injections of lanreotide acetate, all at 120 mg.

Thus, a total of four patients withdrew from the study due to treatment-emergent adverse events, including 3 patients during treatment with 90 mg and one during treatment with 120 mg. This reviewer believes it is unlikely that lanreotide caused the event that led to the withdrawals. Of note, 4 additional patients (#707.0005, 711.0008, 713.0006, and 724.0003) withdrew due to a lack of efficacy.

*Treatment Emergent Adverse Events during the Placebo-Controlled Double-Blind Phase (Weeks 0-4)*

A total of 50 (60%) of the 83 patients in the 3 lanreotide treatment groups experienced at least one adverse event during the double-blind study phase compared to 9 (36%) of the 25 patients in the placebo group. The incidence of any adverse event across lanreotide dose groups during the double-blind phase was 41%, 70% and 69% for the 60, 90 and 120 mg groups, respectively.

**Table 10.1.1.28. Number and Percent of Patients Reporting Treatment-emergent Adverse Events during the Double-blind Phase within each WHOART Body System by Dose as Randomized (Safety Population, Double-blind Phase)**

Body System	Lanreotide Autogel:				Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)	Overall (N = 83)		
Any adverse event	11 (41%)	19 (70%)	20 (69%)	50 (60%)	9 (36%)	59 (55%)
Gastrointestinal	4 (15%)	12 (44%)	14 (48%)	30 (36%)	1 (4%)	31 (29%)
Metabolic & nutritional	4 (15%)	5 (19%)	4 (14%)	13 (16%)	3 (12%)	16 (15%)
Heart rate & rhythm	3 (11%)	2 (7%)	3 (10%)	8 (10%)	0	8 (7%)
Red blood cell	1 (4%)	4 (15%)	1 (3%)	6 (7%)	0	6 (6%)
Application site	1 (4%)	1 (4%)	3 (10%)	5 (6%)	0	5 (5%)
Body as a whole	1 (4%)	0	1 (3%)	2 (2%)	2 (8%)	4 (4%)
Centr & periph nervous	0	1 (4%)	2 (7%)	3 (4%)	1 (4%)	4 (4%)
Liver & biliary	1 (4%)	1 (4%)	1 (3%)	3 (4%)	1 (4%)	4 (4%)
Cardiovascular	1 (4%)	0	1 (3%)	2 (2%)	2 (8%)	4 (4%)
Musculoskeletal	1 (4%)	1 (4%)	0	2 (2%)	1 (4%)	3 (3%)
Skin & appendages	0	2 (7%)	1 (3%)	3 (4%)	0	3 (3%)
Urinary	0	2 (7%)	0	2 (2%)	1 (4%)	3 (3%)
Psychiatric	0	0	2 (7%)	2 (2%)	0	2 (2%)
Respiratory	1 (4%)	1 (4%)	0	2 (2%)	0	2 (2%)
Vascular (extracardiac)	0	1 (4%)	0	1 (1%)	1 (4%)	2 (2%)
Hearing	0	0	0	0	1 (4%)	1 (1%)
Vision	0	0	1 (3%)	1 (1%)	0	1 (1%)
White cell and RES	0	0	1 (3%)	1 (1%)	0	1 (1%)

Source: Applicant's Table 8.1A1

Note: percents are based on the total number of patients included in the safety population within a treatment group or overall.

The most common adverse events (by body system) reported during the double-blind study phase were gastrointestinal disorders. Gastrointestinal events occurred at a higher frequency in lanreotide-treated patients (30 of 83, 36%) compared to placebo-treated patients (1 of 25, 4%). Gastrointestinal events were also more likely to occur in patients who received 120 mg (14 of 29 patients, 48%) and 90 mg (12 of 27, 44%) of lanreotide acetate compared to those patients who received 60 mg (4 of 27, 15%). The most commonly reported events (by preferred term) during the double-blind phase (weeks 0 to 4) were diarrhea (31% vs. 0% of lanreotide-treated and placebo-treated patients, respectively), abdominal pain (7% vs. 4%), bradycardia (8% vs. 0%), weight decrease (8% vs. 0%), anemia (7% vs. 0%) and flatulence (6% vs. 0%). Among these commonly reported events, diarrhea and flatulence exhibited an increased incidence across lanreotide dose. The table below presents the number and percent of patients reporting the most commonly occurring ( $\geq 5\%$  overall incidence) treatment-emergent adverse events by preferred term.

**Table 10.1.1.29. Most Commonly ( $\geq 5\%$ ) Reported Treatment-emergent Adverse Events During the Double-blind Phase by Dose as Randomized and Preferred Term (Safety Population, Double-blind Phase)**

Preferred Term	Lanreotide Autogel:				Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)	Overall (N = 83)		
Diarrhoea	3 (11%)	10 (37%)	13 (45%)	26 (31%)	0	26 (24%)
Abdominal pain	2 (7%)	2 (7%)	2 (7%)	6 (7%)	1 (4%)	7 (6%)
Bradycardia	3 (11%)	2 (7%)	2 (7%)	7 (8%)	0	7 (6%)
Weight decrease	2 (7%)	4 (15%)	1 (3%)	7 (8%)	0	7 (6%)
Anaemia	1 (4%)	4 (15%)	1 (3%)	6 (7%)	0	6 (6%)
Flatulence	0	2 (7%)	3 (10%)	5 (6%)	0	5 (5%)

Sponsor's Table 45, Module 5, Vol 53, pg. 126

Heart rate and rhythm disturbances were more frequently reported in lanreotide-treated patients (8 of 83, 10%) as compared to placebo-treated patients (0 of 25). No increased incidence with lanreotide dose was noted for heart rate and rhythm disturbances (11%, 7%, and 10% for the 60, 90 and 120 mg groups, respectively). Bradycardia was the most commonly reported event within this body system occurring in 11%, 7%, 7% and 0% of patients in the lanreotide 60 mg, 90 mg and 120 mg groups, and the placebo group, respectively.

Application site disorders occurred in 5 (6%) of the 83 lanreotide-treated patients compared to none of the 25 placebo-treated patients. The incidence of application site disorders was highest in the lanreotide 120 mg group (3 of 29 patients, 10%) compared to the 60 mg (1 of 27, 4%) and 90 mg (1 of 27, 4%) treatment groups. Events reported in this body system included injection site mass, injection site pain and injection site reaction each reported in 2 lanreotide-treated patients during the double-blind study phase.

The majority of adverse events reported during the double-blind phase were mild to moderate in severity. Seven patients in the double-blind phase (weeks 0 to 4), including 5 (6%) of 83 lanreotide-treated patients and 2 (8%) of 25 placebo-treated patients, experienced adverse events

judged to be severe in intensity by the investigator. A brief summary of these seven severe events is provided below:

- (1) Worsening bradycardia, assessed as severe in intensity and possibly treatment related, was reported in Patient 701.0001 in the lanreotide 60 mg group at week 4. The event was reported as resolved after completion of the single-blind phase. This patient completed the study through visit 19 (Week 52). The patient's heart rate at baseline was 58 beats/minute (bpm) with a decrease to 37 bpm at week 4; by week 16 the patient's heart rate had increased to 46 bpm and by week 52, to 69 bpm.
- (2) Patient 701.0006 in the lanreotide 90 mg group had severe peripheral ischemia (verbatim term: 'Raynaud-like phenomenon') reported; the event was assessed as possibly related to study treatment. This patient completed the study through visit 19 (Week 52). Peripheral ischemia was reported as ongoing at last assessment.
- (3) Patient 701.0032 in the lanreotide 90 mg group had severe weight decrease report at Week 0 that was ongoing during the study; the event was assessed as unrelated to study treatment. This patient completed the study through visit 19 (Week 52).
- (4) Severe diarrhea, assessed as probably related to study treatment, was reported in Patient 724.0003 in the lanreotide 120 mg group one day after the first dose of study medication; the severe diarrhea was resolved the following day. The patient discontinued the study during the open-label dose-titration phase due to lack of efficacy; the last visit attended was visit 14 (Week 32).
- (5) Severe diarrhea and headache, assessed as probably related to study treatment, were reported on the day of the first dose of lanreotide 120 mg in Patient 734.0008; both events were reported as resolved the following day. This patient completed the study through visit 19 (Week 52).
- (6) In the placebo group, severe carpal tunnel syndrome was reported in Patient 701.0018.
- (7) In the placebo group, severe headache was reported in Patient 704.0003.

*AEs During the Double/Single-Blind Phase (Weeks 0-16)*

The table below presents the number and percent of patients reporting the most commonly occurring ( $\geq 5\%$  overall incidence) treatment-emergent adverse events by preferred term.

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**Table 10.1.1.30. Most Commonly ( $\geq 5\%$ ) Reported Treatment-emergent Adverse Events During the Double/Single-blind Phases by Dose as Randomized and Preferred Term (Safety Population, Double/Single-blind Phase)**

Preferred term	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 34)	90 mg (N = 36)	120 mg (N = 37)	
Diarrhoea	9 (26%)	15 (42%)	24 (65%)	48 (45%)
Abdominal pain	3 (9%)	6 (17%)	7 (19%)	16 (15%)
Cholelithiasis	5 (15%)	6 (17%)	3 (8%)	14 (13%)
Bradycardia	6 (18%)	2 (6%)	2 (5%)	10 (9%)
Anaemia	2 (6%)	5 (14%)	2 (5%)	9 (8%)
Arthralgia	2 (6%)	6 (17%)	1 (3%)	9 (8%)
Flatulence	0	3 (8%)	5 (14%)	8 (7%)
Injection site pain	3 (9%)	2 (6%)	2 (5%)	7 (7%)
Weight decrease	3 (9%)	4 (11%)	2 (5%)	9 (8%)
Fatigue	1 (3%)	3 (8%)	2 (5%)	6 (6%)
Headache	4 (12%)	0	2 (5%)	6 (6%)
Injection site mass	1 (3%)	1 (3%)	4 (11%)	6 (6%)
Nausea	2 (6%)	1 (3%)	3 (8%)	6 (6%)
Gallbladder disorder	3 (9%)	1 (3%)	1 (3%)	5 (5%)
Hyperglycaemia	2 (6%)	2 (6%)	1 (3%)	5 (5%)
Hypertension aggravated	2 (6%)	1 (3%)	2 (5%)	5 (5%)

Sponsor's Table 47, Module 5, Vol 53, pg. 130

Gastrointestinal disorders were the most common types of adverse events reported during the double/single-blind study phases occurring in 60 (56%) of the 107 patients. The incidence of gastrointestinal events increased with lanreotide dose with 35%, 58%, and 73% of patients in the lanreotide 60, 90 and 120 mg treatment groups, respectively, reporting at least one adverse event in the gastrointestinal system disorders body system. The most commonly reported gastrointestinal AE was diarrhea occurring in 48 (45%) of the 107 patients; the incidence of diarrhea increased with lanreotide dose occurring in 26%, 42% and 65% of patients in the 60, 90 and 120 mg lanreotide treatment groups, respectively. Abdominal pain, the second most frequently reported gastrointestinal event during the double/single-blind phase of the study, occurred at a higher incidence in the 2 highest lanreotide dose groups (17% and 19% of patients in the 90 and 120 mg groups, respectively) as compared to the 60 mg group (9%). The only other gastrointestinal events with incidence  $\geq 5\%$  were flatulence and nausea. Flatulence was reported with increasing incidence across lanreotide dose (0%, 8% and 14% for the 60, 90 and 120 mg groups, respectively). The reported incidence of nausea was similar across the 3 lanreotide treatment groups (6%, 3%, and 8% for the 60, 90 and 120 mg groups, respectively). All other gastrointestinal disorders were reported in  $< 5\%$  of the 107 patients during the double/single blind phases.

Metabolic and nutritional system disorders were reported during the double/single-blind study phases in 21 (20%) of the 107 patients. The most commonly reported metabolic and nutritional system disorders were weight decrease and hyperglycemia reported in 9 (8%) and 5 (5%) of the 107 patients, respectively. There was no observed increase in the incidence of these events with lanreotide dose.

Liver and biliary system disorders were reported in 20 (19%) of the 107 patients including 9 (26%) of 34 patients in the 60 mg group, 7 (19%) of 36 patients in the 90 mg group and 4 (11%) of 37 patients in the 120 mg group. The most commonly reported event in this body system was cholelithiasis reported in a total of 14 (13%) of the 107 patients. The second most common GI event was gallbladder disorder (including reports of gallbladder polyp, dilated common bile duct and dilated gallbladder) which was reported in 5 patients overall (5%) including 3 patients in the 60 mg group and 1 each in the 90 and 120 mg groups.

Application site disorders occurred in 15 (14%) of the 107 lanreotide-treated patients. The incidence of application site disorders was highest in the lanreotide 120 mg group (8 of 37 patients, 22%) compared to the 60 mg (3 of 34, 9%) and 90 mg (4 of 36, 11%) groups. The most commonly reported events in this body system were injection site pain and injection site mass reported in 7 (7%) and 6 (6%) of the 107 lanreotide-treated patients. Injection site mass was reported most often in the 120 mg group and injection site pain was reported most often in the 60 mg group.

Heart rate and rhythm disturbances were reported in 14 (13%) of the 107 lanreotide-treated patients during the double/single-blind phases. No increased incidence with lanreotide dose was noted for heart rate and rhythm disturbances with 21%, 6%, and 14% of patients in the 60, 90 and 120 mg groups, respectively, reporting at least one event in this body system. Bradycardia, the most commonly reported heart rate and rhythm disturbance, was reported most frequently in the 60 mg group (6 of 34 patients, 18%); the incidence in the lanreotide 90 mg and 120 mg groups was 2 (6%) of 36 patients and 2 (5%) of 37 patients, respectively.

Anemia was reported in 9 (8%) of the 107 patients including 2 (6%) of 34 patients in the 60 mg group, 5 (14%) of 36 patients in the 90 mg group and 2 (5%) of 37 patients in the 120 mg group. Hypertension aggravated, reported in 5 (5%) of the 107 patients, occurred at a similar incidence across the lanreotide groups (6%, 3% and 5% of patients in the 60, 90 and 120 mg groups, respectively).

The majority of adverse events reported during the double/single-blind phases were mild to moderate in severity. Eighteen (17%) of the 107 patients experienced adverse events judged to be severe in intensity by the investigator during lanreotide treatment in the double/single-blind phase. The reported incidence of severe events increased across lanreotide dose with 3 (9%) of 34 patients in the 60 mg group, 6 (17%) of 36 patients in the 90 mg group and 9 (24%) of 37 patients in the 120 mg group, experiencing at least one event of severe intensity. The most commonly reported severe events were abdominal pain and diarrhea, each reported in 4 (4%) of the 107 patients; all other severe events were reported in only 1 or 2 patients each.

#### *Adverse Events during the Double/Single-blind and Open-label Phases (Weeks 0-52)*

The most commonly reported adverse events during lanreotide treatment across all 3 study phases were diarrhea (48%), cholelithiasis (30%), abdominal pain (21%), bradycardia (14%), arthralgia (13%), anemia (12%), alopecia (12%), injection site mass (10%), flatulence (10%) and nausea (10%). All other events reported during the study occurred in < 10% of the 107 patients. The incidence of diarrhea, abdominal pain and flatulence increased with lanreotide dose. In

addition, the incidence of cholelithiasis and injection site mass was highest during treatment with 120 mg lanreotide acetate.

The sponsor's table below presents the number and percent of patients reporting the most commonly occurring ( $\geq 5\%$  overall incidence) treatment-emergent adverse events across the study by preferred term and dose at event onset.

**Table 10.1.1.31. Most Commonly ( $\geq 5\%$ ) Reported Treatment-emergent Adverse Events by Preferred Term During the Double/Single-blind and Open-label Phases by Dose at Onset of the Event (Safety Population, Double/Single-blind + Open-label Phases)**

Preferred term	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 46) <sup>1</sup>	90 mg (N = 66) <sup>1</sup>	120 mg (N = 74) <sup>1</sup>	
Diarrhoea	10 (22%)	19 (29%)	35 (47%)	51 (48%)
Cholelithiasis	8 (17%)	9 (14%)	18 (24%)	32 (30%)
Abdominal pain	5 (11%)	9 (14%)	11 (15%)	23 (21%)
Bradycardia	7 (15%)	5 (8%)	4 (5%)	15 (14%)
Arthralgia	3 (7%)	8 (12%)	4 (5%)	14 (13%)
Anaemia	3 (7%)	6 (9%)	4 (5%)	13 (12%)
Alopecia	5 (11%)	3 (5%)	7 (9%)	13 (12%)
Injection site mass	2 (4%)	2 (3%)	8 (11%)	11 (10%)
Flatulence	2 (4%)	3 (5%)	7 (9%)	11 (10%)
Nausea	3 (7%)	2 (3%)	6 (8%)	11 (10%)
Injection site pain	3 (7%)	3 (5%)	4 (5%)	10 (9%)
Fatigue	2 (4%)	4 (6%)	4 (5%)	10 (9%)
Hyperglycaemia	3 (7%)	4 (6%)	3 (4%)	10 (9%)
Weight decrease	3 (7%)	4 (6%)	3 (4%)	10 (9%)
Headache <sup>2</sup>	5 (11%)	0	4 (5%)	9 (8%)
Back pain <sup>2</sup>	2 (4%)	3 (5%)	6 (8%)	8 (7%)
Gallbladder disorder	3 (7%)	3 (5%)	2 (3%)	8 (7%)
Rhinitis	1 (2%)	3 (5%)	4 (5%)	8 (7%)
Dizziness	2 (4%)	2 (3%)	3 (4%)	7 (7%)
Vomiting	2 (4%)	0	5 (7%)	7 (7%)
Influenza-like symptoms	1 (2%)	2 (3%)	4 (5%)	6 (6%)
Hypertension aggravated	2 (4%)	2 (3%)	2 (3%)	6 (6%)
Constipation	1 (2%)	2 (3%)	3 (4%)	6 (6%)
Dyspepsia	1 (2%)	4 (6%)	1 (1%)	6 (6%)
Myalgia	2 (4%)	1 (2%)	3 (4%)	6 (6%)
Urinary tract infection	2 (4%)	1 (2%)	3 (4%)	6 (6%)
Anxiety	3 (7%)	1 (2%)	1 (1%)	5 (5%)
Coughing	2 (4%)	3 (5%)	1 (1%)	5 (5%)
Dyspnoea	1 (2%)	2 (3%)	2 (3%)	5 (5%)
Upper resp tract infection	2 (4%)	0	3 (4%)	5 (5%)

Percents are based on the total number of patients included in the safety population within a treatment group or overall.

<sup>1</sup> Number of patients included in each dose group is based on the total number of patients who received at least one dose at that dose level; total across the 3 dose groups does not add to 107.

Sponsor's Table 49, Module 5, Vol 53, pg. 134

The table below uses body system and preferred term. Additionally, for the AE hyperglycemia, I would combine the AEs of hyperglycemia (6) + AE elevated HbA1C (5) + new onset DM (4

minus 1 subject also listed under elevated HbA1C=3) + aggravated DM (2) = 16/107 (15%).  
 Likewise, for the AE of hypertension, I would include HTN (3) + aggravated HTN (6) = 9/107 (8%).

**Table 10.1.1.32 Most Commonly Reported Treatment-emergent Adverse Events by Body System/Preferred Term During the Double/Single-blind and Open-label Phases by Dose at Onset of the Event (Safety Population, Double/Single-blind + Open-label Phases)**

<b>Body System/Preferred Term</b>	<b>Lanreotide 60 mg (N=46) N (%)</b>	<b>Lanreotide 90 mg (N=66) N (%)</b>	<b>Lanreotide 120 mg (N=74) N (%)</b>	<b>Total (N=107)</b>
<b>Gastrointestinal System Disorders</b>	<b>16 (35%)</b>	<b>28 (42%)</b>	<b>46 (62%)</b>	<b>72 (67%)</b>
Diarrhea	10 (22%)	19 (29%)	35 (47%)	51 (48%)
Abdominal pain	5 (11%)	9 (14%)	11 (15%)	23 (21%)
Flatulence	2 (4%)	3 (5%)	7 (9%)	11 (10%)
Nausea	3 (7%)	2 (3%)	6 (8%)	11 (10%)
Vomiting	2 (4%)	0	5 (7%)	7 (7%)
Constipation	1 (2%)	2 (3%)	3 (4%)	6 (6%)
Dyspepsia	1 (2%)	4 (6%)	1 (1%)	6 (6%)
GI neoplasm benign	1 (2%)	2 (3%)	1 (1%)	4 (4%)
Anorexia	0	1 (2%)	2 (3%)	3 (3%)
Hemorrhoids	1 (2%)	0	2 (3%)	3 (3%)
Gastroesophageal reflux	0	0	1 (1%)	1 (1%)
<b>Liver and Biliary System Disorders</b>	<b>14 (30%)</b>	<b>11 (17%)</b>	<b>22 (30%)</b>	<b>41 (38%)</b>
Cholelithiasis (includes sludge)	8 (17%)	9 (14%)	18 (24%)	32 (30%)
Gallbladder disorder	3 (7%)	3 (5%)	2 (3%)	8 (7%)
Bilirubinemia	2 (4%)	1 (2%)	0	3 (3%)
Hepatomegaly	0	1 (2%)	2 (3%)	3 (3%)
<b>Musculoskeletal Disorders</b>	<b>6 (13%)</b>	<b>12 (18%)</b>	<b>14 (19%)</b>	<b>28 (26%)</b>
Arthralgia	3 (7%)	8 (12%)	4 (5%)	14 (13%)
Myalgia	2 (4%)	1 (2%)	3 (4%)	6 (6%)
Muscle weakness	1 (2%)	0	2 (3%)	3 (3%)
Skeletal pain	0	2 (3%)	1 (1%)	3 (3%)
<b>Body as a Whole – General Disorders</b>	<b>9 (20%)</b>	<b>12 (18%)</b>	<b>19 (26%)</b>	<b>34 (32%)</b>
Fatigue	2 (4%)	4 (6%)	4 (5%)	10 (9%)
Back pain	2 (4%)	2 (3%)	4 (5%)	7 (7%)
Influenza-like sxs	1 (2%)	2 (3%)	4 (5%)	6 (6%)
<b>Respiratory System Disorders</b>	<b>8 (17%)</b>	<b>9 (14%)</b>	<b>13 (18%)</b>	<b>27 (25%)</b>
Rhinitis	1 (2%)	3 (5%)	4 (5%)	8 (7%)
<b>Urinary System Disorders</b>	<b>4 (9%)</b>	<b>6 (9%)</b>	<b>10 (14%)</b>	<b>20 (19%)</b>
Urinary tract infection	2 (4%)	1 (2%)	3 (4%)	6 (6%)
<b>Metabolic &amp; Nutritional Disorders</b>	<b>11 (24%)</b>	<b>12 (18%)</b>	<b>14 (19%)</b>	<b>35 (33%)</b>
Hyperglycemia	3 (7%)	4 (6%)	3 (4%)	10 (9%)
Weight decrease	3 (7%)	4 (6%)	3 (4%)	10 (9%)

Diabetes Mellitus	0	1 (2%)	3 (4%)	4 (4%)
DM aggravated	1 (2%)	0	1 (1%)	2 (2%)
Hypoglycemia	1 (2%)	1 (2%)	2 (3%)	4 (4%)
<b>Application Site Disorders</b>	<b>4 (9%)</b>	<b>7 (11%)</b>	<b>14 (19%)</b>	<b>22 (21%)</b>
Injection site mass	2 (4%)	2 (3%)	8 (11%)	11 (10%)
Injection site pain	3 (7%)	3 (5%)	4 (5%)	10 (9%)
Injection site reaction	0	1 (2%)	2 (3%)	3 (3%)
<b>CV Disorders, General</b>	<b>4 (9%)</b>	<b>4 (6%)</b>	<b>9 (12%)</b>	<b>16 (15%)</b>
Hypertension aggravated	2 (4%)	2 (3%)	2 (3%)	6 (6%)
Hypertension	1 (2%)	0	2 (3%)	3 (3%)
<b>Heart Rate &amp; Rhythm Disorders</b>	<b>9 (20%)</b>	<b>6 (9%)</b>	<b>8 (11%)</b>	<b>21 (20%)</b>
Bradycardia	7 (15%)	5 (8%)	4 (5%)	15 (14%)
<b>Myo, Endo, Pericardial &amp; Valve Disorders</b>	<b>2 (4%)</b>	<b>3 (5%)</b>	<b>5 (7%)</b>	<b>9 (8%)</b>
Heart valve disorders (includes Aortic valve sten/Incom and mitral insuff)	2 (4%)	3 (5%)	3 (4%)	8 (7%)
<b>Central &amp; Peripheral Nervous System</b>	<b>8 (17%)</b>	<b>8 (12%)</b>	<b>10 (14%)</b>	<b>26 (24%)</b>
Headache	4 (9%)	0	4 (5%)	8 (7%)
Dizziness	2 (4%)	2 (3%)	3 (4%)	7 (7%)
<b>Red Blood Cell Disorders</b>	<b>3 (7%)</b>	<b>6 (9%)</b>	<b>4 (5%)</b>	<b>13 (12%)</b>

A patient is counted only once for each body system and preferred term.

Dictionary = WHOART.

Patients are grouped by the dose at onset. Sorted by descending frequency of the total injected column within body system.

Note: n1 (respectively n2 or n3) = number of patients receiving at least one dose of lanreotide 60 mg (respectively 90 mg or 120 mg).

A patient is counted in the columns 60,90 and 120 mg, if he/she received the three doses.

This table concerns all the treatment-emergent adverse events started after the injection of V3 [Week 0] (except the adverse events started in the Double-Blind phase, for patients randomized to placebo).

The sponsor was asked to provide additional information on the subjects that developed the onset or worsening of diabetes mellitus during the trial. There were a total of 108 patients in the safety population for study E-28-52030-717. At baseline, 27 of these patients had active diabetes mellitus; two patients had a medical history of diabetes mellitus that was recorded as not active; and 79 patients had no recorded history of diabetes mellitus. Of the 79 patients with no recorded history of diabetes mellitus at baseline, four patients (5%) experienced AEs of diabetes during the study. Three of the patients were receiving 120 mg lanreotide acetate, and one 90 mg lanreotide acetate, at the time of the event; none of the events were resolved at study end. In the two patients who had had a medical history of diabetes mellitus that was recorded as not active at baseline, one experienced a progression of diabetes mellitus.

Of the 27 patients with active diabetes mellitus at baseline, nine (33%) had some form of AE after initiation of study drug that could be attributed to the worsening of diabetes mellitus or disturbances of glucose homeostasis. One of these nine patients also reported an SAE (a severe, diabetic nephropathy; receiving lanreotide acetate 90 mg) and was recorded within this group. From baseline until last value available or max HbA1c value, the majority of patients' HbA1c and fasting glucose values decreased or remained stable, taking into account assay variability.

With regard to more pronounced changes in HbA1c of 0.5% or more, 6/27 patients with active diabetes mellitus showed increases (range 0.5 to 1.7%), 14/27 had HbA1c changes < 0.5%, while 10/27 patients showed decreases of 0.5% or more (range 0.5 to 7.8%).

Application site disorders occurred during the 3 study phases in 22 (21%) of the 107 patients. The incidence of application site disorders increased with lanreotide dose occurring in 9%, 11% and 19% of patients during treatment with 60, 90 and 120 mg, respectively. The most commonly reported events in this body system were injection site mass and injection site pain reported in 11 (10%) and 10 (9%) of the 107 patients, respectively. The incidence of injection site mass was highest during treatment with 120 mg group (11%) compared to treatment with 60 mg (4%) and 90 mg (3%). Injection site pain was reported with similar incidence across the 3 dose levels occurring in 7%, 5% and 5% of patients during treatment with 60, 90 and 120 mg, respectively. Heart rate and rhythm disturbances were reported in 21 (20%) of the 107 patients during the 3 study phases. Bradycardia, the most commonly reported heart rate and rhythm disturbance, was reported in 15 (14%) of all 107 patients including 15%, 8% and 5% of patients during treatment with 60, 90 and 120 mg of lanreotide.

Disorders of the cardiovascular system were reported in a total of 16 (15%) of the 107 patients during lanreotide treatment; the incidence of cardiovascular disorders was 9%, 6% and 12% during treatment with 60, 90 and 120 mg lanreotide. Hypertension aggravated was the most commonly reported cardiovascular disorder occurring in 6 (6%) of the 107 patients. A similar incidence of hypertension aggravated was reported during treatment with 60 mg (4%), 90 mg (3%) and 120 mg (3%) lanreotide.

A total of 13 (12%) of the 107 patients experienced red blood cell disorders during lanreotide treatment including 7%, 9% and 5% of patients during treatment with 60, 90 and 120 mg lanreotide, respectively. Anemia was the most commonly reported red blood cell disorder occurring in 13 (12%) of patients.

The sponsor was asked to provide additional information on the subjects with hypothyroidism at baseline and during the course of the study. Within the ITT population (N=108) for Study 717 at baseline, 17 patients (15.7%) reported a history of goiter, 13 patients (12%) reported a history of hypothyroidism, two patients (1.9%) reported a history of hypoparathyroidism, one patient (0.9%) reported a history of toxic nodular goiter, one patient (0.9%) reported a history of thyroiditis, two patients (1.9%) reported a history of thyroid neoplasms, and two patients (1.9%) reported a history of decreased TSH. Four patients (3.7%) had undergone a thyroidectomy, one patient (0.9%) had undergone a partial thyroidectomy, and one patient (0.9%) had undergone a parathyroidectomy.

A total of 23 patients (21.3%) reported prior or concomitant thyroid therapy at screening. Twenty-one of these patients (19.4%) had received some form of thyroid hormones, and three (2.8%) had received other thyroid therapy; one patient received both. Seventeen of the above patients were still receiving thyroid hormones at study entry; three of whom had their regimens altered after administration of lanreotide acetate.

- 717.0001: Female, 55 years of age. Prior administration of levothyroxine 75 µg/day orally, indicated for multinodular goiter, was ceased at Week 10. Levothyroxine 50 µg/day orally, was initiated at Week 12 and continued to Week 23. The previous dose of 75 µg/day orally, was reinstated between Week 24 and Week 31; then reduced once again to 50 µg/day orally, Week 32 to ongoing at the end of study. The patient received lanreotide acetate 60 mg throughout the study;
- 713.0008: Female, 63 years of age. Prior administration of levothyroxine 0.175 mg/day orally, was increased to 0.2 mg/day at Week 20 and remained ongoing at the end of study. The treatment was indicated for hypothyroidism. The patient was in the placebo group until Week 4, then received lanreotide acetate 60 mg until the first titration (Week 20), at which time her dosage was increased to lanreotide acetate 90 mg;
- 702.0008: Male, 52 years of age. Prior, concomitant and ongoing administration of levothyroxine sodium tablets 100 µg/day orally, indicated for hypothyroidism. This was changed to levothyroxine 0.1 mg/day orally, at Week 3 and remained ongoing at the end of study. The patient was receiving lanreotide acetate 60 mg at the time that the additional therapy was initiated, but was later titrated up to the 120 mg dose.

A further four patients began new thyroid hormone therapy during the study.

- 725.0007: Female, 65 years of age with no relevant history. Started on thyroxine 50 µg/day orally, at Week 32. This was increased to 100 µg/day at Week 36, and remained ongoing at the end of study. The treatment was indicated for hypothyroidism. The patient's lanreotide acetate dose was 120 mg throughout the study;
- 715.0001: Female, 68 years of age with no relevant history. Began treatment for hyperthyroidism with nemercozle 60 mg/day orally, at Week 0. This was decreased to 40 mg/day orally, at Week 5, at which time she also began levothyroxine 75 mg/day orally. The patient underwent a thyroidectomy at Week 9. Her lanreotide acetate dose was 90 mg throughout the study;
- 716.0004: Female, 53 years of age with no relevant history. Treated with levothyroxine 50 µg/day orally, Aug 2001 to ongoing; listed as concomitant but not prior, indicated for thyrotropic deficiency. Thyrotropic deficiency was diagnosed in 1999, but for the purpose of this report the levothyroxine therapy is conservatively listed here as new. Patient's final dose was 120 mg lanreotide acetate;
- 718.0003: Female, 58 years of age with no relevant history. Treated with levothyroxine 25 µg/day orally, no start date to October 2001; listed as concomitant but not prior, indicated for goiter. The patient had a history of nodular goiter dating back to 1975; but since the start date of levothyroxine treatment cannot be established, for the purpose of this report the therapy is conservatively listed here as new. Patient's final dose was 120 mg lanreotide acetate.

Medication and dose remained unchanged throughout the study for 14 of 17 the patients who were receiving thyroid therapy at baseline:

Two other thyroid related AEs were recorded during the study:

- A 54 year old female patient, 719.0002, recorded a non-serious, mild, possibly related AE of thyroid cyst at Week -5, prior to receiving the study drug. Patient's final dose was 60 mg lanreotide acetate;
- A 68 year old female patient, 715.0001, experienced a serious and severe thyroid carcinoma in Week 10; and was discontinued from the study. The patient had received three injections of lanreotide acetate 90 mg prior to the event. Patient's final dose was 90 mg lanreotide acetate.

There was one (1/107, <1%) report of hypothyroidism as an AE during the study:

- A 65 year old female patient receiving lanreotide acetate 120 mg, 725.0007, experienced an AE of hypothyroidism at Week 32. This was moderate in intensity, and was considered to be possibly related to treatment.

The majority of adverse events reported during lanreotide treatment across the 3 study phases were mild to moderate in severity. Thirty-two (30%) of the 107 lanreotide-treated patients experienced adverse events judged to be severe in intensity by the investigator including 15%, 17% and 23% of patients during treatment with 60, 90 and 120 mg lanreotide, respectively. The most commonly reported events of severe intensity during lanreotide treatment over the 3 study phases were abdominal pain (7 patients, 7%), diarrhea (6 patients, 6%) and hypertension aggravated (3 patients, 3%); all other severe events were reported in only one or 2 patients. Of note is Patient 701.0030 (59 year-old Female) who was on 90 mg of lanreotide at the time of onset of the AE of "worsening tricuspid regurgitation/heart valve disorders" and "increase in fatigue not related to acromegaly/fatigue. The onset of the AE for the heart valve disorder occurred at Day 113 (Week 16) and for fatigue was Day 168 (Week 24), duration was ongoing. The patient continued study drug and no treatment was required. This patient later developed the SAE of metastatic adenocarcinoma of the right lung on Day 419 (Week 59).

Safety results in terms of treatment-naïve and non-treatment-naïve patient populations:

The sponsor was asked by this reviewer to present the safety results separately for treatment-naïve and non-treatment-naïve populations (as requested in the 6 July 2004 pre-NDA meeting for lanreotide acetate). The sponsor reanalyzed the data for Study 717 separately for the three populations as defined in the clinical protocol: treatment "Naïve" (Naïve); not treated within three months prior to study entry; and previously treated (non-treatment naïve). These populations are further defined below:

- Naïve - not previously treated with somatostatin or SSA but may have had surgery and/or radiotherapy and/or other medication;
- Not treated within the 3 months prior to study entry - any previous treatment with somatostatin or SSA was to be stopped within 3 months of study entry to provide successful washout/active disease at study baseline;
- Previously Treated - previous treatment with somatostatin or SSA that was confirmed ongoing at baseline (Visit 1).

Due to the relatively small number of patients in these subpopulations reanalyses of the study

717 efficacy data by region (e.g. US, EU, Hong Kong), as performed for the overall population of patients in the clinical study report, were not done.

The table below shows the most common adverse events in study 717 by somatostatin analog history (Naïve, Not treated within 3 month, Previously treated). The System Organ Class (SOC) 'Gastrointestinal disorders' has the highest percentage of adverse events across all treatment groups, and a numerically higher percentage among the Naïve (73.3%) and Not treated for 3 months (69.2%) groups than the Previously treated group (62.7%). Within the SOC Gastrointestinal disorders, the Preferred Terms (PT) diarrhea and abdominal discomfort have numerically higher percentages among the Naïve (diarrhea 40.0%, abdominal discomfort 6.7%), and Not treated for 3 months (diarrhea 59.0%, abdominal discomfort 7.7%) groups than the Previously treated group (diarrhea 29.4%, abdominal discomfort 3.9%). Similarly, the PTs cholelithiasis and headache were notably more frequent in the Naïve (46.7% and 20.0% respectively) and Not treated within 3 months groups (46.2% and 5.1% respectively) than the Previously treated group (15.7% and 3.9% respectively). The High Level Term (HLT) Musculoskeletal & connective tissue signs and symptoms Not Elsewhere Classified (NC) had a lower percentage of adverse events in the Naïve (0%) and Not treated within 3 months groups (7.7%) than the Previously treated group (15.7%).

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**Table 10.1.1.33 Most Common Treatment Emergent Adverse Events (incidence >15% or 2 or more patients) by Somatostatin Analog History**

MedDRA SOC HLT PT	Somatostatin Analog history					
	Naïve (N=15)		Not Treated Within 3 months (N=39)		Previously Treated (N=51)	
	N	%	N	%	N	%
<b>Patients with any TEAE</b>	15	100.0	39	100.0	42	82.4
<b>Gastrointestinal disorders</b>	11	73.3	27	69.2	32	62.7
<i>Diarrhoea (excl infective)</i>	6	40.0	23	59.0	15	29.4
Diarrhoea	6	40.0	23	59.0	15	29.4
<i>Faeces abnormal</i>	1	6.7	7	17.9	6	11.8
Loose stools	1	6.7	7	17.9	5	9.8
<b>Gastrointestinal &amp; abdominal pains (excl oral and throat)</b>	3	20.0	5	12.8	10	19.6
Abdominal pain	2	13.3	4	10.3	9	17.6
<b>Gastrointestinal signs &amp; symptoms NEC</b>	1	6.7	4	10.3	3	5.9
Abdominal discomfort	1	6.7	3	7.7	2	3.9
Nausea & vomiting symptoms	2	13.3	7	17.9	6	11.8
<b>Hepatobiliary disorders</b>	8	53.3	18	46.2	13	25.5
<i>Cholecystitis &amp; cholelithiasis</i>	7	46.7	18	46.2	8	15.7
Cholelithiasis	7	46.7	18	46.2	8	15.7
<b>General disorders and administration site conditions</b>	8	53.3	11	28.2	18	35.3
<i>Injection &amp; infusion site reactions</i>	6	40.0	4	10.3	11	21.6
Asthenic conditions	4	26.7	2	5.1	6	11.8
<b>Investigations</b>	7	46.7	14	35.9	14	27.5
<i>Physical examination procedures</i>	3	20.0	4	10.3	4	7.8
Weight decreased	3	20.0	3	7.7	4	7.8
<b>Nervous system disorders</b>	7	46.7	7	17.9	11	21.6
<i>Headaches NEC</i>	3	20.0	2	5.1	2	3.9
Headache	3	20.0	2	5.1	2	3.9
<b>Musculoskeletal &amp; connective tissue disorders</b>	6	40.0	8	20.5	15	29.4
<i>Joint related signs &amp; symptoms</i>	3	20.0	5	12.8	7	13.7
Arthralgia	3	20.0	5	12.8	6	11.8
Muscle pains	3	20.0	0	0	2	3.9
Myalgia	3	20.0	0	0	2	3.9
Musculoskeletal & connective tissue signs and symptoms NEC	0	0	3	7.7	8	15.7
<b>Cardiac disorders</b>	5	33.3	5	12.8	16	31.4
<i>Supraventricular arrhythmias</i>	3	20.0	2	5.1	11	21.6
Sinus bradycardia	3	20.0	1	2.6	8	15.7
<b>Skin &amp; subcutaneous tissue disorders</b>	5	33.3	10	25.6	8	15.7
<i>Alopecia</i>	4	26.7	4	10.3	4	7.8
Alopecia	3	20.0	2	5.1	3	5.9
<b>Infections &amp; Infestations</b>	4	26.7	10	25.6	15	29.4
<i>Upper respiratory tract infections</i>	1	6.7	3	7.7	5	9.8
Upper respiratory tract infection	1	6.7	1	2.6	0	0
<b>Vascular disorders</b>	4	26.7	4	10.3	7	13.7
<i>Vascular hypertensive disorders NEC</i>	3	20.0	2	5.1	4	7.8
Hypertension	3	20.0	2	5.1	4	7.8
<b>Blood &amp; lymphatic system disorders</b>	3	20.0	3	7.7	5	9.8
<i>Anemias NEC</i>	3	20.0	3	7.7	5	9.8
Anaemia	3	20.0	3	7.7	5	9.8

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Source: Sponsor's Amendment 0008: Table AE.717.1.

*Laboratory Parameters*

Hematology and biochemistry clinical laboratory tests were obtained at screening (visit 1) and weeks 4, 16 and 52 (end of study) corresponding to visits 4, 10 and 19 and submitted to the central laboratory for analysis. The clinically significant changes in hematology or chemistry parameters associated with lanreotide acetate following repeated injections were anemia (~12% patients), hyperglycemia (9%), hypoglycemia (4%), increased alkaline phosphatase (3%), hypercholesterolemia (3%) and bilirubinemia (3%).

*Reviewer note: Thyroid Stimulating Hormone and free T4 was not monitored during the course of this trial.*

**Hematology:**

Analyses focused on measures of central tendency

The table below presents mean ( $\pm$  SD) hematology parameters at baseline, week 52 and LVA for the double/single-blind and open-label study phases. Across all 107 patients, small mean decreases from baseline to week 52 and LVA were noted for all red cell parameters, including hemoglobin, hematocrit and red blood cell count. No dose-related trends were noted across the 3 treatment groups for change from baseline in red cell parameters. Mean changes in white cell count from baseline to week 52 and LVA were  $+0.20 (\pm 1.39)$  and  $+0.27 (\pm 1.39) \times 10^9/L$ , respectively, across all 107 patients; no trends were noted across the 3 treatment groups for changes from baseline in white cell count. Small mean increases from baseline to week 52 and LVA of  $+5.2 (\pm 37.0)$  and  $+6.7 (\pm 43.6) \times 10^9/L$  were noted for platelet count; no trends for changes from baseline in this parameter were noted across the 3 treatment groups.

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**Table 10.1.1.34. Hematology Parameters (Mean ± SD) at Baseline, Week 52, and LVA during the Double/Single-blind and Open-label Study Phases by Last Dose Administered (Safety Population, Double/Single-blind + Open-label Phases)**

Parameter:	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 21)	90 mg (N = 17)	120 mg (N = 69)	
<b>Hemoglobin (mmol/L)</b>				
Baseline	8.11 ± 0.90	8.08 ± 0.56	8.20 ± 0.84	8.16 ± 0.81
Week 52	8.04 ± 0.73	7.84 ± 0.66	8.11 ± 0.89	8.06 ± 0.83
LVA	8.04 ± 0.73	7.73 ± 0.71	8.10 ± 0.87	8.03 ± 0.83
<b>Hematocrit (frac of 1)</b>				
Baseline	0.395 ± 0.040	0.393 ± 0.027	0.397 ± 0.040	0.396 ± 0.038
Week 52	0.387 ± 0.034	0.374 ± 0.032	0.390 ± 0.042	0.387 ± 0.040
LVA	0.387 ± 0.034	0.372 ± 0.033	0.390 ± 0.041	0.386 ± 0.039
<b>Red blood cells (x10<sup>12</sup>/L)</b>				
Baseline	4.36 ± 0.29	4.24 ± 0.35	4.33 ± 0.46	4.32 ± 0.42
Week 52	4.30 ± 0.31	4.15 ± 0.37	4.26 ± 0.47	4.25 ± 0.43
LVA	4.30 ± 0.31	4.11 ± 0.38	4.26 ± 0.47	4.24 ± 0.43
<b>White blood cells (x10<sup>9</sup>/L)</b>				
Baseline	5.49 ± 1.71	5.33 ± 1.35	5.88 ± 1.73	5.72 ± 1.67
Week 52	5.87 ± 1.89	5.32 ± 1.01	6.07 ± 2.22	5.93 ± 2.04
LVA	5.87 ± 1.89	5.67 ± 1.07	6.09 ± 2.18	5.98 ± 1.98
<b>Platelets (x 10<sup>9</sup>/L)</b>				
Baseline	248.1 ± 59.6	243.6 ± 82.7	234.1 ± 48.7	238.0 ± 57.0
Week 52	251.5 ± 51.2	240.7 ± 86.4	239.0 ± 51.9	241.8 ± 56.6
LVA	251.5 ± 51.2	261.8 ± 90.2	240.4 ± 51.0	245.9 ± 58.9

The total number of patients included in each analysis varied between 96 and 106 patients.  
 Sponsor's Table 56, Module 5, Vol 53, pg. 150

*Analyses focused on outliers or shifts from normal to abnormal*

The table below presents shifts from baseline to week 4 during the double-blind study phase for hematology parameters. A higher proportion of patients in the 3 lanreotide treatment groups had shifts to low for red blood cell parameters as compared to the placebo group. A higher proportion of patients in the 120 mg lanreotide group had a shift to low white cell count compared to the placebo group and the 60 and 90 mg lanreotide groups. No differences were noted between the active treatment groups and the placebo group for shifts from baseline to week 4 for platelet count.

**Table 10.1.1.35. Hematology Shifts from Baseline to Week 4 during the Double-blind Study Phase by Dose as Randomized (Safety Population, Double-blind Phase)**

Parameter:	Lanreotide Autogel:			Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)		
Hemoglobin					
Shifted to low	2/26 (8%)	3/25 (12%)	1/26 (4%)	0/23	6/100 (6%)
Shifted to high	0/26	0/25	0/26	0/23	0/100
Hematocrit					
Shifted to low	2/26 (8%)	5/25 (20%)	6/26 (23%)	0/23	13/100 (13%)
Shifted to high	0/26	0/25	0/26	0/23	0/100
Red blood cells					
Shifted to low	2/26 (8%)	3/25 (12%)	1/26 (4%)	1/23 (4%)	7/100 (7%)
Shifted to high	0/26	0/25	0/26	0/23	0/100
White blood cells					
Shifted to low	1/26 (4%)	0/25	3/26 (12%)	1/23 (4%)	5/100 (5%)
Shifted to high	0/26	0/25	0/26	0/23	0/100
Platelets					
Shifted to low	0/25	1/25 (4%)	1/26 (4%)	0/23	2/99 (2%)
Shifted to high	0/25	1/25 (4%)	0/26	0/23	1/99 (1%)

Sponsor's Table 58, Module 5, Vol 53, pg. 154

Shifts from baseline to Week 16 to below the normal range were observed in lanreotide-treated patients overall 11% for red blood cell parameters, 17% for hematocrit, and 15% for hemoglobin. There was no trend across the lanreotide dose groups for an increase in the incidence of shifts to below the normal range with increasing dose. The majority of the shifts in red cell parameters were from normal baseline to low at Week 16. Two patients, both in the 90 mg treatment group, had a shift in hemoglobin from a low baseline value to a very low Week 16 value:

Patient 716.0004, a 53 year old female randomized to placebo/lanreotide 90 mg had a history of hemorrhoids and a baseline hemoglobin of 6.45 mmol/L (low). This patient experienced mild gastrointestinal bleeding and mild anemia both assessed as unrelated to study treatment during the study. Hemoglobin level was 6.35 mmol/L (low) at Week 4 and decreased to 5.85 mmol/L (very low) at Week 16; by Week 52 the patient's hemoglobin level was in the normal range (7.75 mmol/L).

Patient 734.0001, a 43 year old male randomized to placebo/lanreotide 90 mg had a baseline hemoglobin of 8.15 mmol/L (low); medical history was significant for panhypopituitarism. Hemoglobin level was 8.45 mmol/L (low) at Week 4 and 7.05 mmol/L (very low) at Week 16; the Week 52 the patient's hemoglobin had increased slightly to 7.15 mmol/L (low). Adverse events reported during the study included diarrhea and eczema.

Only 1 or 2 patients in any of the treatment groups had shifts in white cell count or platelet count; no consistent trends were noted across lanreotide dose for shifts from baseline in these parameters.

Shifts from baseline to LVA (last value available) during the double/single-blind and open-label study phases to below the normal range were observed in lanreotide-treated patients overall 11% for red blood cell parameters, 18% for hematocrit, and 15% for hemoglobin. There was no trend across the lanreotide dose groups for an increase in the incidence of shifts to below the normal

range with increasing dose. The majority of the shifts in red cell parameters were from normal baseline to low at LVA. Two patients had shifts in red cell parameters to a very low value at LVA:

Patient 731.0006, a 63 year old male randomized to placebo/lanreotide 120 mg had a baseline hematocrit of 0.337 (low). This patient experienced mild urinary tract infection and severe anemia. Hematocrit level was 0.334 and 0.340 at weeks 4 and 16, respectively, and decreased to 0.274 (very low) at week 51 (LVA).

Patient 728.0004, a 63 year old male randomized to lanreotide 90 mg and dose titrated to 120 mg by the end of the study had a history of hemorrhoids and a baseline hemoglobin of 7.70 mmol/L (low). No adverse events were reported associated with anemia. Hemoglobin level was 7.45 and 7.75 mmol/L (low) at Weeks 4 and 16, respectively, and decreased to 7.05 mmol/L (very low) at Week 52.

A total of 5 (5%) of 104 patients had a shift to a low white cell count from baseline to LVA and 2 (2%) had a shift to high at this time point. None of the shifts in white cell count were to very low or very high.

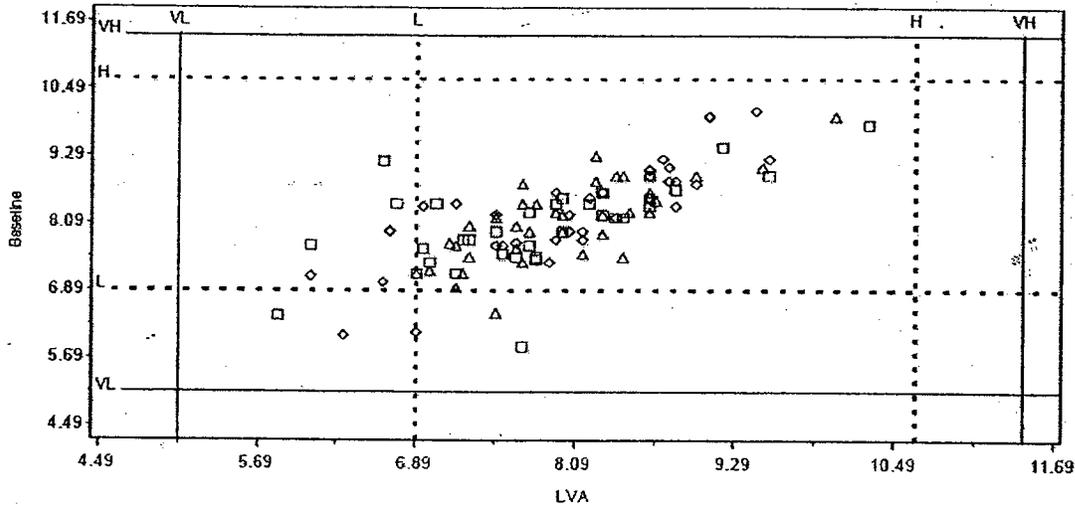
Shifts to abnormal in platelet counts were uncommon with 1 (1%) of 103 patients having a shift from baseline to a low value at LVA. Two (2%) of 103 patients had a shift to a high platelet count from baseline to LVA, including one patient with a shift to a very high value:

Patient 713.0003, a 55 year old female randomized to lanreotide 120 mg had a baseline platelet count of 437 x109/L (high). No adverse events were reported associated with increased platelet count which was 382 (normal) and 507 x 109/L (very high) at Weeks 4 and 16, respectively, and decreased to 484 x109/L (very high) at Week 52 at which time the patient was receiving 90 mg lanreotide.

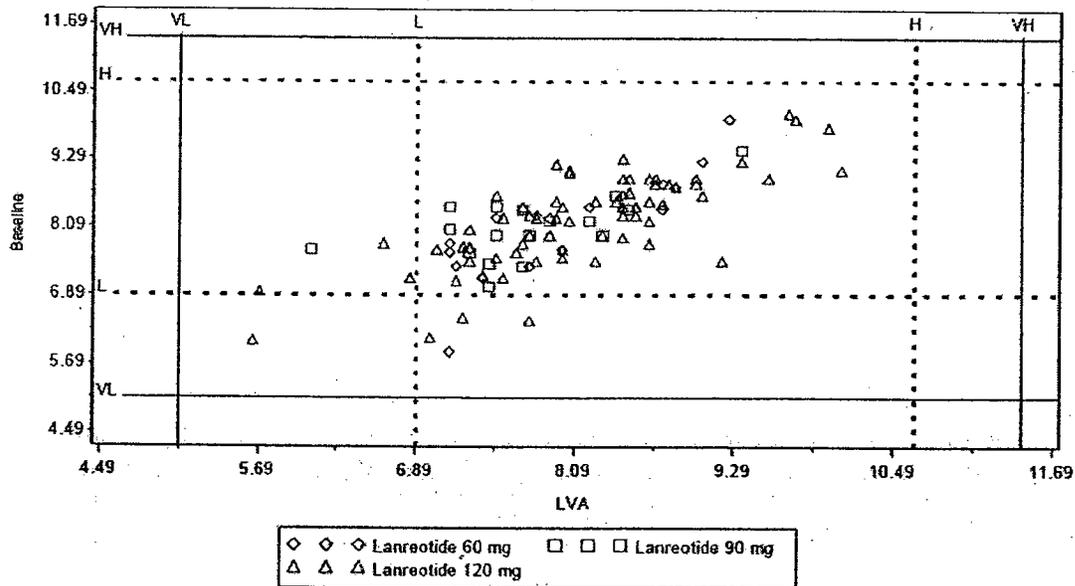
*Marked outliers and dropouts for laboratory abnormalities*

There were no dropouts for laboratory abnormalities in this trial. The two figures below shows that there were 6 subjects (3 on 60 mg and 3 on 90 mg) who has a normal hemoglobin level at baseline but a low hemoglobin level by Week 16 but only 4 subjects (1 on 90 mg, 3 on 120 mg) at Week 52 who had a normal baseline hemoglobin and developed a low hemoglobin by the end of the study.

**Figure 10.1.1.2 Laboratory Data - Hematology in the DB+SB Phase (Safety Population) Hemoglobin (mmol/L)**



**Figure 10.1.1.3 Laboratory Data - Hematology in the DB+SB+OL Phase (Safety Population) Hemoglobin (mmol/L)**



Sponsors Figures 13.2A and 13.3A Vol 58

Overall, a total of 15 (14%) of the 107 lanreotide-treated patients had hematology abnormalities that were reported as clinically significant by the investigator at some time during the 3 study phases that were not reported as clinically significantly abnormal at baseline. During the double-blind phase (i.e., at or before Week 4), 5 patients, including 1 each in the 60 mg lanreotide group (Patient 701.0001) and the placebo group (Patient 701.0025) and 3 patients in the 90 mg group (Patients 703.0001, 711.0006 and 711.0008), had decreases in hemoglobin, hematocrit or red

blood cell count reported as clinically significant abnormalities. In addition, 1 patient in the 120 mg group (Patient 701.0028) had a decrease in white cell count reported as a clinically significant abnormality. During the single-blind phase (i.e., at or before Week 16), 10 patients had clinically significant hematology findings reported (including 4 of the patients with these abnormalities also reported during the double-blind phase); the clinically significant findings included decreases in hemoglobin, hematocrit, red cell count and white cell count. The 10 patients comprised 3 patients in the 60 mg group (Patients 701.0025, 701.0001 and 707.0005), 3 in the 90 mg group (Patients 701.0013, 711.0008 and 716.0004) and 4 patients in the 120 mg group (Patients 701.0018, 701.0028, 713.0003 and 725.0006). During the open-label dose-titration phase (i.e., up through study end), a total of 6 patients had clinically significant hematology findings reported (including 3 of the patients with these abnormalities also reported during the double/single-blind phase); the clinically significant findings included decreases in hemoglobin, hematocrit, red cell count and white cell count. The 6 patients comprised 2 patients whose last dose administered was 60 mg (Patients 701.0013 and 725.0002), one whose last dose was 90 mg (Patients 725.0006) and 3 whose last dose was 120 mg (Patients 701.0028, 702.0008 and 731.0006).

The table below presents all hematology laboratory abnormalities that were reported as adverse events by the investigator during the 3 study phases by dose at onset of the adverse event. As shown, the most common laboratory abnormalities reported as adverse events during lanreotide treatment were anemia (13 patients, 12%) and leucopenia (3 patients, 3%); all other reported laboratory abnormalities occurred in only 1 or 2 patients each during the 52-week study. There was no apparent increase in the incidence of any laboratory abnormality reported as an adverse event across lanreotide dose. The majority of laboratory abnormalities reported as adverse events were assessed as mild to moderate in severity; one report of anemia was assessed as severe in intensity. Patient 731.0006 experienced severe anemia at weeks 45 and 51 during treatment with 120 mg; the former event was reported as resolved within 15 days and the latter within 1 day. The patient's hematocrit and hemoglobin were 0.274 and 5.7 mmol/L at week 51; both in the very low range.

**Table 10.1.1.36. Laboratory Abnormalities Reported as Treatment-emergent Adverse Events During the Double/Single-blind and Open-label Phases by Preferred Term and Dose at Onset of the Event (Safety Population, Double/Single-blind + Open-label Phase)**

Preferred term	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 46) <sup>1</sup>	90 mg (N = 66) <sup>1</sup>	120 mg (N = 74) <sup>1</sup>	
<b>Hematology:</b>				
Anaemia	3 (7%)	6 (9%)	4 (5%)	13 (12%)
Leucopenia	0	0	3 (4%)	3 (3%)
Leukocytosis	1 (2%)	1 (2)	0	2 (2%)
Anaemia hypochromic	0	1 (2%)	0	1 (<1%)

Percentages are based on the total number of patients included in the safety population within a treatment group or overall.  
<sup>1</sup> Number of patients included in each dose group is based on the total number of patients who received at least one dose at that dose level; total across the 3 dose groups does not add to 107.  
 Sponsor's Table 64, Module 5, Vol 53, pg. 163

Chemistry

*Analyses focused on measures of central tendency*

The table below presents mean ( $\pm$  SD) chemistry parameters at baseline, week 52 and LVA for the double/single-blind and open-label study phases.

**Table 10.1.1.37. Chemistry Parameters (Mean  $\pm$  SD) at Baseline, Week 52 and LVA during the Double/Single-blind and Open-label Study Phases by Last Dose Administered (Safety Population, Double/Single-blind + Open-label Phases)**

Parameter:	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 21)	90 mg (N = 17)	120 mg (N = 69)	
AST (U/L)				
Baseline	21.2 $\pm$ 9.8	19.7 $\pm$ 6.1	17.8 $\pm$ 6.1	18.8 $\pm$ 7.1
Week 52	19.2 $\pm$ 5.2	20.3 $\pm$ 8.1	19.5 $\pm$ 5.9	19.5 $\pm$ 6.0
LVA	19.0 $\pm$ 5.0	19.5 $\pm$ 7.1	19.7 $\pm$ 6.1	19.5 $\pm$ 6.0
ALT (U/L)				
Baseline	20.1 $\pm$ 11.3	17.5 $\pm$ 8.5	17.0 $\pm$ 10.2	17.7 $\pm$ 10.2
Week 52	16.7 $\pm$ 5.7	16.9 $\pm$ 7.4	17.6 $\pm$ 8.1	17.3 $\pm$ 7.5
LVA	16.6 $\pm$ 5.6	16.8 $\pm$ 6.8	17.8 $\pm$ 8.9	17.4 $\pm$ 8.0
Alkaline phosphatase (U/L)				
Baseline	68.0 $\pm$ 26.2	86.5 $\pm$ 36.7	81.2 $\pm$ 33.9	79.3 $\pm$ 33.1
Week 52	71.1 $\pm$ 30.6	65.5 $\pm$ 17.1	75.4 $\pm$ 31.1	73.3 $\pm$ 29.6
LVA	70.3 $\pm$ 30.0	74.1 $\pm$ 24.2	75.3 $\pm$ 30.3	74.2 $\pm$ 29.2
Blood Glucose (mmol/L)				
Baseline	6.32 $\pm$ 1.52	6.61 $\pm$ 2.15	6.85 $\pm$ 4.15	6.71 $\pm$ 3.50
Week 52	5.85 $\pm$ 0.93	6.00 $\pm$ 1.07	6.47 $\pm$ 1.98	6.29 $\pm$ 1.74
LVA	5.80 $\pm$ 0.90	6.13 $\pm$ 0.96	6.40 $\pm$ 1.95	6.24 $\pm$ 1.67
Hgb A1c (frac of 1)				
Baseline	0.062 $\pm$ 0.007	0.063 $\pm$ 0.014	0.064 $\pm$ 0.019	0.064 $\pm$ 0.016
Week 52	0.062 $\pm$ 0.007	0.060 $\pm$ 0.007	0.064 $\pm$ 0.013	0.063 $\pm$ 0.011
LVA	0.062 $\pm$ 0.007	0.063 $\pm$ 0.010	0.064 $\pm$ 0.013	0.063 $\pm$ 0.011
Bilirubin ( $\mu$ mol/L)				
Baseline	11.4 $\pm$ 5.2	10.6 $\pm$ 6.5	12.4 $\pm$ 7.9	11.9 $\pm$ 7.2
Week 52	13.1 $\pm$ 6.0	10.3 $\pm$ 4.7	12.5 $\pm$ 8.6	12.3 $\pm$ 7.7
LVA	13.3 $\pm$ 5.9	10.0 $\pm$ 4.4	12.5 $\pm$ 8.8	12.3 $\pm$ 7.8
Creatinine ( $\mu$ mol/L)				
Baseline	53.0 $\pm$ 15.4	63.1 $\pm$ 18.1	63.3 $\pm$ 17.8	61.2 $\pm$ 17.7
Week 52	60.4 $\pm$ 14.1	64.5 $\pm$ 17.3	66.9 $\pm$ 20.1	65.2 $\pm$ 18.7
LVA	60.9 $\pm$ 13.9	63.5 $\pm$ 20.3	66.1 $\pm$ 20.0	64.6 $\pm$ 19.0
Sodium (mmol/L)				
Baseline	141.9 $\pm$ 2.3	141.4 $\pm$ 4.5	140.8 $\pm$ 2.7	141.1 $\pm$ 3.0
Week 52	141.2 $\pm$ 1.9	140.8 $\pm$ 4.5	140.8 $\pm$ 3.3	140.9 $\pm$ 3.2
LVA	141.2 $\pm$ 1.9	141.0 $\pm$ 3.9	141.0 $\pm$ 3.3	141.0 $\pm$ 3.2
Potassium (mmol/L)				
Baseline	4.24 $\pm$ 0.34	4.29 $\pm$ 0.36	4.29 $\pm$ 0.39	4.28 $\pm$ 0.37
Week 52	4.24 $\pm$ 0.36	4.25 $\pm$ 0.34	4.38 $\pm$ 0.45	4.33 $\pm$ 0.42
LVA	4.29 $\pm$ 0.42	4.28 $\pm$ 0.29	4.37 $\pm$ 0.44	4.34 $\pm$ 0.41
Calcium (mmol/L)				
Baseline	2.33 $\pm$ 0.08	2.31 $\pm$ 0.12	2.37 $\pm$ 0.12	2.35 $\pm$ 0.11
Week 52	2.27 $\pm$ 0.09	2.27 $\pm$ 0.05	2.33 $\pm$ 0.12	2.31 $\pm$ 0.11
LVA	2.27 $\pm$ 0.09	2.29 $\pm$ 0.14	2.33 $\pm$ 0.12	2.31 $\pm$ 0.12
Phosphate (mmol/L)				
Baseline	1.30 $\pm$ 0.16	1.34 $\pm$ 0.22	1.34 $\pm$ 0.21	1.33 $\pm$ 0.20
Week 52	1.23 $\pm$ 0.14	1.20 $\pm$ 0.13	1.29 $\pm$ 0.18	1.26 $\pm$ 0.17
LVA	1.24 $\pm$ 0.14	1.24 $\pm$ 0.18	1.29 $\pm$ 0.18	1.27 $\pm$ 0.17

The total number of patients included in each analysis varied between 96 and 107 patients.

Sponsor's Table 57, Module 5, Vol 53, pg. 152

*Analyses focused on outliers or shifts from normal to abnormal*

The table below presents shifts from baseline to week 4 during the double-blind study phase for chemistry parameters. Few subjects in any of the 4 treatment groups had shifts from baseline to week 4 noted for any chemistry parameter with the exception of phosphate.

**Table 10.1.1.38. Chemistry Shifts from Baseline to Week 4 during the Double-blind Study Phase by Dose as Randomized (Safety Population, Double-blind Phase)**

Parameter:	Lanreotide Autogel:			Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)		
AST					
Shifted to low	0/26	0/24	0/27	0/23	0/100
Shifted to high	0/26	0/24	0/27	0/23	0/100
ALT					
Shifted to low	0/26	0/24	0/27	0/23	0/100
Shifted to high	0/26	1/24 (4%)	1/27 (4%)	1/23 (4%)	3/100 (3%)
Alkaline phosphatase					
Shifted to low	0/26	0/24	0/27	0/23	0/100
Shifted to high	1/26 (4%)	1/24 (4%)	1/27 (4%)	0/23	3/100 (3%)
Fasting Blood Glucose					
Shifted to low	0/23	0/22	0/20	0/18	0/83
Shifted to high	1/23 (4%)	1/22 (5%)	1/20 (5%)	1/18 (6%)	4/83 (5%)
Hgb A1c					
Shifted to low	0/27	0/27	0/28	0/24	0/106
Shifted to high	2/27 (7%)	1/27 (4%)	0/28	1/24 (4%)	4/106 (4%)
Bilirubin					
Shifted to low	0/26	0/25	0/27	0/23	0/101
Shifted to high	0/26	0/25	0/27	0/23	0/101
Creatinine					
Shifted to low	2/26 (8%)	1/24 (4%)	2/27 (7%)	1/23 (4%)	6/100 (6%)
Shifted to high	0/26	0/24	1/27 (4%)	0/23	1/100 (1%)
Sodium					
Shifted to low	0/27	0/27	0/28	0/23	0/105
Shifted to high	0/27	0/27	1/28 (4%)	1/23 (4%)	2/105 (2%)
Potassium					
Shifted to low	0/26	0/24	0/27	0/23	0/100
Shifted to high	1/26 (4%)	0/24	2/27 (7%)	1/23 (4%)	4/100 (4%)
Calcium					
Shifted to low	0/27	0/27	1/28 (4%)	0/23	1/105 (<1%)
Shifted to high	0/27	2/27 (7%)	1/28 (4%)	0/23	3/105 (3%)
Phosphate					
Shifted to low	0/26	0/24	0/27	0/23	0/100
Shifted to high	3/26 (12%)	2/24 (8%)	2/27 (7%)	6/23 (26%)	13/100 (13%)

Sponsor's Table 59, Module 5, Vol 53, pg. 155

Only 1 or 2 subjects in any of the 3 treatment groups had clinically relevant shifts from baseline to Week 16 for AST, ALT, alkaline phosphatase, hemoglobin A1c, bilirubin, creatinine, sodium, potassium, or calcium. Five patients had shifts from baseline to Week 16 in fasting blood glucose including 4 patients who shifted to high glucose and one who shifted to low glucose. Most shifts in fasting blood glucose were observed in the 90 mg treatment group however no trend was

noted across the treatment groups for shifts in fasting blood glucose. One patient in the 120 mg group had a shift in potassium from normal to very high at the Week 16 evaluation.

Only 1 or 2 of the lanreotide-treated subjects had clinically relevant shifts to high or low from baseline to LVA for AST, ALT, alkaline phosphatase, bilirubin, creatinine, sodium or calcium. No shifts to very high were noted from baseline to LVA in any chemistry parameter. Nine patients had shifts from baseline normal values to high values at LVA in fasting blood glucose and in hemoglobin A1c. No trend was discernible across the three treatment groups for shifts in fasting blood glucose and HgbA1c. Six patients had shifts in phosphate to above the normal range at LVA; no trend was noted across the three treatment groups for shifts in phosphate. One patient had a shift to very low value for a clinical chemistry parameter (sodium). This patient (#702.0008), randomized to 60 mg lanreotide had a shift from a baseline low sodium value (129 mmol/L) to a very low value at week 53 (123 mmol/L).

*Marked outliers and dropouts for laboratory abnormalities*

Twenty (19%) of the 107 lanreotide-treated patients had chemistry abnormalities that were reported as clinically significant by the investigator at some time during the 3 study phases that were not reported as clinically significantly abnormal at baseline. The most commonly reported clinically significant chemistry abnormality was an increase in hemoglobin A1c reported in 11 patients overall (Patients 701.0001, 701.0011, 701.0017, 703.0003, 707.0005, 716.0004, 719.0012, 725.0002, 728.0006, 733.0005 and 733.0011); in 5 of these patients the abnormalities were reported only at the last study visit. Six of the 11 patients with clinically significant elevations in hemoglobin A1c also had clinically significant increases in glucose noted including one patient who also had an elevation in phosphate. Two additional patients (Patients 714.0001 and 724.0003) had clinically significant increases in fasting glucose reported; the former patient also had a clinically significant elevation in alkaline phosphatase reported. In 3 patients (Patients 701.0016, 713.0005 and 713.0007), clinically significant increases in bilirubin were reported. Other clinically significant abnormalities included 1 report of low sodium in Patient 713.0003, one report of low calcium in Patient 713.0008, 1 report of elevated phosphate in Patient 702.0008 and 1 report of elevated alkaline phosphatase Patient 714.0002.

The most common laboratory abnormalities reported as adverse events during lanreotide treatment were hyperglycemia (10 patients, 9%), hypoglycemia (4 patients, 4%), and increased alkaline phosphatase, hypercholesterolemia and bilirubinemia (3 patients, 3%); all other reported laboratory abnormalities occurred in only 1 or 2 patients each during the 52-week study. There was no apparent increase in the incidence of any laboratory abnormality reported as an adverse event across lanreotide dose. The majority of laboratory abnormalities reported as adverse events were assessed as mild to moderate in severity; one report of hypoglycemia was assessed as severe in intensity. Patient 712.0001 experienced severe hypoglycemia on Study Day 84 (Week 12) during treatment with 120 mg that was judged to be unrelated to study treatment; glucose value was not reported at that time. The event was reported as resolved within 1 day.

**Table 10.1.1.39. Laboratory Abnormalities Reported as Treatment-emergent Adverse Events During the Double/Single-blind and Open-label Phases by Preferred Term and Dose at Onset of the Event (Safety Population, Double/Single-blind + Open-label Phase)**

Preferred term	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 46) <sup>1</sup>	90 mg (N = 66) <sup>1</sup>	120 mg (N = 74) <sup>1</sup>	
<b>Chemistry:</b>				
Hyperglycaemia	3 (7%)	4 (6%)	3 (4%)	10 (9%)
Hypoglycaemia	1 (2%)	1 (2%)	2 (3%)	4 (4%)
Phosphatase alkaline increased	1 (2%)	1 (2%)	1 (1%)	3 (3%)
Hypercholesterolemia	2 (4%)	2 (3%)	0	3 (3%)
Bilirubinaemia	2 (4%)	1 (2%)	0	3 (3%)
Hyperphosphataemia	1 (2%)	1 (2%)	0	2 (2%)
Hypercalcaemia	0	1 (2%)	0	1 (<1%)
Hyperlipaemia	0	1 (2%)	0	1 (<1%)
Hypocalcaemia	0	1 (2%)	0	1 (<1%)
Hypokalaemia	0	1 (2%)	0	1 (<1%)
Hypomagnesaemia	0	1 (2%)	0	1 (<1%)
Hponatraemia	0	1 (2%)	0	1 (<1%)

Percents are based on the total number of patients included in the safety population within a treatment group or overall.

<sup>1</sup> Number of patients included in each dose group is based on the total number of patients who received at least one dose at that dose level; total across the 3 dose groups does not add to 107.

Sponsor's Table 64, Module 5, Vol 53, pg. 163

### *Vital Signs*

Vital signs, including systolic and diastolic blood pressure and pulse, and weight were measured at weeks 0, 4, 16 and 52 (end of study) corresponding to visits 3, 4, 10 and 19; measurements were also to be obtained in the event of early withdrawal. There were no clinically significant changes in vital sign parameters associated with lanreotide acetate following repeated injections.

### *Analyses focused on measures of central tendencies*

The table below presents mean ( $\pm$ ) SD for vital signs parameters during the double-blind study phase. There were no clinically significant differences noted between the lanreotide treatment groups and the placebo group for changes in vital signs between baseline and Week 4. Mean and median changes between these time points were small for all vital signs parameters and all treatment groups.

**Table 10.1.1.40. Vital Signs Parameters (Mean ± SD) at Baseline and Week 4 during the Double-blind Study Phase by Dose as Randomized (Safety Population, Double-blind Phase)**

Parameter:	Lanreotide Autogel:			Placebo (N = 25)	Total (N = 108)
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)		
Weight (kg)					
Baseline	80.1 ± 15.7	81.5 ± 14.1	87.1 ± 19.7	86.4 ± 16.6	83.8 ± 16.7
Week 4	80.4 ± 15.8	80.5 ± 13.9	85.8 ± 19.4	84.6 ± 16.1	82.8 ± 16.5
Systolic BP (mmHg)					
Baseline	130.7 ± 21.1	132.4 ± 18.8	135.1 ± 18.4	127.4 ± 15.9	131.6 ± 18.7
Week 4	129.1 ± 22.0	133.5 ± 20.1	136.5 ± 26.7	127.6 ± 15.5	131.9 ± 21.7
Diastolic BP (mmHg)					
Baseline	80.0 ± 10.5	79.4 ± 14.7	84.1 ± 8.4	77.3 ± 11.3	80.4 ± 11.5
Week 4	76.4 ± 10.3	79.6 ± 11.3	82.7 ± 13.2	77.6 ± 9.4	79.2 ± 11.3
Heart rate (b/min)					
Baseline	78.0 ± 21.3	73.3 ± 12.2	72.7 ± 9.3	70.1 ± 11.6	73.6 ± 14.4
Week 4	69.3 ± 13.5	70.4 ± 10.6	67.7 ± 10.5	68.2 ± 10.9	68.9 ± 11.3

Sponsor's Table 65, Module 5, Vol 53, pg. 164

The table below presents mean (± SD) for vital signs parameters during the double/single-blind and open-label study phases. Mean changes from baseline to week 52 and LVA for all vital signs parameters were small and not clinically meaningful.

**Table 10.1.1.41. Vital Signs Parameters (Mean ± SD) at Baseline, Week 52 and LVA during the Double/Single-blind and Open-label Study Phases by Last Dose Administered (Safety Population, Double/Single-blind + Open-label Phases)**

Parameter:	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 21)	90 mg (N = 17)	120 mg (N = 69)	
Weight (kg)				
Baseline	83.3 ± 16.0	81.6 ± 17.9	84.4 ± 16.9	83.7 ± 16.8
Week 52	83.1 ± 17.6	80.3 ± 12.1	82.3 ± 18.1	82.2 ± 17.2
LVA	83.1 ± 17.6	77.0 ± 15.1	82.4 ± 17.9	81.7 ± 17.4
Systolic BP (mmHg)				
Baseline	133.7 ± 17.9	128.5 ± 21.9	132.0 ± 18.2	131.8 ± 18.6
Week 52	132.8 ± 19.2	129.2 ± 20.3	128.2 ± 17.0	129.3 ± 17.8
LVA	132.8 ± 19.2	129.2 ± 17.9	129.2 ± 17.7	129.9 ± 17.9
Diastolic BP (mmHg)				
Baseline	84.4 ± 9.6	77.2 ± 12.8	79.9 ± 11.7	80.4 ± 11.6
Week 52	83.0 ± 11.7	78.4 ± 11.7	78.8 ± 10.6	79.7 ± 11.0
LVA	83.0 ± 11.7	77.8 ± 10.5	79.6 ± 10.7	80.0 ± 10.9
Heart rate (b/min)				
Baseline	74.5 ± 9.3	77.5 ± 28.9	72.6 ± 9.8	73.7 ± 14.4
Week 52	70.7 ± 9.1	67.6 ± 15.9	67.5 ± 10.8	68.2 ± 11.2
LVA	70.7 ± 9.1	69.4 ± 15.6	67.3 ± 10.7	68.3 ± 11.3

The total number of patients included in each analysis varied between 95 (week 52) and 107 patients.  
 Sponsor's Table 67, Module 5, Vol 53, pg. 166

*Analyses focused on outliers or shifts from normal to abnormal*

Marked outliers and dropouts for vital sign abnormalities:

As shown in the table below, vital signs abnormalities and body weight changes reported as adverse events during the double/single-blind study phases included bradycardia (15 patients, 14%), weight decrease (10 patients, 9%), hypertension aggravated (6 patients, 6%), hypertension (3 patients, 3%) and weight increase (1 patient, <1%). There was no increase in incidence with lanreotide dose for any of these reported events.

**Table 10.1.1.42. Vital Signs Abnormalities Reported as Treatment-emergent Adverse Events During the Double/Single-blind and Open-label Phases by Preferred Term and Dose at Onset of the Event (Safety Population, Double/Single-blind + Open-label Phases)**

Preferred term	Lanreotide Autogel:			Total (N = 107)
	60 mg (N = 46) <sup>1</sup>	90 mg (N = 66) <sup>1</sup>	120 mg (N = 74) <sup>1</sup>	
Bradycardia	7 (15%)	5 (8%)	4 (5%)	15 (14%)
Weight decrease	3 (7%)	4 (6%)	3 (4%)	10 (9%)
Hypertension aggravated	2 (4%)	2 (3%)	2 (3%)	6 (6%)
Hypertension	1 (2%)	0	2 (3%)	3 (3%)
Weight increase	1 (2%)	0	0	1 (<1%)

Sponsor's Table 68, Module 5, Vol 53, pg. 166

Five patients had 6 vital signs abnormalities reported as severe in intensity (3 reports of hypertension aggravated and one report each of bradycardia, hypertension and weight decrease):

Patient 701.0001 had worsening bradycardia reported as a possibly related severe event on Study Day 29 (week 4) during treatment with 60 mg. The patient's baseline heart rate was 58 bpm decreased to 37 bpm at week 4 increased to 46 bpm at week 16 and to 69 bpm at week 52. This patient also had anemia and elevated HgbA1c as an adverse event.

Patient 701.0015 had exacerbation of hypertension reported as a possibly related severe event on Study Day 85 (Week 12) during treatment with 120 mg. The patient's baseline blood pressure was 178/87 mmHg with an increase to 243/126 mmHg noted at Week 4 and a blood pressure of 186/98 reported at Week 16. The patient was receiving benazepril and triamterene with hydrochlorothiazide at study entry; no changes were noted in her anti-hypertensive medication during the study. This patient discontinued the study at week 24 due to the growth of a pre-existing meningioma.

Patient 701.0017 had worsening hypertension reported as a possibly related event of moderate intensity on Study Day 39 (Week 5) during treatment with 60 mg; the intensity of this worsening in hypertension increased to severe on Study Day 364 (Week 52) during continued treatment with 60 mg. The patient's baseline blood pressure was 178/93 mmHg and 162/86 mmHg at week 4 and 154/83 mmHg at Week 16. The hypertension worsened to 199/97 mmHg at Week 52. The patient was receiving lisinopril with hydrochlorothiazide and atenolol at study entry; lisinopril was added at Week 6, amlodipine was added during only 5 days at week 7 and guanfacine was added at week 8 to attempt to control the patient's hypertension. Abdominal arteriography, performed at Week 5 revealed a bilateral renal artery disease. This patient also had mild bradycardia reported as a probably related event at Week 16; no treatment was required for this event.

Patient 701.0032 randomized to 90 mg had severe decrease in weight reported at Week 0 and worsening hypertension reported as a possibly related severe event on Study Day 92 (Week 13) during treatment with 90 mg. The patient's baseline blood pressure was 165/93 mmHg with no change noted at Week 4 (167/94 mmHg) and a blood pressure of 173/96 mmHg reported at Week 16 and 154/91 mmHg at Week 52. The patient was receiving diltiazem at study entry; losartan 25 mg was added at Week 14 for the worsening hypertension with an increase in the dose from 25 to 50 mg noted at week 22.

Patient 733.0002 had severe hypertension reported as an adverse event during treatment with 60 mg on Study Day 306 (Week 43). Blood pressure reported at that time was 190/130 mmHg. The patient was treated with nifedipine for the hypertensive crisis and then placed on amlodipine to control hypertension. The patient's baseline blood pressure was 160/100 mmHg; blood pressure reported at Week 3, 15 and 51 was 170/100, 155/95 and 145/100, respectively.

#### Standard analyses and explorations of ECG data

An electrocardiogram (ECG) was obtained at Weeks 0, 4, 16 and 52 (end of study) corresponding to visits 3, 4, 10 and 19. Echocardiography was done at Visit 33 (Week 0/Injection #1), Visit 10 (Week 16/Injection #5) and Visit 19 (Week 52, but procedure done only in case of withdrawal or discontinuation). ECGs were collected and a central read and assessment was performed.

#### *Analyses focused on measures of central tendency*

Changes in Centralized ECG Data to Week 4, Double-blind Phase, Comparison to Placebo: Mean ( $\pm$ SD) for ECG intervals at baseline and as a change from baseline to Week 4/LVA are displayed in the table below for the 3 lanreotide dose groups, the pool of all lanreotide-treated patients and the placebo group. There were no statistically significant differences between any lanreotide dose group and the placebo group for change from baseline to Week 4 for PR, QRS or QTcF intervals. The only significant and consistent change was a decrease in heart rate in the lanreotide patients as compared to controls. This decrease in heart rate is consistent with the observed concomitant increase in RR interval and increase in QT interval (but not corrected QT interval).

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<sup>3</sup> These procedures did not need to be performed if there was documentation that the procedure was performed within the previous 3 months and the results did not give the investigator cause to repeat it (i.e., all data were collected according to protocol and CRF requirements).

**Table 10.1.1.43. Mean ( $\pm$ SD) Baseline and Change from Baseline to Week 4/LVA in ECG Parameters by Dose as Randomized (Safety Population, Double-blind Phase, N=108)**

ECG Parameter	Lanreotide Autogel:				Placebo (N=25)
	60 mg (N=27)	90 mg (N=27)	120 mg (N=29)	Overall (N=83)	
<b>RR Interval (msec)</b>					
N	25	25	28	78	21
Baseline Mean $\pm$ SD	797.8 $\pm$ 161.4	829.6 $\pm$ 176.2	820.0 $\pm$ 134.2	815.9 $\pm$ 155.8	867.0 $\pm$ 175.6
Mean change $\pm$ SD	123.5 $\pm$ 130.9	126.7 $\pm$ 132.5	146.6 $\pm$ 146.3	132.8 $\pm$ 135.8	48.4 $\pm$ 123.5
p-value <sup>1</sup>	<0.001	<0.001	<0.001	<0.001	0.088
p-value <sup>2</sup>	0.092	0.063	0.018	0.018	--
<b>PR Interval (msec)</b>					
N	25	24	27	76	21
Baseline Mean $\pm$ SD	152.5 $\pm$ 23.7	152.4 $\pm$ 25.8	164.1 $\pm$ 18.1	156.6 $\pm$ 23.0	158.8 $\pm$ 22.4
Mean change $\pm$ SD	6.2 $\pm$ 13.9	6.4 $\pm$ 15.0	5.7 $\pm$ 13.3	6.1 $\pm$ 13.8	1.4 $\pm$ 7.8
p-value <sup>1</sup>	0.036	0.047	0.033	<0.001	0.412
p-value <sup>2</sup>	0.258	0.237	0.226	0.154	--
<b>QRS Interval (msec)</b>					
N	25	25	28	78	21
Baseline Mean $\pm$ SD	95.8 $\pm$ 21.7	92.2 $\pm$ 17.8	90.2 $\pm$ 12.7	92.7 $\pm$ 17.5	89.1 $\pm$ 10.0
Mean change $\pm$ SD	2.5 $\pm$ 6.3	0.6 $\pm$ 8.2	3.2 $\pm$ 6.9	2.2 $\pm$ 7.1	2.9 $\pm$ 7.3
p-value <sup>1</sup>	0.056	0.698	0.022	0.009	0.089
p-value <sup>2</sup>	0.840	0.372	0.823	0.861	--
<b>QT Interval (msec)</b>					
N	25	25	28	78	21
Baseline Mean $\pm$ SD	367.1 $\pm$ 34.7	360.4 $\pm$ 37.0	360.6 $\pm$ 32.3	362.6 $\pm$ 34.3	372.9 $\pm$ 37.7
Mean change $\pm$ SD	15.8 $\pm$ 17.3	16.8 $\pm$ 25.7	23.8 $\pm$ 25.5	19.0 $\pm$ 23.2	7.2 $\pm$ 29.4
p-value <sup>1</sup>	<0.001	0.003	<0.001	<0.001	0.276
p-value <sup>2</sup>	0.303	0.324	0.046	0.106	--
<b>QTcF Interval (msec)</b>					
N	25	25	28	78	21
Baseline Mean $\pm$ SD	397.2 $\pm$ 24.1	385.3 $\pm$ 24.9	386.0 $\pm$ 24.0	389.3 $\pm$ 24.6	392.3 $\pm$ 26.7
Mean change $\pm$ SD	-0.6 $\pm$ 11.4	-1.2 $\pm$ 18.1	4.1 $\pm$ 17.0	0.9 $\pm$ 15.8	0.8 $\pm$ 22.0
p-value <sup>1</sup>	0.808	0.752	0.208	0.603	0.868
p-value <sup>2</sup>	0.952	0.336	0.826	0.765	--
<b>Heart Rate (bpm)</b>					
N	25	25	28	78	21
Baseline Mean $\pm$ SD	78.1 $\pm$ 15.1	75.6 $\pm$ 16.5	75.0 $\pm$ 10.6	76.2 $\pm$ 14.0	72.0 $\pm$ 14.8
Mean change $\pm$ SD	-8.4 $\pm$ 7.7	-10.7 $\pm$ 12.6	-11.1 $\pm$ 10.2	-10.1 $\pm$ 10.3	-3.1 $\pm$ 9.9
p-value <sup>1</sup>	<0.001	<0.001	<0.001	<0.001	0.168
p-value <sup>2</sup>	0.187	0.019	0.010	0.012	--

1 p-value for change from baseline

2 p-value for comparison of each lanreotide group to placebo

Sponsor's Table 69, Module 5, Vol 53, pg. 172

**Changes in ECG Data to End of Study, Double/Single-blind + Open-label Phases:**

The table below presents descriptive statistics for ECG parameters at baseline and the end of the study (Week 52 or LVA) as well as changes from baseline to this time point across all 107 patients who received lanreotide. Across all lanreotide-treated patients, mean ( $\pm$ SD) increases in RR, PR, QRS, QT and QTcF interval of 118.1 ( $\pm$ 163.1), 9.4 ( $\pm$ 14.5), 2.6 ( $\pm$ 9.3), 21.4 ( $\pm$ 35.8), and 5.4 ( $\pm$ 23.8) msec, respectively, were noted between baseline and end of study and a mean ( $\pm$ SD) decrease of -8.4 ( $\pm$ 14.8) bpm noted for heart rate. Analysis of these changes from baseline to end of study across all lanreotide-treated patients was statistically significant for all parameters assessed. All mean values were within clinically accepted normal limits. None of the

pairwise comparisons among the lanreotide treatment doses for changes from baseline were statistically significant.

**Table 10.1.1.44. Descriptive Statistics for ECG Parameters at Baseline and End of Study and for Change from Baseline to End of Study (Safety Population, N=107)**

ECG Parameter	Lanreotide Autogel, N=107		
	Baseline	End of Study Week 52/LVA	Change from Baseline to End of Study
<b>RR Interval (msec)</b>			
N	102	107	102
Median	803.5	913.0	123.5
Mean ± SD	837.5 ± 168.4	955.4 ± 208.4	118.1 ± 163.1
Minimum, Maximum	505, 1404	457, 1612	-321, 695
<b>PR Interval (msec)</b>			
N	100	105	100
Median	158.0	165.0	6.0
Mean ± SD	157.4 ± 22.5	167.5 ± 25.1	9.4 ± 14.5
Minimum, Maximum	90, 225	87, 238	-21, 52
<b>QRS Interval (msec)</b>			
N	102	107	102
Median	89.0	91.0	2.0
Mean ± SD	92.5 ± 16.3	94.8 ± 18.8	2.6 ± 9.3
Minimum, Maximum	73, 161	73, 180	-15, 43
<b>QT Interval (msec)</b>			
N	102	107	102
Median	360.0	383.0	23.5
Mean ± SD	367.0 ± 35.6	388.2 ± 39.8	21.4 ± 35.8
Minimum, Maximum	283, 463	290, 514	-96, 135
<b>QTcF Interval (msec)</b>			
N	102	107	102
Median	390.5	395.0	3.5
Mean ± SD	390.7 ± 23.7	395.9 ± 26.3	5.4 ± 23.8
Minimum, Maximum	327, 445	328, 542	-56, 104
<b>Heart Rate (bpm)</b>			
N	102	107	102
Median	75.0	66.0	-9.5
Mean ± SD	74.6 ± 14.8	66.1 ± 15.5	-8.4 ± 14.8
Minimum, Maximum	43, 119	37, 149	-51, 72

Sponsor's Table 71, Module 5, Vol 53, pg. 175

*Analyses focused on outliers or shifts from normal to abnormal*

The majority of all patients (72 of 98 with data available) had ECG assessments interpreted as normal at the core ECG laboratory at both baseline and week 4/LVA; 20 patients had abnormal ECGs at baseline that were also assessed as abnormal at Week 4/LVA. Four patients, including 1 (5%) of 20 in the placebo group, 2 (8%) of 25 in the lanreotide 60 mg group and 1 (4%) of 28 in the lanreotide 120 mg group had a shift from a normal ECG at baseline to an abnormal assessment at week 4/LVA.

The majority of all patients (73 of 101 with data available) had ECG assessments interpreted as normal at the core ECG laboratory at both baseline and week 52/LVA; 22 patients had abnormal ECGs at baseline that were also assessed as abnormal at the end of the study. Five patients (5/101, 5%), including 1 (5%) of 21 whose last dose administered was 60 mg, 2 (13%) of 16

whose last dose administered was 90 mg, and 2 (3%) of 64 whose last dose administered was 120 mg group had a shift from a normal ECG at baseline to an abnormal assessment at week 52/LVA.

#### *Marked outliers and dropouts for ECG abnormalities*

A total of 5 patients with normal ECGs at baseline had clinically significant abnormalities on ECGs at their last evaluation on study. Four of the five patients (Patients 701.0013, 701.0018, 701.0028 and 703.0009) had mild bradycardia reported as an adverse event during the study; Patient 701.0013 also had mild first degree heart block reported. All of these events were assessed as possibly or probably related to study treatment; dose at onset of these events was 60 mg in one patient, 90 mg in one and 120 mg in two patients. The remaining patient with a normal baseline ECG and treatment-emergent clinically significant abnormalities on ECG during the study was Patient 731.0006 who experienced severe atrial fibrillation at Week 51. This patient had severe mitral insufficiency at baseline and would thus be at risk to develop AFib secondary to this pre-existing cardiac condition.

In conclusion, mean quantitative cardiac electrophysiologic, as assessed by central review of ECG, were within normal limits for this population. Lanreotide-treated patients had a decrease in heart rate and concomitant changes in the ECG intervals that follow heart rate.

Treatment-emergent adverse events related to ECG assessment and reported in the Heart Rate and Rhythm Disorders body system during the entire study included bradycardia (14%), atrial arrhythmia (2%), atrial fibrillation (2%), heart block (2%), ventricular arrhythmia (<1%) and bundle branch block (<1%).

#### *Special Safety Studies*

##### *Echocardiography*

Echocardiography was done at Visit 3<sup>4</sup> (Week 0/Injection #1), Visit 10 (Week 16/Injection #5) and Visit 19 (Week 52, but procedure done only in case of withdrawal or discontinuation). Echocardiography was also to be obtained in the event of early withdrawal. Information recorded in the CRF included left ventricular systolic function (ejection fraction), regurgitation at the pulmonic, tricuspid, mitral and aortic valves and stenosis of the mitral and aortic valves. Echocardiographies were collected and a central read and assessment was performed. There were two board certified cardiologists reading the echocardiograms. Each echocardiogram was read independently by both readers. Both readers were blinded to the subject's identification, date of echocardiogram measurement, clinical history and treatment sequence (and therefore drug-exposure status). Each discrepant echocardiogram reading between the two independent board certified cardiologists was re-evaluated in a consensus read. A consensus read was performed when the qualitative valvular reads performed by the two independent board certified cardiologists differed. The cardiologists met and reviewed the tape together and come to

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<sup>4</sup> These procedures did not need to be performed if there was documentation that the procedure was performed within the previous 3 months and the results did not give the investigator cause to repeat it (i.e., all data were collected according to protocol and CRF requirements).