

groups of patients throughout the study. Six percent of patients in the lanreotide group had clinically significant mitral regurgitation at baseline compared with 4% at Month 12. The corresponding prevalence in the octreotide group was 2% at both assessments. Clinically significant aortic regurgitation was present in 10% to 11% of patients in both treatment groups at the baseline and Month 12 assessments.

This reviewer concludes that the echocardiographic evaluation did not demonstrate a meaningful difference in the risk of developing new or worsening valvular regurgitation or significant regurgitation in patients treated with lanreotide compared to octreotide. Of note, clinically significant valvular regurgitation was defined for this study as moderate or severe dysfunction for the mitral, pulmonic and tricuspid valves and mild or worse for the aortic valve. Additionally, this study is an observational treatment study of a size and duration adequate to detect nothing less than a marked difference in the cardiovascular adverse event profile of the two drugs, lanreotide and octreotide. This study will not support or defend the cardiac safety of lanreotide, but rather permits a characterization of the valvular changes expected among patients of the type recruited during courses of therapy with lanreotide or octreotide. This study lacked a control group that was treated with a non-somatostatin analogue but otherwise matched for variables related to the underlying disease.

#### **10.1.4 Study number: E-88-52030-087**

**Study Title:** Phase II Multi-center, Open-label Study, Evaluating the Safety and Efficacy of Multiple Deep Subcutaneous Administrations of Lanreotide Acetate (60, 90, 120 mg) in Acromegalic patients with IGF-1 Level Abnormal

**Investigators:** This was a multicenter study conducted by 6 principal investigators. The coordinating investigator for the study was Dr Shlomo Melmed at the Pituitary Center, Los Angeles, CA, USA.

**Study center(s):** The study was conducted at 6 clinical centers in the USA.

**Study period:** 21 May 2001 to 14 November 2002

**Phase of Development:** II

**Publications Based on the Study:** None

**Primary Objectives:** The primary objective of this study was to document the safety of lanreotide acetate in terms of adverse events at all visits.

#### **Secondary Objectives:**

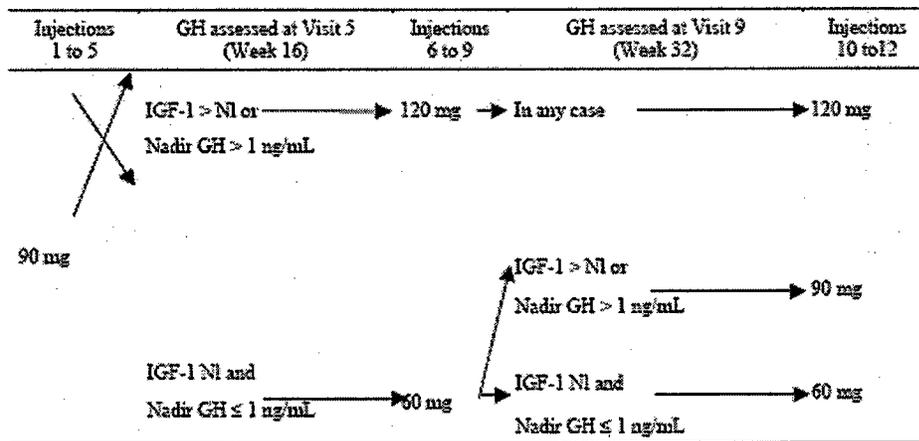
- To document the safety of lanreotide acetate in terms of end of study physical examination (including electrocardiogram [ECG], echocardiography, and blood pressure), standard hematology and chemistry laboratory assessments, and gallbladder ultrasound.

- To evaluate the efficacy of lanreotide acetate 90 mg after 4 injections in acromegalic patients having IGF-1 level above normal (age adjusted).
- To evaluate the efficacy of lanreotide acetate (60, 90, or 120 mg) over time in acromegalic patients having IGF-1 levels above normal (age adjusted).
- To evaluate the effect of repeated injections of lanreotide acetate on nadir GH during oral glucose tolerance test (OGTT).
- To document the evolution of acromegaly symptoms between baseline, week 16, and the end of the study.
- To characterize lanreotide acetate in terms of blood levels of lanreotide at weeks 16 and 32 and at the end of the study and blood level of antibodies to lanreotide acetate at the end of the study (no pharmacokinetic analysis was conducted due to the limited sample size).

**Design:**

This was an open-label, multicenter study designed to evaluate the safety and efficacy of lanreotide acetate in patients with active acromegaly (IGF-1 level above normal) who were screen failures for study E-28-52030-717. The study comprised 3 study phases: a wash-out phase required only for patients who had been treated with a somatostatin analog or a dopaminergic agonist since their screen visit in study E-28-52030-717, a fixed-dose phase (Week 0 to 16) in which all patients were to receive 5 deep subcutaneous injections of lanreotide acetate 90 mg at 28-day intervals, and an open label dose-titration phase (Week 20-48) in which patients were to receive 7 deep subcutaneous injections of lanreotide acetate at 28-day intervals; during this phase, 2 dose adjustments could take place (to 60 or 120 mg) at Week 20 and Week 36 based on GH and IGF-1 levels assessed at the prior visit.

**Figure 10.1.4.1: Dose Adjustment**



IGF-1 > NI = above the upper limit of normal range (age adjusted).  
 IGF-1 NI = in the normal ranges or below the lower limit of normal range (age adjusted).  
 Nadir GH represents the lowest GH level during the OGTT (blood sample at 60 or 120 minutes).  
 Sponsor's Figure 1, Vol 101

**Patient Population:**

Patients 18 years of age or older with active acromegaly (IGF-1 level above normal) who were screen failures for study E-28-52030-717 based on their mean GH levels. Specifically, patients who were screen failures because they had never received a somatostatin analog or dopaminergic agonist or who had received these treatments but discontinued the therapy at least 3 months prior to visit 1 in study E-28-52030-717 and who had mean GH levels  $\leq 5$  ng/mL at that visit were specific candidates for this study as were patients who were receiving somatostatin analogs or dopaminergic agonists at visit 1 of study E-28-52030-717, entered the wash-out phase for that study, but had mean serum GH levels  $\leq 3$  ng/mL or had a  $< 100\%$  increase in mean GH levels from visit 1 at visits 2 and 2A.

Main exclusion criteria included receipt of radiotherapy for acromegaly within 3 years or pituitary surgery within 3 months prior to visit 1; anticipated need for pituitary surgery or radiotherapy during the study period; any prior receipt of lanreotide acetate or GH antagonist; known hypersensitivity to any of the test materials or related compounds; and clinically significant renal or hepatic abnormalities.

**Treatment Groups:**

Eleven patients were treated and analyzed; including 4, 2 and 5 patients whose last dose received was 60, 90 and 120 mg lanreotide acetate, respectively.

**Duration of Treatment:**

Each enrolled patient participated in the study for a maximum of 56 weeks, depending on the wash-out duration; patient participation included a wash-out phase of up to 8 weeks, a 16-week fixed dose phase, and a 32-week dose-titration phase.

**Endpoints:**

Efficacy: IGF-1 levels, nadir GH during oral glucose tolerance test (OGTT), acromegaly symptoms at Weeks 0, 16, 32, and 48; evaluations also were to be performed in the event of early withdrawal.

Safety: monitoring for adverse events, physical examination (including ECG, echocardiography, blood pressure), standard hematology and biochemistry analysis, gallbladder ultrasound, anti-lanreotide antibodies levels, concomitant medications. Lab and U/S studies were done at Week 0 and end-of-study (Week 48).

**Statistical Analyses:**

The intent-to-treat (ITT) population includes all patients who received at least one dose of study medication. The safety population is identical to the ITT population. No formal statistical significance testing was conducted. Assessment of treatment effects was made using data summaries. Efficacy endpoints were analyzed for the ITT population. All safety tabulations are based on the safety population and are descriptive in nature.

**Protocol Amendments:**

The original study protocol, dated 26 October 2000, was amended once on 16 February 2001. The primary reason for the protocol amendment was to add echocardiography and anti-lanreotide

antibodies to the safety evaluations and to change the evaluation of GH levels from mean levels from 7 blood samples over 3 hours to the nadir GH level during OGTT.

### **Results:**

#### **Patient Demographics**

A total of 11 patients with acromegaly were enrolled and treated in this study. The 11 patients comprised 8 (73%) males and 3 (27%) females; 91% of patients were Caucasian and 1 patient (9%) was Hispanic. Median age was 59 years across all 11 patients with a range of 40 to 80 years. Most of the patients (8 patients, 73%) were 40 to 65 years of age at study entry and 3 patients (27%) were >65 years of age. All (100%) of the 11 patients had at least one ongoing medical condition at study entry. The most common ongoing medical conditions were hypertension (45%), allergic rhinitis (36%) and other anterior pituitary disorders (27%). All other ongoing conditions were reported in 2 patients or fewer. There were 2 reports of ongoing medical conditions related to the gallbladder. Patient 701.0020 had cholelithiasis and Patient 704.0004 had gallbladder sludge at study entry.

#### **Patient Disposition**

Twelve patients were screened for study enrollment; one of these patients was not treated on study because it was anticipated that the patient would require pituitary surgery or receive radiotherapy during the study period. A total of 11 patients were enrolled and treated. Of the 11 patients who received at least one injection of lanreotide acetate during the study, 9 (82%) completed the study as planned and 2 (18%) patients did not complete the study. Patient 702.0002, who was receiving lanreotide acetate 90 mg, was lost to follow-up during the 90 mg fixed dose phase. All other patients completed the 90 mg fixed dose phase of the study. Patient 701.0020 withdrew from the study because of adverse events (nervousness and dizziness) after his dose was decreased to 60 mg during the dose titration phase.

#### **Patient Exposure to Study Drug**

Nine (82%) of the 11 patients treated in this study received all 12 injections of lanreotide acetate as planned including 1 patient who received 90 mg only, 5 patients who received 90 mg and had the dose reduced to 60 mg and 5 patients who received 90 mg followed by dose titration to 120 mg. The mean ( $\pm$  SD) cumulative lanreotide acetate dose administered across all 11 patients was 998 ( $\pm$  332) mg and the mean ( $\pm$  SD) duration of study drug exposure was 318 ( $\pm$  76) days.

#### **Concomitant Medication Use**

Ten (91%) of the 11 patients received concomitant medications. The most commonly administered types of medications were anilides (6 patients, 55%); nonsteroidal antiinflammatory/antirheumatic products and propionic acid derivatives (4 patients each, 36%); platelet aggregation inhibitors excluding heparin, multivitamins and other plain vitamin preparations (3 patients each, 27%). Beta blocking agents, bulk producers, corticosteroids, glucocorticoids, natural opium alkaloids, ACE inhibitors (plain), 3-oxoandrosen (4) derivatives, ascorbic acid (plain), calcium, diphenylpropylamine derivatives, drugs used in erectile dysfunction, folic acid and derivatives and HMG:COA reductase inhibitors were each used by 2 patients (18%).

### Efficacy Outcomes

#### GH

At baseline, the mean ( $\pm$  SD) nadir serum GH level during OGTT was 6.2 ( $\pm$  6.9) ng/mL. Decreases from baseline in mean nadir GH were seen at each post-baseline assessment. At Week 16, Week 48 and LVA, mean ( $\pm$  SD) percent decreases from baseline were 62.8% ( $\pm$  29.7), 61.9% ( $\pm$  30.0) and 63.8% ( $\pm$  28.9), respectively. Of the 10 patients with post-baseline GH measurements, 7 (70%) achieved nadir GH levels  $<1.0$  ng/mL after the oral glucose tolerance test (OGTT). Six out of 10 (60%) also achieved a GH  $<2.5$  ng/mL prior to OGTT (random). Three out of 10 patients (30%) were unable to achieve a nadir GH level after OGTT  $<1.0$  ng/mL or random GH  $<2.5$  ng/mL. Pt 704.0001 had a nadir GH level after OGTT of  $\sim$  ng/mL at Week 0 which decreased to  $\sim$  ng/mL at Week 51. Pt 706.0002 had a nadir GH level after OGTT of  $\sim$  ng/mL at Week -13 which decreased to  $\sim$  ng/mL at Week 51. However, Pt 702.0007 had a nadir GH level after OGTT of  $\sim$  ng/mL at Week 0 which increased to  $\sim$  ng/mL at Week 56.

#### IGF-1

At baseline, the mean ( $\pm$  SD) serum IGF-1 concentration was 678 ( $\pm$  281) ng/mL. Decreases from baseline in mean IGF-1 concentration were seen at each post-baseline assessment. At Week 16, Week 48 and LVA, mean ( $\pm$  SD) percent decreases from baseline of 57.5% ( $\pm$  17.2), 51.6% ( $\pm$  20.0) and 52.5% ( $\pm$  19.0), respectively.

Following 5 injections of lanreotide acetate 90 mg (Week 16), 7 (70%) of 10 patients assessed had normalized (age-adjusted) IGF-1 levels. Only four (40%) of 10 patients with post-baseline IGF-1 data continued to have normalized IGF-1 concentrations at the last assessment and 3 patients (30%) had normalized IGF-1 concentrations at Week 16 and 32, but above normal values at week 48. The remaining 3 (30%) patients had IGF-1 concentrations above normal at all assessments.

#### Normal age-adjusted IGF-1 and nadir GH $<1.0$ ng/mL after OGTT

Four out of ten patients (40%) with post-baseline assessments had achieved a normal IGF-1 and GH  $<1.0$  ng/mL during OGTT by the end of the study.

#### Acromegaly Symptoms

For each of the acromegaly symptoms evaluated (headache, perspiration, fatigue, swelling of extremities, joint pain, impotence and oligomenorrhea), the intensity of the symptom was stable from baseline to the last assessment for the majority of patients. Improvement from baseline to the last assessment was seen for perspiration (1 patient; Patient 701.0020), fatigue (2 patients; Patients 702.0001 and 705.0001), swelling of extremities (3 patients; Patients 702.0001, 702.0007, and 706.0002), joint pain (2 patients; Patients 701.0020 and 702.0001) and impotence (1 patient; Patient 701.0020). Worsening of a symptom (impotence) was seen for 1 patient (Patient 704.0002) at the last evaluation.

#### Safety Data:

Ten (91%) of the 11 patients experienced at least one adverse event during the study. The most commonly reported adverse events were abdominal pain (45%), diarrhea (36%), weight decrease

(36%), flatulence (27%) and nausea (27%). With the exception of nausea, these commonly reported events occurred most often while patients were receiving lanreotide acetate 90 mg. No increase in the occurrence of adverse events was noted during administration of the higher dose (120 mg) of lanreotide acetate.

The majority of adverse events were mild to moderate in severity. Four (36%) patients experienced severe events, including dizziness, headache, tendon disorder and pulmonary emboli.

There were no deaths reported during the study. One patient experienced a serious adverse event (pulmonary emboli) while receiving lanreotide acetate 120 mg; the events was unlikely to be related to study treatment. One other patient withdrew from the study because of treatment-emergent adverse events (nervousness and dizziness), which occurred while the patient was receiving the 60 mg dose of lanreotide acetate; these events were judged to be possibly related to study treatment.

There were no clinically significant changes in hematology, chemistry or vital signs parameters during the study.

One patient with a normal ECG at baseline had a clinically significant abnormal ECG evaluation at the end of study. ECG abnormalities reported as adverse events in this patient included mild non-specific T wave and transient junctional rhythm abnormalities along with mild sinus bradycardia and occasional premature ventricular contractions; all were assessed as possibly related to study treatment.

One patient who received 120 mg lanreotide acetate as his last dose had a clinically significant change on echocardiography from baseline to end of study. This patient had worsening of aortic regurgitation (none to physiologic) and abnormal pulmonic regurgitation (none to mild). Seven out of 11 subjects had baseline and post-baseline echocardiograms.

Of the six patients who had gallbladder ultrasound data available at baseline and post-baseline and had no gallstones at baseline, one patient (17%) developed the new onset of gallstones. No patient had new onset of sludge at the post-baseline assessment.

#### *Deaths*

No patient deaths occurred during this study.

#### *Serious Adverse Events*

One patient experienced serious adverse events during the study. Patient 702.0007, who was receiving lanreotide acetate 120 mg, experienced pulmonary emboli (verbatim terms multiple bilateral pulmonary thrombosis right knee DVT and mild pulmonary emboli - inconclusive) on study day 190 (week 27, DVT) and on day 270 (week 38, pulmonary emboli). The events were judged to be unrelated to study treatment.

#### *Adverse Events that Led to study Withdrawal*

One patient withdrew from the study because of treatment-emergent adverse events. Patient 701.0020, who was receiving 60 mg lanreotide acetate, withdrew from the study because of nervousness of moderate intensity and dizziness of severe intensity which began on study day 230 (week 32). The nervousness and dizziness were both judged to be possibly related to study treatment.

*Treatment Emergent Adverse Events*

Ten (91%) of the 11 patients experienced at least one adverse event during the study. Table 10.1.4.1 presents the number and percent of patients reporting the most commonly occurring ( $\geq 10\%$  overall incidence) treatment-emergent adverse events by WHOART preferred term and lanreotide acetate dose at onset of the event. No dose-related increase in the incidence of adverse events was apparent.

**Table 10.1.4.1. Number (%) of Patients With the Most Commonly Reported ( $\geq 10\%$  of patients) Treatment emergent Adverse Events by Preferred Term and Dose at Onset (Safety Population)**

Preferred Term	Lanreotide Autogel:			Total (N = 11)
	60 mg (N = 5) <sup>1</sup>	90 mg (N = 11) <sup>1</sup>	120 mg (N = 5) <sup>1</sup>	
At least 1 adverse event	4 (80%)	10 (91%)	4 (80%)	10 (91%)
Abdominal pain	1 (20%)	4 (36%)	1 (20%)	5 (45%)
Diarrhoea	1 (20%)	4 (36%)	1 (20%)	4 (36%)
Weight decrease	1 (20%)	4 (36%)	1 (20%)	4 (36%)
Flatulence	0	3 (27%)	1 (20%)	3 (27%)
Nausea	2 (40%)	1 (9%)	0	3 (27%)
Alopecia	2 (40%)	1 (9%)	0	2 (18%)
Anxiety	0	2 (18%)	0	2 (18%)
Dizziness	2 (40%)	0	0	2 (18%)
Fatigue	0	2 (18%)	0	2 (18%)
Influenza-like symptoms	0	1 (9%)	1 (20%)	2 (18%)
Purpura	0	1 (9%)	1 (20%)	2 (18%)

Data source: Sponsor's Section 10.3.1, Table 14.3.1B, Table 9

<sup>1</sup> The number of patients included in each dose group is based on the total number of patients who received at least one dose at that level; the total across 3 dose groups does not add to 11.

The most common adverse events reported during the study were gastrointestinal disorders occurring in 7 (64%) of the 11 patients. Six (55%) patients experienced gastrointestinal disorders while receiving lanreotide acetate 90 mg and 2 (40%) patients each experienced gastrointestinal disorders while receiving lanreotide acetate 60 mg and 120 mg. The most commonly reported gastrointestinal disturbance was abdominal pain reported in 5 (45%) of the 11 patients. Other commonly reported gastrointestinal events were diarrhea, flatulence and nausea reported in 4 (36%), 3 (27%) and 3 (27%) of the 11 patients, respectively. The only other gastrointestinal event reported during the study was vomiting, reported in 1 patient (9%).

Other commonly reported treatment-emergent adverse events were weight decrease reported in 4 (36%) of the 11 patients, and fatigue, influenza-like symptoms, dizziness, purpura, anxiety and alopecia each reported in 2 (18%) of the 11 patients.

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Application site disorders were reported in 1 (9%) of the 11 patients and included injection site pain while the patient was receiving lanreotide acetate 60 mg and 90 mg and skin nodule while the patient was receiving lanreotide acetate 90 mg.

#### *Laboratory Parameters*

No laboratory abnormalities were reported as adverse events.

#### *Hematology*

No clinically meaningful changes in hematology parameters were noted from baseline to week 48 or LVA.

One patient had a shift from baseline to low at LVA (week 51). Patient 706.0002, who received lanreotide acetate 120 mg as her last dose, had a shift in RBCs from normal ( $4.0 \times 10^{12}/L$ ) at baseline to low ( $3.8 \times 10^{12}/L$  at week 51) and a shift in hematocrit from normal (0.381 fraction of 1) at baseline to low (0.337 fraction of 1) at week 51. None of the patients had a shift to a high, very high or very low hematology value from baseline to LVA.

#### *Chemistry*

Very few patients had shifts from baseline to LVA noted for any chemistry parameter. One patient (Patient 704.0001), who received lanreotide acetate 120 mg as his last dose, had a shift in alkaline phosphatase from normal (111 U/L) at baseline to high (144 U/L) at LVA (week 51). Another patient (Patient 706.0002), who also received lanreotide acetate 120 mg as her last dose, had a shift in AST from normal (27 U/L) at baseline to high (51 U/L) at LVA (week 51). One patient (Patient 701.0020) whose last dose was 60 mg had a shift in sodium from a baseline normal value (143 mmol/L) to a high value at LVA (149 mmol/L, week 40). No shifts to very low or very high were noted for any patient for any chemistry parameter.

#### *Anti-lanreotide Antibodies*

Samples for determination of anti-lanreotide antibodies were not analyzed due to the small number of patients enrolled in this study.

#### *Vital Signs*

Vital signs abnormalities and body weight changes reported as adverse events included weight decrease (4 patients, 36%), bradycardia (1 patient, 9%) and weight increase (1 patient, 9%). All of these events were reported as mild to moderate in severity.

#### *ECG*

At baseline, 7 of the 11 patients had an abnormal overall ECG evaluation. The clinically significant abnormalities noted at baseline included marked sinus arrhythmia with first degree A-V block and non-specific ST and T wave abnormality; right bundle branch block; old inferior myocardial infarction; and left axis deviation with non-specific T wave abnormality. The ECG findings were unchanged for 3 of these 4 patients at the end of study evaluation; one patient did not have an end of study ECG.

Two patients who had normal ECG evaluations at baseline had abnormal evaluations at the end of study. The abnormal evaluation was judged to be clinically significant for Patient 701.0020 and not clinically significant for Patient 705.0001. The last dose received for both of these patients was 60 mg. The clinically significant ECG abnormalities reported in Patient 701.0020 included mild nonspecific T wave and transient junctional rhythm abnormalities along with mild sinus bradycardia and occasional premature ventricular contractions; all were reported as adverse events and assessed as possibly related to study treatment.

One patient (702.0007) who had an abnormal (not clinically significant) ECG evaluation at baseline had a normal ECG evaluation at the end of study; the last dose this patient received was 120 mg.

Two patients had normal ECG evaluations at baseline and end of study; the last dose received for both patients was 120 mg.

#### *Special Safety Studies*

##### *Gallbladder Ultrasound*

Gallbladder findings were assessed at Baseline and week 48 and at the time of early withdrawal. At baseline, 2 (22%) of 9 patients who had a baseline ultrasound performed had gallstones present on ultrasound. Eight of these 9 patients had a baseline and post-baseline gallbladder assessment. Seven (88%) of the 8 patients had no change from baseline including 5 patients with no gallstones at both time points and 2 patients who had gallstones present at both baseline and at the last assessment. One patient without gallstones at baseline had gallstones present on ultrasound at the post-baseline assessment (Patient 702.0001, 120 mg group); cholelithiasis was reported as a treatment-emergent adverse event for this patient. Thus, one out of 6 patients (17%) developed the new onset of cholelithiasis.

Two (22%) of 9 patients with a baseline ultrasound performed had sludge present at the baseline assessment. All 8 of the patients with a post-baseline ultrasound had no change from baseline, including 7 patients with no sludge at both time points and 1 patient who had sludge present at both baseline and the last assessment.

##### *Echocardiogram*

Seven out of 11 patients had baseline and post-baseline echocardiograms. One patient had a clinically significant change on echocardiography from baseline to the end of study evaluation. Patient 702.0001 (last dose received 120 mg), a 40-year-old White male, had no pulmonic or aortic valve regurgitation and mild tricuspid and mitral valve regurgitation at baseline. At end of study (Week 51), the patient had mild pulmonic valve regurgitation and physiologic tricuspid, mitral, and aortic valve regurgitation. Worsening of aortic regurgitation (from none to physiologic) and abnormal echo pulmonic regurgitation (change from no regurgitation to mild) were reported as mild adverse events.

#### **Sponsor's Conclusions:**

Treatment with lanreotide acetate at doses of 60, 90 and 120 mg was safe and well tolerated. Only 1 patient withdrew from the study because of adverse events (dizziness and anxiety). Nine (82%) patients received all 12 injections of lanreotide acetate as planned. No deaths were reported during the study and only one patient experienced serious adverse events (pulmonary emboli), which were judged unrelated to study treatment.

As has been observed in other studies with lanreotide, the most commonly reported treatment-emergent adverse events were primarily gastrointestinal disturbances, including reports of abdominal pain (45% of patients), diarrhea (36%), flatulence (27%) and nausea (27%). With the exception of nausea, these commonly reported events occurred most often while patients were receiving lanreotide acetate 90 mg.

The majority of adverse events were mild to moderate in severity. Four patients experienced at least one adverse event of severe intensity during the study. The injections were well tolerated. Injection site reactions occurred only in one patient and included injection site pain and skin nodule.

Lanreotide acetate was effective in reducing mean nadir serum GH levels during OGTT and serum IGF-1 levels. After 5 injections of lanreotide acetate 90 mg (week 16), the mean ( $\pm$  SD) nadir serum GH level during OGTT decreased 63.6% ( $\pm$  33.7) and at the last on-study assessment, the mean percent decrease was 63.8% ( $\pm$  28.9). Mean ( $\pm$  SD) serum IGF-1 concentration decreased 57.5% ( $\pm$  17.2) following 5 injections of lanreotide acetate 90 mg; at the last assessment, the mean percent decrease was 52.5% ( $\pm$  19.0).

In conclusion, lanreotide acetate at doses of 60, 90 and 120 mg was safe and well tolerated in a small number of patients with acromegaly.

#### **Medical Officer's Conclusions:**

##### **Efficacy:**

Of the 10 patients with post-baseline GH measurements, 7 (70%) achieved nadir GH levels  $<1.0$  ng/mL after the oral glucose tolerance test (OGTT). Six out of 10 (60%) also achieved a GH  $<2.5$  ng/mL prior to OGTT (random).

Following 5 injections of lanreotide acetate 90 mg (Week 16), 7 (70%) of 10 patients assessed had normalized (age-adjusted) IGF-1 levels. Only four (40%) of 10 patients with post-baseline IGF-1 data continued to have normalized IGF-1 concentrations at the last assessment and 3 patients (30%) had normalized IGF-1 concentrations at Week 16 and 32, but above normal values at week 48. The remaining 3 (30%) patients had IGF-1 concentrations above normal at all assessments.

Thus, four out of ten patients (40%) with post-baseline assessments had achieved a normal IGF-1 and GH  $<1.0$  ng/mL during OGTT by the end of the study.

##### **Safety:**

The most commonly reported adverse events were abdominal pain (45%), diarrhea (36%), weight decrease (36%), flatulence (27%) and nausea (27%).

There were no deaths reported during the study. One patient experienced a serious adverse event (pulmonary emboli) while receiving lanreotide acetate 120 mg.

One patient withdrew from the study because of treatment-emergent adverse events (nervousness and dizziness), which occurred while the patient was receiving the 60 mg dose of lanreotide acetate.

There were no clinically significant changes in hematology, chemistry or vital signs parameters during the study.

One patient with a normal ECG at baseline had a clinically significant abnormal ECG evaluation at the end of study (mild non-specific T wave, transient junctional rhythm abnormalities, mild sinus bradycardia and occasional premature ventricular contractions).

One patient who received 120 mg lanreotide acetate as his last dose had a clinically significant change on echocardiography from baseline to end of study. This patient had worsening of aortic regurgitation (none to physiologic) and abnormal pulmonic regurgitation (none to mild). Seven out of 11 subjects had baseline and post-baseline echocardiograms.

Of the six patients who had gallbladder ultrasound data available at baseline and post-baseline and had no gallstones at baseline, one patient (17%) developed the new onset of gallstones. No patient had new onset of sludge at the post-baseline assessment.

#### **10.1.5 Study number E-28-52030-076**

**Study Title:** Phase II, randomized, parallel groups, double-blind pharmacokinetic study of lanreotide acetate (60, 90, or 120 mg) after 4 deep subcutaneous injections (administered every 28 days) in acromegalic patients

**Investigators:** The study was conducted by Professor Marcello D. Bronstein.

**Study center(s):** The study was conducted at Hospital das Clinicas/University Sao Paulo, São Paulo, Brazil

**Study period:** 29 October 2001 to 29 July 2002

**Phase of Development:** II

**Publications Based on the Study:** None

**Primary Objectives:** The primary objective of this study was to characterize the pharmacokinetic profile of lanreotide acetate in acromegalic patients following multiple deep subcutaneous (s.c.) injections.

**Secondary Objectives:** The secondary objectives included the evaluation of the effectiveness of lanreotide acetate [based on mean growth hormone (GH) levels, insulin-like growth factor-1 (IGF-1) levels and clinical symptoms] and the evaluation of the treatment tolerability.

**Design:** This was a phase II, randomized, parallel group, double-blind study designed to evaluate the pharmacokinetic profile of lanreotide acetate (60, 90, and 120 mg) in patients with active acromegaly. Patients were randomized on a 1:1:1 basis to receive 4 deep subcutaneous injections of fixed doses of 60, 90 or 120 mg lanreotide acetate at 28-day intervals.

**Patient Population:** Patients 18 years of age or older with active acromegaly, defined by a mean GH serum level > 5 ng/mL (mean GH value was calculated from blood samples collected at 0, 30, 60, 90, 120, 150 and 180 minutes after a run-in period off-medication for 21 to 42 days).

Main exclusion criteria included receipt of radiotherapy for acromegaly within 3 years or pituitary surgery within 3 months prior to visit V1; anticipated need for pituitary surgery or radiotherapy during the study period; any prior receipt of lanreotide acetate, lanreotide 30 mg, GH antagonist, or octreotide long-acting formulation; short-acting formulation of octreotide within 5 days prior to visit V2a; short-acting formulation or long acting formulation of a dopaminergic agonist within 7 or 14 days, respectively, prior to visit V2a; known hypersensitivity to any of the test materials or related compounds; and clinically significant renal, cardiac or hepatic abnormalities.

**Treatment Groups:** A total of 20 patients were screened and 18 patients were randomized and received at least one dose of study treatment including 6 patients each who received 60, 90 and 120 mg lanreotide acetate. The patient received a fixed dose of 60, 90 or 120 mg lanreotide acetate based on random assignment.

**Duration of Treatment:** Each enrolled patient participated in the study for 18 to 27 weeks depending on the duration of the screening period required to meet the entry criteria; patient participation included a screening period of 2 to 11 weeks and a treatment period of 16 weeks.

Duration of study drug exposure was 112 days in all 18 patients.

**Endpoints:**

Pharmacokinetics:

This will not be reviewed in this document. Please refer to the Biopharmaceutical Review.

Efficacy:

- Mean GH levels (mean value of 7 blood samples taken at 30 minutes intervals over a 3-hour period) obtained at screening, baseline and at visits V10, V11, V12 and V19.
- IGF-1 levels obtained at baseline and at visits V10, V11, V12 and V19.

- Acromegaly symptoms obtained at screening, baseline and at visits V10, V11, V12 and V19.

**Safety:**

The following safety assessments were conducted: monitoring for adverse events, clinical laboratory tests, physical examinations, vital signs (blood pressure and heart rate), electrocardiogram (ECG), echocardiography, ultrasound of gall bladder and concomitant medications.

**Statistical Analyses:**

The intent-to-treat (ITT) and safety populations include all randomized patients who received at least one dose of study medication. The per protocol (PP) population includes all randomized patients who received at least one dose of the study medication and who did not have major protocol deviations.

Descriptive statistics, including mean, median, standard deviation, coefficient of variation, minimum and maximum values of the serum levels and the pharmacokinetic parameters as well as the confidence intervals at each sampling time (visit) were determined.

No primary efficacy endpoint was defined for this pharmacokinetic study. Secondary efficacy endpoints including the proportion of patients with mean GH  $\leq 2.5$  ng/mL and  $\leq 5.0$  ng/mL, normalized IGF-1, and changes from Baseline in mean GH and IGF-1 are tabulated for both the ITT and PP populations; changes from Baseline in acromegaly symptoms are analyzed only for the ITT population.

All safety tabulations are based on the safety population and were descriptive in nature; no formal statistical testing was conducted.

**Protocol Amendments:**

The original study protocol, dated 26 February 2001, was amended once on 10 September 2001. The primary changes made by protocol amendment were the addition of the safety assessments of echocardiography and electrocardiograms obtained at visits V3 and V19 and clarification on the timing of the gall bladder assessments.

**Results:**

**Patient Demographics**

The study population was comprised of 12 women (67%) and 6 men (33%); median age was 41.5 years with a range of 28 to 67 years. Sixteen (89%) of the 18 patients were Caucasian and 2 (11%) were Black. Median serum GH and IGF-1 levels at baseline were 25.4 and 747.0 ng/mL, respectively.

**Table 10.1.5.1 Time since Diagnosis and Previous Treatment for Acromegaly (ITT and Safety Population)**

Disease Characteristic	Lanreotide Autogel:			Total (N = 18)
	60 mg (N = 6)	90 mg (N = 6)	120 mg (N = 6)	
Time since diagnosis (years)				
Median	1.7	5.7	4.8	3.8
Mean ± SD	3.6 ± 4.1	6.2 ± 5.7	6.1 ± 5.5	5.3 ± 5.0
Minimum, Maximum	0.4, 10.7	0.0, 12.8	1.6, 16.7	0.0, 16.7
Previous acromegaly treatment <sup>1</sup> , N (%)				
Surgery	1 (17%)	3 (50%)	4 (67%)	* 8 (44%)
Radiotherapy	1 (17%)	3 (50%)	2 (33%)	6 (33%)
Acromegaly treatment at Visit VI <sup>1</sup> , N (%)				
No treatment/stopped ≥3 months ago	4 (67%)	2 (33%)	3 (50%)	9 (50%)
Octreotide short-acting	2 (33%)	4 (67%)	3 (50%)	9 (50%)
Dopaminergic agent short-acting	0	1 (17%)	1 (17%)	2 (11%)

Data source: Sponsor's Section 14.1, Table 5.2

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.

A total of 17 (94%) of the 18 patients had at least one ongoing medical condition at study entry. The most common ongoing medical conditions were diabetes mellitus (44%), hypertension (33%), hypothyroidism (17%), goiter (17%), and anemia (17%). All other ongoing conditions were reported in 2 patients or fewer. There was 1 report of an ongoing medical condition related to the gall bladder. Patient 001.0011 in the 120 mg treatment group, had cholelithiasis at study entry.

#### Patient Disposition

A total of 18 patients received at least one injection of lanreotide acetate during the study including 6 patients each who received 60 mg, 90 mg and 120 mg. All 18 patients completed the study as planned through visit 19, each receiving a total of 4 injections of lanreotide acetate at their assigned dose. These 18 patients are included in the ITT population for the analysis of efficacy and pharmacokinetics and the safety population.

#### 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. The most commonly administered types of medications were biguanides and oral iron preparations (each 5 patients, 28%), glucocorticoids, plain thiazides and thyroid hormones (each 4 patients, 22%), and antidiarrheals; fast-acting insulin, natural and synthetic estrogens, and progestogens (each 3 patients, 17%). All other prior and concomitant medications were administered to 2 patients or fewer.

#### Efficacy Outcomes

None of the 18 patients had mean GH ≤ 5.0 ng/mL or normalized IGF-1 (age-adjusted) at study baseline.

At the end of the study (day 112), 6 (33%) of the 18 patients had mean GH levels  $\leq$  5.0 ng/mL, including 2 of 6 patients in the 60 mg group, 1 of 6 in the 90 mg group and 3 of 6 in the 120 mg group. Three (17%) of the 18 patients had mean levels  $\leq$  2.5 ng/mL; all 3 had received lanreotide 120 mg, and 5 patients (28%) had normalized IGF-1 levels, including 1 of 6 in each of the 60 and 90 mg groups and 3 of 6 in the 120 mg group.

Three (17%) of the 18 patients had both mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 (age-adjusted) by day 112; all 3 of these patients had received lanreotide 120 mg.

A progressive decrease in mean GH was noted from baseline over time on study with mean ( $\pm$  SD) decreases of 51.3 ( $\pm$  28.0), 54.3 ( $\pm$  33.7), 57.1 ( $\pm$  33.0), and 60.6 ( $\pm$  27.6) ng/mL noted at days 28, 56, 84 and 112, respectively. Mean IGF-1 decreased from baseline to day 56 with a plateau noted between days 56 and 112; mean ( $\pm$ SD) decreases in IGF-1 of 15.9 ( $\pm$  24.7), 20.1 ( $\pm$  25.9), 19.4 ( $\pm$  24.8), and 19.1 ( $\pm$  27.9) ng/mL were noted at days 28, 56, 84 and 112, respectively.

More than half of the 18 patients showed improvement by day 112 in the acromegaly symptoms of perspiration (78% with improvement), swelling of extremities (61%), and headache (56%) and one-third or more showed improvement in fatigue (44%) and joint pain (33%).

#### Safety Data:

##### *Deaths*

None

##### *Serious Adverse Events*

None

##### *Adverse Events that Led to study Withdrawal*

None

##### *Treatment Emergent Adverse Events*

The most common adverse events reported during the study were gastrointestinal disorders reported in 14 (78%) of the 18 patients including 5, 4 and 5 patients in the 60, 90 and 120 mg treatment groups, respectively.

The most commonly reported events were diarrhea (8 patients, 44%), flatulence (6, 33%), nausea (4, 22%), abdominal pain (3, 17%), vomiting (3, 17%), headache (3, 17%), constipation (2, 11%) and cholelithiasis (2, 11%). The latter events were reports of biliary sludge noted on gallbladder ultrasound for 2 patients in the lowest lanreotide dose group (60 mg).

Application site disorders were reported in 2 (11%) of the 18 patients and included injection site pain in one patient in the 60 mg group and injection site reaction and injection site mass in one patient in the 120 mg group.

The majority of all reported events were mild to moderate in severity. Only one patient experienced an event (headache) that was assessed as severe in intensity by the investigator.

**Table 10.1.5.2. Most Commonly ( $\geq 10\%$ ) Reported Treatment-emergent Adverse Events by Preferred Term (Safety Population)**

Preferred Term	Lanreotide Autogel:			Total (N = 18)
	60 mg (N = 6)	90 mg (N = 6)	120 mg (N = 6)	
Diarrhoea	3 (50%)	2 (33%)	3 (50%)	8 (44%)
Flatulence	2 (33%)	1 (17%)	3 (50%)	6 (33%)
Nausea	2 (33%)	1 (17%)	1 (17%)	4 (22%)
Abdominal pain	0	1 (17%)	2 (33%)	3 (17%)
Headache	2 (33%)	1 (17%)	0	3 (17%)
Vomiting	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Cholelithiasis	2 (33%)	0	0	2 (11%)
Constipation	0	1 (17%)	1 (17%)	2 (11%)

Data source: Sponsor's Section 14.3.1, Table 8.1B

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

*Laboratory Parameters*

**Hematology:**

A small mean ( $\pm$  SD) decrease of  $-0.1 (\pm 0.9)$  mmol/L was noted for hemoglobin across the 18 patients included in the safety population. The table below presents shifts from baseline to day 112 for all hematology parameters. Few patients had any shifts from baseline noted to day 112. All shifts that were noted were to the low range; no patient had a shift to a very low hemoglobin, hematocrit, red cell count, white cell count or platelet count.

**Table 10.1.5.3. Hematology Shifts from Baseline to Day 112 (Visit V19) (Safety Population)**

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Parameter:	Lanreotide Autogel:			Total (N = 18)
	60 mg (N = 6)	90 mg (N = 6)	120 mg (N = 6)	
Hemoglobin				
Shifted to low	0/6	0/6	2/6 (33%)	2/18 (11%)
Shifted to high	0/6	0/6	0/6	0/18
Hematocrit				
Shifted to low	1/6 (17%)	0/6	1/6 (17%)	2/18 (11%)
Shifted to high	0/6	0/6	0/6	0/18
Red blood cells				
Shifted to low	1/6 (17%)	1/6 (17%)	1/6 (17%)	3/18 (17%)
Shifted to high	0/6	0/6	0/6	0/18
White blood cells				
Shifted to low	2/6 (33%)	0/6	0/6	2/18 (11%)
Shifted to high	0/6	0/6	0/6	0/18
Platelets				
Shifted to low	1/6 (17%)	1/6 (17%)	1/6 (17%)	3/18 (17%)
Shifted to high	0/6	0/6	0/6	0/18

Data source: Sponsor's Section 14.3.5 Table 9.2C.

Note: 'shifted to low' means a shift from normal, high or very high to low or a shift from low, normal, high or very high to very low; 'shifted to high' means a shift from normal, low or very low to high or a shift from high, normal, low or very low to very high

A total of 3 patients had hematology abnormalities that were reported as adverse events including 2 patients in the 60 mg group and one in the 120 mg group.

In the 60 mg group, Patient 001.0003 had low hemoglobin at baseline (7.26 mmol/L; normal range 7.45 – 9.93 mmol/L) with hematocrit and red blood cell count at the low end of the normal range (0.35 and  $4.0 \times 10^{12}/L$ , respectively; normal ranges 0.35 to 0.47 and  $4.0$  to  $5.4 \times 10^{12}/L$ , respectively); at day 112, the hemoglobin, hematocrit and red cell count had all decreased from baseline (6.45 mmol/L, 0.31, and  $3.28 \times 10^{12}/L$ , respectively) with both the hemoglobin and hematocrit reported as clinically significant by the investigator.

Patient 001.0017, also in the 60 mg group, had very low hemoglobin (4.90 mmol/L) and low hematocrit (0.27) at baseline with a red cell count in the normal range ( $4.46 \times 10^{12}/L$ ). On Day 112 the hemoglobin and hematocrit had increased slightly to 5.03 mmol/L and 0.28, respectively, but the red cell count had decreased to  $4.02 \times 10^{12}/L$ , which was reported as clinically significant by the investigator.

Patient 001.0012 in the 120 mg group had hemoglobin, hematocrit and red cell count in the normal range (8.38 mmol/L, 0.41, and  $4.80 \times 10^{12}/L$ ) at baseline; normal ranges were 7.45 to 9.93 mmol/L (hemoglobin), 0.35 to 0.47 (hematocrit), and  $4.0$  to  $5.4 \times 10^{12}/L$  (red cell count). By Day 112 all red cell parameters had decreased with values of 6.45 mmol/L, 0.30 and  $3.55 \times 10^{12}/L$  for hemoglobin, hematocrit and red cell count, respectively. All were reported as clinically significant and mild anemia was reported as an adverse event possibly related to study treatment.

Chemistry:

Table 10.1.5.4 presents shifts from baseline to day 112 during study for all chemistry parameters. Very few subjects in any of the 3 treatment groups had shifts from baseline to day 112 noted for any chemistry parameter. No shifts to very high or very low were noted for any patient for any chemistry parameter.

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**Table 10.1.5.4. Chemistry Shifts from Baseline to Day 112 (Visit V19) (Safety Population)**

**APPEARS THIS WAY  
ON ORIGINAL**

Parameter:	Lanreotide Autogel:			Total (N = 18)
	60 mg (N = 6)	90 mg (N = 6)	120 mg (N = 6)	
AST				
Shifted to low	0/6	0/6	0/6	0/18
Shifted to high	0/6	0/6	0/6	0/18
ALT				
Shifted to low	1/6 (17%)	0/6	0/6	1/18 (6%)
Shifted to high	0/6	0/6	1/6 (17%)	1/18 (6%)
Alkaline phosphatase				
Shifted to low	0/6	0/6	0/6	0/18
Shifted to high	1/6 (17%)	0/6	0/6	1/18 (6%)
Albumin				
Shifted to low	0/6	0/6	0/6	0/18
Shifted to high	0/6	0/6	0/6	0/18
GGT				
Shifted to low	0/6	0/6	0/6	0/18
Shifted to high	1/6 (17%)	0/6	0/6	1/18 (6%)
Bilirubin				
Shifted to low	0/6	0/6	0/6	0/18
Shifted to high	0/6	0/6	0/6	0/18
Fasting Blood Glucose				
Shifted to low	0/6	0/6	1/5 (20%)	1/17 (6%)
Shifted to high	1/6 (17%)	0/6	0/6	1/17 (6%)
Creatinine				
Shifted to low	1/6 (17%)	0/6	0/6	1/18 (6%)
Shifted to high	0/6	0/6	0/6	0/18
Sodium				
Shifted to low	0/6	1/6 (17%)	0/6	1/18 (6%)
Shifted to high	0/6	0/6	0/6	0/18
Potassium				
Shifted to low	0/6	0/6	1/6 (17%)	1/18 (6%)
Shifted to high	0/6	0/6	0/6	0/18
Calcium				
Shifted to low	0/6	0/6	0/6	0/18
Shifted to high	0/6	0/6	0/6	0/18
Phosphate				
Shifted to low	0/6	0/6	0/6	0/18
Shifted to high	0/6	1/6 (17%)	1/6 (17%)	2/18 (11%)

Data source: Sponsor's Section 14.3.5, Table 9.3C.

Note: 'shifted to low' means a shift from normal, high or very high to low or a shift from low, normal, high or very high to very low; 'shifted to high' means a shift from normal, low or very low to high or a shift from high, normal, low or very low to very high.

#### Lanreotide Antibodies:

The presence of putative antibodies to lanreotide acetate was observed in one of the 18 patients. Putative antibodies were determined in the pre-treatment sample for Patient 001.0016. The sponsor confirmed that this patient had not received previous treatment with lanreotide. Prior therapy with short-acting octreotide was reported with the last dose administered 3 weeks prior to the first lanreotide dose. This patient's mean serum GH levels did not decrease below 5 ng/mL at any time during the study.

### *Vital Signs*

There were no clinically meaningful changes from baseline to day 112 for any vital signs parameters over all 18 patients included in the safety population. Mean ( $\pm$  SD) weight increased  $+2.7 (\pm 3.8)$  kg from baseline to day 112 across all 18 patients. Mean ( $\pm$  SD) systolic and diastolic blood pressure showed small mean decreases of  $-5.0 (\pm 12.9)$  and  $-3.1 (\pm 12.5)$  mmHg, respectively, from baseline to day 112 across all 18 patients. Mean ( $\pm$  SD) heart rate also decreased ( $-5.9 \pm 9.0$  beats/minute) across all 18 patients between baseline and day 112.

Two patients had vital signs abnormalities reported as adverse events. Patient 001.0010 in the lanreotide 90 mg group had mild bradycardia reported as an adverse event on day 84 of the study. The patient's heart rate was 60 at study entry, 56 on days 56 and 84, and 50 on Day 112. Patient 001.0018 in the lanreotide 60 mg group had mild tachycardia reported as an adverse event at Study Day 0.

### *Special Safety Studies*

#### Gallbladder Ultrasound:

At baseline, 2 of the 18 patients had gallstones present and 16 patients did not have gallstones noted on ultrasound. Results were identical at visit V19 (day 112); both patients with gallstones present at baseline still had gallstones at the end of study and all 16 patients without gallstones still did not have this finding on gallbladder ultrasound.

None of the patients had sludge present at the baseline assessment. At visit V19 (day 112) 2 patients, both in the lanreotide 60 mg dose group (Patients 001.0007 and 001.0014) had sludge reported, the remaining 16 patients did not have sludge noted on gallbladder ultrasound. For both patients, the presence of the biliary sludge was reported as an adverse event (WHOART preferred term, cholelithiasis); the events were assessed as probably related to study treatment by the investigator and were reported as ongoing at the end of the study.

#### Clinical Site Echocardiography:

One patient had a treatment-emergent clinically significant abnormality reported by the investigator on echocardiography. At the end of study evaluation, Patient 001.0010 in the 90 mg group had physiologic regurgitation at the pulmonic and tricuspid valves and mild mitral valve regurgitation reported that was not observed at baseline; no stenosis was noted. This patient had a history of Wolf-Parkinson-White syndrome and aortic ectasia. Mild mitral valve regurgitation was reported as an adverse event on day 113.

### *Other*

Based on a request by the Food and Drug Administration with regard to detailed analyses of cardiac safety studies, the sponsor conducted a retrospective centralized analysis of all ECG and echocardiography data collected in this study.

### *Centralized ECG Results*

Based on the central ECG review, none of the 17 patients with data available had a shift from a normal ECG at baseline to an abnormal assessment at the end of the study. The majority of patients (12 of 17) had ECG assessments interpreted as normal at the core ECG laboratory at both visits V3 and V19. Five patients (Patient Nos. 001.0002, 001.0010, 001.0014, 001.0019 and 001.0020) had abnormal ECGs at baseline that were also assessed as abnormal at visit V19.

#### *Centralized Echocardiography Results*

Seventeen out of 18 patients had echo results at baseline and Day 112.

In evaluating the echoes, the grades of 'none' and 'physiologic' were not considered clinically meaningful and therefore shifts between these categories were summarized as no change by this reviewer.

Mitral regurgitation evaluation was adequate and available at both visit V3 and visit V19 in 13 of the 18 patients (72%). All patients had mild or less mitral regurgitation on both visits. In the clinic site echo assessment, two patients showed a worsening from baseline to visit V19 in regurgitation: Pt No. 001.0018 had physiologic MR at baseline which worsened by one grade to mild at Day 112; Pt No. 001.0010 had no MR at baseline which worsened by two grades to mild at Day 112. In the centralized echo assessment, two patients showed a worsening from baseline to visit V19 in regurgitation: Pt Nos. 001.0018 and 001.0020 had physiologic MR at baseline which worsened by one grade to mild at Day 112. Pt No. 001.0010 who had no MR at baseline which worsened by two grades to mild at Day 112 by the clinic site interpretation, was evaluated as having mild MR at baseline which improved to physiologic by study end by the centralized echo interpretation.

A total of 13 of 18 patients had adequate assessment of aortic regurgitation at both visits to assess for a change over time. No patients had mild, moderate or severe aortic regurgitation during the study. None of the patients showed a change in aortic regurgitation over time on study.

Tricuspid regurgitation was assessed at both baseline and visit V19 in a total of 10 of the 18 patients. No patient had moderate or severe tricuspid regurgitation during the study. Both the clinic site and centralized reading of the echo showed an improvement in TR in Pt. No. 001.0001: mild at baseline to physiological at Day 112 by centralized echo and shift from mild to none by the clinic site evaluation. Both the clinic site and centralized reading of the echo showed a worsening in TR in Pt. No. 001.0020: physiological at baseline to mild at Day 112 by centralized echo and shift from none to mild by the clinic site evaluation.

Lastly, pulmonary regurgitation was adequately assessed on the echocardiograms at baseline and visit V19 in 9 patients. No patients had moderate or severe pulmonary regurgitation during the study. There were no clinically significant changes in pulmonary regurgitation by clinic site or centralized reading during the study.

In conclusion, this reviewer believes the minor changes in valvular regurgitation during the course of Study 076 most likely represent both the variability in the degree of valvular regurgitation over time and measurement variability.

**Sponsor's Conclusions:**

In conclusion, Lanreotide acetate, at doses of 60, 90 and 120 mg, effectively reduced mean serum GH and IGF-1 levels in ~ one-third of patients after 4 administrations separated by 28 days with a clear trend toward a dose-response relationship.

By the end of the study (day 112), one-third of the patients (6 of 18) had mean GH levels  $\leq$  5.0 ng/mL, including 2 of 6 patients in the 60 mg group, 1 of 6 in the 90 mg group and 3 of 6 in the 120 mg group. On Day 112, 3 (17%) of 18 patients had mean GH levels  $\leq$  2.5 ng/mL. All 3 of these patients were receiving 120 mg lanreotide).

Normalized IGF-1 levels (age-adjusted) were obtained in 5 (28%) of the 18 patients by the end of the study (day 112) including 1 of 6 patients in the 60 mg group, 1 of 6 in the 90 mg group and 3 of 6 in the 120 mg group.

Three (17%) of the 18 patients had both mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 (age-adjusted) and by day 112.

More than half of patients showed improvement by day 112 in the acromegaly symptoms of perspiration, swelling of extremities, and headache and one-third or more showed improvement in fatigue and joint pain.

These 3 dose levels of lanreotide acetate were safe and well tolerated in a small number of patients with active acromegaly. The most commonly reported adverse events were primarily gastrointestinal in nature and included diarrhea (44%), flatulence (33%), and nausea (22%). Injection site reactions, including reports of injection site pain and injection site mass, occurred in only 2 patients.

Cardiac abnormalities are not uncommon in patients with acromegaly. Heart rate and rhythm disturbances were reported as adverse events in 2 patients and included one report each of bradycardia and tachycardia. Based on centralized analysis of ECG and echocardiography data with review by a board certified cardiologist, electrocardiographic and echocardiographic analysis was unremarkable. Mean quantitative cardiac electrophysiologic and cardiac chamber dimensions were within normal ranges for the population and did not appear to exhibit any change over time. Valvular regurgitations were typical of those commonly seen in a general population and did not appear to show any change over time.

No clinically meaningful changes in hematology or clinical chemistry were noted during lanreotide treatment. Analysis of vital signs and body weight did not reveal any clinically meaningful changes over time on treatment. Putative antibodies to lanreotide were observed in

one of 18 patients in a pretreatment sample. The sponsor confirmed that this patient had not received previous treatment with lanreotide; prior therapy with short-acting octreotide was reported.

#### **Medical Officer's Conclusions:**

##### Efficacy

None of the 18 patients had mean GH  $\leq$  5.0 ng/mL or normalized IGF-1 (age-adjusted) at study baseline.

At the end of the study (day 112), 6 (33%) of the 18 patients had mean GH levels  $\leq$  5.0 ng/mL, including 2 of 6 patients in the 60 mg group, 1 of 6 in the 90 mg group and 3 of 6 in the 120 mg group. Three (17%) of the 18 patients had mean levels  $\leq$  2.5 ng/mL; all 3 had received lanreotide 120 mg, and 5 patients (28%) had normalized IGF-1 levels, including 1 of 6 in each of the 60 and 90 mg groups and 3 of 6 in the 120 mg group.

Three (17%) of the 18 patients had both mean GH  $\leq$  2.5 ng/mL and normalized IGF-1 (age-adjusted) by day 112; all 3 of these patients had received lanreotide 120 mg.

More than half of the 18 patients showed improvement by day 112 in the acromegaly symptoms of perspiration (78% with improvement), swelling of extremities (61%), and headache (56%) and one-third or more showed improvement in fatigue (44%) and joint pain (33%).

##### Safety

The most common adverse events reported during the study were gastrointestinal disorders reported in 14 (78%) of the 18 patients including 5, 4 and 5 patients in the 60, 90 and 120 mg treatment groups, respectively.

The most commonly reported events were diarrhea (8 patients, 44%), flatulence (6, 33%), nausea (4, 22%), abdominal pain (3, 17%), vomiting (3, 17%), headache (3, 17%), constipation (2, 11%) and cholelithiasis (2, 11%). The latter events were reports of biliary sludge noted on gallbladder ultrasound for 2 patients in the lowest lanreotide dose group (60 mg).

Application site disorders were reported in 2 (11%) of the 18 patients and included injection site pain in one patient in the 60 mg group and injection site reaction and injection site mass in one patient in the 120 mg group.

A total of 3 patients had hematology abnormalities (anemia) that were reported as adverse events including 2 patients in the 60 mg group and one in the 120 mg group. Incidence of new onset cholelithiasis was 0%; incidence of new onset sludge was 2/18 (11%).

There were no clinically meaningful changes in echocardiograms in terms of cardiac chamber dimensions or valvular regurgitations during the course of this study.

#### 10.1.6 Study Number E-28-52030-709

**Study Title:** Open, comparative multi-center phase III study evaluating the efficacy of three repeated deep subcutaneous administrations of lanreotide acetate (60, 90 or 120 mg) at fixed doses in acromegalic patients previously treated with lanreotide 30 mg PR.

Study E-28-52030-709 and the follow up study E-28-52030-710 are replacements for the cancelled studies E-33-52030-708 and E-54-52030-709 respectively.

**Investigators:** Thirty-one investigators participated in the study; the co-ordinating investigator was Dr. P. Caron.

**Study center(s):** Thirty-one study centers from nine countries (Belgium, Denmark, Finland, France, Germany, Hungary, Poland, Spain and the UK) participated in the study; Dr. P. Caron was affiliated to the Service d'endocrinologie, CHU de Rangueil, 31054 Toulouse, France.

**Study period:** 25 June 1998 to 18 Nov 1999

**Phase of Development:** III

**Publications Based on the Study:** None

#### **Primary Objectives:**

The primary objective of the study was to demonstrate that, after three repeated deep subcutaneous (s.c.) injections of lanreotide acetate (administered every 28 days at a fixed dose), in acromegalic patients previously treated with lanreotide 30 mg PR, lanreotide acetate formulation is no less effective than lanreotide 30 mg PR on GH level (the mean of nine samples over four hours).

#### **Secondary Objectives:**

The secondary objectives were:

- 1) To demonstrate that after three repeated deep s.c. injections of lanreotide acetate (administered every 28 days at a fixed dose), in acromegalic patients previously treated with lanreotide 30 mg PR, lanreotide acetate formulation is no less effective than lanreotide 30 mg PR on IGF-1 level.
- 2) To document the following parameters after one and three repeated monthly administrations of lanreotide acetate at fixed doses: normalization of GH ( $\leq 5$  ng/mL and  $\leq 2.5$  ng/mL) and IGF-1 levels, serum GH and IGF-1 levels, evolution of acromegaly symptoms, lanreotide serum levels, anti-lanreotide antibodies and safety (local and systemic tolerance, standard hematology and biochemistry, ultrasound of gall-bladder and anti-diabetic treatment).
- 3) To compare the previous parameters after three repeated administrations of lanreotide

acetate to those observed just before the fifth injection of lanreotide 30 mg PR in the run-in period.

**Design:**

Open, multi-center comparison of the efficacy and safety of three repeated administrations of lanreotide acetate at fixed doses every 28 days with five injections of lanreotide 30 mg PR at fixed dosing intervals, in acromegalic patients previously treated with lanreotide 30 mg PR.

**Patient Population:**

144 patients were recruited from 31 centers and received at least one run-in dose of lanreotide 30 mg PR. 133 patients received at least one dose of lanreotide acetate of which 132 patients (Intention-to-Treat [ITT] population) also had GH and IGF-1 data. There were 107 patients in the PP population.

**Inclusion criteria:**

Lanreotide 30 mg PR: Patients > 18 years of age, treated with lanreotide 30 mg PR for at least three months prior to the first visit in the study, who within the previous five years had a documented diagnosis of active acromegaly (defined as basal GH >5 ng/mL or elevated IGF-1 [age and sex adjusted] or GH level > 2 ng/mL after oral glucose tolerance testing [OGTT] measured after the most recent surgical or radiation treatment).

Lanreotide acetate: Patients with a GH level  $\leq$  10 ng/mL just before the fifth injection of lanreotide 30 mg PR (at the end of the dosing interval of the fourth injection of lanreotide 30 mg PR).

**Exclusion Criteria (complete list in Vol 164, pg 34):**

- The patient had a pituitary surgery (adenomectomy) within six months before the first visit,
- The patient received radiotherapy for acromegalic disease within one year before the first visit,
- The patient was predicted to require pituitary surgery (adenomectomy) or to receive radiotherapy during the study period,
- The patient was receiving lanreotide 30 mg PR at a dosing interval greater than 16 days or less than five days at the first visit,
- The patient was a female at risk of pregnancy during the study,
- The patient was currently receiving a dopamine agonist or a somatostatin analogue other than lanreotide 30 mg PR at the moment of the first visit (R1),
- The patient had clinically significant renal or hepatic abnormalities,

**Treatment Groups:**

Lanreotide acetate: Three deep s.c. injections of lanreotide acetate administered every 28 days at identical doses (60, 90 or 120 mg). The patient will switch to 60, 90 or 120 mg of lanreotide acetate if the dosing interval of lanreotide 30 mg PR at the end of the run-in period is between 12 and 16 days, 8 and 11 days, or 5 and 7 days, respectively.

Lanreotide 30 mg PR (run-in period): Five i.m. injections of lanreotide 30 mg PR administered at a fixed dosing interval. The dosing interval was based on the last dosing interval of lanreotide 30 mg PR before study entry (between 5 and 16 days).

**Duration of Treatment:**

Patients were to receive five injections of lanreotide 30 mg PR at 5 to 16 day intervals (a dosing period of 25 to 80 days) followed by three injections of lanreotide acetate every 28 days (a dosing period of 84 days).

**Endpoints:**

**Efficacy:** GH (the mean of nine blood samples over four hours), IGF-1 levels and acromegaly symptoms (night sweats, headache, asthenia, swelling of extremities and joint pain).

**Safety:** Adverse events (AEs), local tolerance, systemic tolerance, vital signs (blood pressure and heart rate), standard hematology and biochemistry, anti-lanreotide antibodies, ultrasound of gall bladder, weight, physical examination and concomitant medication (including anti-diabetic medication).

**Statistical Analyses:**

The primary population for the assessment of efficacy was the PP population. Summary tables were produced for the PP and the ITT populations. The assessment of safety was based on the safety population.

The primary endpoints for the assessment of non-inferiority were the GH levels at the end of the fourth dosing interval of lanreotide 30 mg PR (Visit R5) and at the end of the third dosing interval of lanreotide acetate (Visit V4). Analysis of variance testing was performed and lanreotide acetate was considered as non-inferior to lanreotide 30 mg PR if the upper limit of the 95% confidence interval did not exceed 1.25. This approach is similar to that recommended to test for non-inferiority of pharmacokinetic parameters. The secondary efficacy endpoints were analyzed using McNemar's test.

All efficacy and safety data were summarized by descriptive statistics for each visit and for the changes between the end of the third dosing interval of lanreotide acetate and the end of the fourth dosing interval of lanreotide 30 mg PR: mean, SD, median, minimum and maximum for continuous data; number and percentage of patients in each class for categorical data. No formal statistical tests were performed on the safety data. AEs were summarized by body system and preferred term. Concomitant medications were summarized by type and class of medication.

**Results:**

**Patient Demographics**

In the safety population (N=144), age ranged from 24 to 78 years. There were a similar percentage of males and females (48% vs. 52%, respectively). 99% patients were Caucasian and 1% were African. Median time since diagnosis of acromegaly was 8 years. 77% patients had had previous pituitary surgery and 44% patients had had previous radiotherapy. Almost half (49%)

patients had received lanreotide 30 mg PR before the study at a dosing interval of 14 days compared to 29% patients and 18% patients who had been dosed at 10 and 7 day intervals, respectively. The most common medical history was hypertension reported by 54 (38%) patients.

There were 69 reports (N=144) of a history of gallbladder disorder: calculus (lithiasis) of gallbladder without cholecystitis or obstruction (43 patients), other disorders of the gallbladder (11 patients), cholecystectomy (9 patients), cholesterolosis of gallbladder (3 patients), other specified disorder of gallbladder (2 patients) and chronic cholecystitis (1 patient). Gallbladder ultrasound data for the safety population at baseline: 40 (28%; N=141) patients reported lithiasis and 10 (7%; N=141) patients reported sludge at baseline.

#### Patient Disposition

Four (3%; N=144) patients withdrew from the study during the run-in period: patients 2409 and 2901 withdrew due to SAEs that were unrelated to lanreotide; patients 203 and 805 withdrew due to a protocol deviation of no documented active acromegaly within the previous five years. These four patients were excluded from the ITT population.

One hundred and forty (97%; N=144) patients completed the run-in period but seven of these patients were not eligible to start treatment with lanreotide acetate: six patients (patients 507, 603, 703, 802, 2006 and 3201) had a GH level > 10 ng/mL at Visit R5 and patient 501 had a protocol deviation of not receiving lanreotide 30 mg PR for at least three months prior to the first visit (R1). These seven patients were also excluded from the ITT population.

One hundred and thirty-three (92%; N=144) patients continued to receive at least one dose of lanreotide acetate. Two patients (14%; N=144) withdrew from the study after treatment with lanreotide acetate: patient 504 withdrew due to an AE (abdominal pain, diarrhea, hot flashes, nausea, tenesmus) and patient 704 withdrew due to a protocol deviation. The remaining 131 (91%; N=144) patients completed the study. Patient 504 was also excluded from the ITT population for not having any GH or IGF-1 data recorded after receiving at least one dose of lanreotide acetate. The remaining 132 (92%; N=144) patients were included in the ITT population.

#### Patient Exposure to Study Drug

133 patients received at least one dose of lanreotide acetate: 69 patients received 60 mg, 41 received 90 mg, and 23 received 120 mg. 132 (>99%; N=133) patients received 3 injections as planned in the study.

#### Concomitant Medication Use

Somatostatin analogues (other than lanreotide) and dopaminergic agonists were not to be permitted as concomitant medications during the study. The most common concomitant medications for both treatments were thyroid hormones and glucocorticoids. The numbers and percentages of patients who took each class of concomitant medication were similar during the run-in period with lanreotide 30 mg PR and during lanreotide acetate treatment.

#### Primary Efficacy Outcomes

**Non-inferiority Analysis of GH:**

The upper bound 95% confidence interval of the ratio of the geometric means of GH levels at the end of the fourth interval of lanreotide 30 mg PR and at the end of the third interval of lanreotide acetate was 1.078. This is lower than the 1.25 limit, supporting that lanreotide acetate is no less effective than lanreotide 30 mg PR.

**GH Over Time:**

**Table 10.1.6.1 Summary of GH levels (ng/mL) (Intention-to-Treat Population)**

	End 4th interval lanreotide 30mg PR {visit R5} {N=132}	End 1st interval lanreotide autogel {visit V2} {N=132}	End 3rd interval lanreotide autogel {visit V4} {N=132}
<b>All lanreotide autogel doses</b>			
Mean	2.88	3.58	3.02
S.D.	1.99	2.87	2.28
Median	2.57	2.77	2.30
Minimum	0.5	0.5	0.5
Maximum	8.5	17.3	10.5
N	132	132	131
<b>Lanreotide autogel 60mg</b>			
Mean	2.62	3.07	2.56
S.D.	1.78	2.18	1.88
Median	2.41	2.63	1.99
Minimum	0.5	0.5	0.5
Maximum	7.8	11.0	8.4
N	68	68	67
<b>Lanreotide autogel 90mg</b>			
Mean	2.67	3.70	3.15
S.D.	1.06	3.52	2.72
Median	2.18	2.72	2.26
Minimum	0.5	0.5	0.5
Maximum	8.5	17.3	10.5
N	41	41	41
<b>Lanreotide autogel 120mg</b>			
Mean	4.03	4.89	4.10
S.D.	2.12	3.09	2.18
Median	3.48	4.58	3.63
Minimum	0.6	0.7	0.5
Maximum	7.5	12.6	7.9
N	23	23	23

Sponsors Table 55, Vol 164, pg 155

Median GH was similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR. In general, median GH levels were highest in the 120 mg lanreotide acetate group and lowest in the 60 mg lanreotide acetate group.

There was no evidence of a group/region by treatment interaction for the primary endpoint on the ITT population (p=0.2152), or for IGF-1 for either the PP population (p=0.4404) or the ITT population (p=0.5316).

Secondary Efficacy Outcomes

**Non-inferiority Analysis of IGF-1**

The upper bound 95% confidence interval of the ratio of the geometric means of IGF-1 levels at the end of the fourth interval of lanreotide 30 mg PR and at the end of the third interval of

lanreotide acetate was 1.022. This is lower than the 1.25 limit, supporting that lanreotide acetate is no less effective than lanreotide 30 mg PR.

#### IGF-1 over Time

Median IGF-1 was similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR. In general, IGF-1 levels were highest in the 120 mg lanreotide acetate group and lowest in the 60 mg lanreotide acetate group.

The lowest GH and IGF-1 levels were achieved with 60 mg lanreotide acetate and the highest GH and IGF-1 levels were observed with 120 mg lanreotide acetate. This reflects the nature of the patients who were assigned to each dosing level. Patients who responded well to treatment with lanreotide 30 mg PR were dosed less frequently (12 to 16 days) and were subsequently assigned to low doses of lanreotide acetate (60 mg). On the other hand, patients who did not respond well to treatment with lanreotide 30 mg PR were dosed more frequently (5 to 7 days) and were subsequently assigned to high doses of lanreotide acetate (120 mg).

#### GH ≤ 5 ng/mL, GH ≤ 2.5 ng/mL and Normalized IGF-1

The number of patients with GH ≤ 5 ng/mL, GH ≤ 2.5 ng/mL and normalized IGF-1 are summarized in Table 10.1.6.2

**Table 10.1.6.2 Number Of Patients With GH Levels ≤ 2.5 ng/ml, GH Levels ≤ 5 ng/ml, And Normalized IGF-1 Levels (Intention-To-Treat Population)**

	End 4th interval lanreotide 30mg PR (visit R5) (N=132)	End 1st interval lanreotide autogel (visit V2) (N=132)	End 3rd interval lanreotide autogel (visit V4) (N=132)
GH ≤ 2.5ng/mL?			
Yes	62 (47%)	53 (40%)	71 (54%)
No	70 (53%)	79 (60%)	60 (46%)
Total	132 (100%)	132 (100%)	131 (100%)
GH ≤ 5ng/mL?			
Yes	114 (86%)	104 (79%)	106 (81%)
No	18 (14%)	28 (21%)	25 (19%)
Total	132 (100%)	132 (100%)	131 (100%)
Normalized IGF-1?			
Yes	60 (45%)	57 (43%)	65 (50%)
No	72 (55%)	75 (57%)	66 (50%)
Total	132 (100%)	132 (100%)	131 (100%)
GH ≤ 2.5 and Normalized IGF-1			
Yes	41 (31%)	37 (28%)	50 (38%)
No	91 (69%)	95 (72%)	81 (62%)
Total	132 (100%)	132 (100%)	131 (100%)

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Sponsors Table 63, Vol 164, pg 163

In the ITT and PP population overall, the percentage of patients with GH ≤ 2.5 ng/mL and normalized IGF-1 (both separately and together) were higher at the end of the third interval of lanreotide acetate than at the end of the fourth interval of lanreotide 30 mg PR. The percentage of patients with GH ≤ 5 ng/mL was lower at the end of the third interval of lanreotide acetate than at the end of the fourth interval of lanreotide 30 mg PR.

### Acromegaly Symptoms

Acromegalic symptom data are presented in Table 10.1.6.3

The total numbers and percentages of patients with each acromegalic symptom were similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR. Most patients reported acromegalic symptoms that were mild or moderate in severity.

**Table 10.1.6.3 Summary of Acromegalic Symptoms (Intention-To-Treat Population)**

	Baseline (visit R1) (N=132)	End 4th interval lanreotide 30mg PR (visit R5) (N=132)	End 3rd interval lanreotide autogel (visit V4) (N=132)
<b>Night sweats</b>			
None	90 (68%)	102 (77%)	104 (80%)
Mild	23 (17%)	20 (15%)	19 (15%)
Moderate	13 (10%)	8 (6%)	3 (2%)
Severe	6 (5%)	2 (2%)	4 (3%)
Total	132 (100%)	132 (100%)	130 (100%)
<b>Headache</b>			
None	84 (64%)	95 (72%)	93 (71%)
Mild	27 (20%)	20 (15%)	18 (14%)
Moderate	11 (8%)	12 (9%)	15 (11%)
Severe	10 (8%)	5 (4%)	4 (3%)
Total	132 (100%)	132 (100%)	130 (100%)
<b>Asthenia</b>			
None	72 (55%)	93 (70%)	93 (71%)
Mild	26 (20%)	20 (15%)	22 (17%)
Moderate	30 (23%)	17 (13%)	11 (8%)
Severe	4 (3%)	2 (2%)	4 (3%)
Total	132 (100%)	132 (100%)	130 (100%)
<b>Swelling of extremities</b>			
None	73 (55%)	89 (67%)	94 (72%)
Mild	36 (27%)	22 (17%)	25 (19%)
Moderate	20 (15%)	19 (14%)	9 (7%)
Severe	3 (2%)	2 (2%)	2 (2%)
Total	132 (100%)	132 (100%)	130 (100%)
<b>Joint pain</b>			
None	65 (49%)	87 (66%)	84 (65%)
Mild	41 (31%)	24 (18%)	20 (15%)
Moderate	17 (13%)	17 (13%)	20 (15%)
Severe	9 (7%)	4 (3%)	6 (5%)
Total	132 (100%)	132 (100%)	130 (100%)

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Sponsors Table 67, Vol 164, pg 167

### *Efficacy Conclusions*

- Lanreotide acetate is no less effective in maintaining GH and IGF-1 levels than lanreotide 30 mg PR after three dosing intervals of lanreotide acetate compared to four dosing intervals of lanreotide 30 mg PR.
- Median GH and median IGF-1 were similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR.
- Median GH and median IGF-1 levels were highest in the 120 mg lanreotide acetate group and lowest in the 60 mg lanreotide acetate group at the end of the fourth interval of lanreotide 30 mg PR and at the end of the third interval of lanreotide acetate.
- The increases in the percentages of patients with GH  $\leq 2.5$  ng/mL and both GH  $\leq 2.5$  ng/mL and normalized IGF-1 from the end of the fourth interval of lanreotide 30 mg PR to the end of the third interval of lanreotide acetate were statistically significant.

- The total numbers and percentages of patients with each acromegalic symptom were similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR.

Safety Data:

*Deaths*  
None

*Serious Adverse Events*

Four (3%; N=144) patients reported the following SAEs during treatment with lanreotide 30 mg PR: patient 2801 reported back pain, patient 2409 reported neoplasm, patient 1501 reported bronchitis and patient 2901 reported hemoptysis.

One (<1%; N=133) patient reported an SAE during treatment with lanreotide acetate: patient 606 reported an inflicted injury.

Two (1%; N=144) patients withdrew during treatment with lanreotide 30 mg PR due the following SAEs: patient 2409 withdrew due to neoplasm and patient 2901 withdrew due to hemoptysis.

All these SAEs were assessed as not related to lanreotide treatment.

*Adverse Events that Led to study Withdrawal*

Two (1%; N=144) patients withdrew during treatment with lanreotide 30 mg PR due the following SAEs: patient 2409 withdrew due to neoplasm and patient 2901 withdrew due to hemoptysis.

One additional patient (<1%; N=133) patient (patient 504) withdrew during treatment with lanreotide acetate due to the following AEs: hot flushes, abdominal pain, diarrhoea, nausea and tenesmus. (Note that the AEs of hot flushes and nausea occurred on the day of the first lanreotide acetate injection and are included in both the lanreotide 30 mg PR and lanreotide acetate columns in Table 10.1.6.4 although the patient withdrew from the study during treatment with lanreotide acetate.)

**Table 10.1.6.4 Number Of Patients Reporting Adverse Events Causing Withdrawal (Safety Population)**

Body System (1) Adverse event	Lanreotide 30mg PR (N=144)	Lanreotide autogel (N=133)
Any adverse event	3 (2%)	1 (<1%)
<b>BODY AS A WHOLE - GENERAL DISORDERS</b>	1 (<1%)	1 (<1%)
HOT FLASHES	1 (<1%)	1 (<1%)
<b>GASTRO-INTESTINAL SYSTEM DISORDERS</b>	1 (<1%)	1 (<1%)
ABDOMINAL PAIN	0	1 (<1%)
DIARRHOEA	0	1 (<1%)
NAUSEA	1 (<1%)	1 (<1%)
TENESMUS	0	1 (<1%)
<b>NEOPLASM</b>	1 (<1%)	0
NEOPLASM NOS	1 (<1%)	0
<b>RESPIRATORY SYSTEM DISORDERS</b>	1 (<1%)	0
HEMODYNIA	1 (<1%)	0

(1) Body system totals are not necessarily the sum of individual adverse events  
 Sponsors Table 80, Vol 164, pg 191

*Treatment Emergent Adverse Events*

During both treatment periods, at least 40% of AEs reported were classified as gastro-intestinal system disorders (42% [N=133] during lanreotide acetate treatment vs. 56% [N=144] during lanreotide 30 mg PR treatment). The most commonly reported AEs during both periods of treatment were diarrhea, abdominal pain, nausea and constipation.

**Table 10.1.6.5 Number Of Patients Reporting AEs By Body System (Safety Population)**

Body System	Lanreotide 30 mg PR N = 144 n (%)	Lanreotide Autogel N = 133 n (%)
Any AE	108 (75)	107 (80)
Gastro-intestinal system disorders	80 (56)	56 (42)
Uncoded term	19 (13)	33 (25)
Metabolic and nutritional disorders	13 (9)	24 (18)
Liver and biliary system disorders	10 (7)	23 (17)
Body as a whole –general disorders	10 (7)	16 (12)
Centr & periph nervous system disorders	13 (9)	10 (8)
Skin and appendages disorders	6 (4)	0 (7)
Respiratory system disorders	8 (6)	8 (6)
Musculo-skeletal system disorders	3 (2)	6 (5)
Psychiatric disorders	3 (2)	5 (4)
Reproductive disorders, female	4 (3)	2 (2)
Secondary terms	2 (1)	4 (3)
Application site disorders	0 (0)	2 (2)
Cardiovascular disorders, general	2 (1)	2 (2)
Endocrine disorders	1 (<1)	2 (2)
Platelet bleeding & clotting disorders	1 (<1)	2 (2)
Red blood cell disorders	2 (1)	3 (2)
Resistance mechanism disorders	0 (0)	2 (2)
Reproductive disorders, male	2 (1)	1 (<1)
Heart rate and rhythm disorders	1 (<1)	1 (<1)
Neoplasm	1 (<1)	1 (<1)
Myo endo pericardial & valve disorders	0 (0)	1 (<1)

Data Source: Sponsor's Table 79 in section 14.3.1

Note: The denominator of each percentage is the number of patients who received at least one dose of lanreotide 30 mg PR or lanreotide acetate (N=144 and N=133, respectively).

The number of patients reporting AEs with an incidence of  $\geq 5\%$  are summarized for the safety population in Table 10.1.6.6.

**Table 10.1.6.6 Number of Patients Reporting AEs with an Incidence  $\geq 5\%$  (Safety Population)**

Adverse Event	Lanreotide 30 mg PR N = 144 n (%)	Lanreotide Autogel N = 133 n (%)
Any AE	108 (75)	107 (80)
Diarhoea	55 (38)	38 (29)
Abdominal pain	31 (22)	23 (17)
Nausea	26 (18)	12 (9)
Constipation	15 (10)	13 (10)
Hyperglycaemia	5 (3)	11 (8)
Headache	9 (6)	5 (4)
Gall bladder sludge	4 (3)	8 (6)
Flatulence	3 (2)	7 (5)
Vomiting	7 (5)	3 (2)
Cholelithiasis	2 (1)	7 (5)
Hyperphosphataemia	4 (3)	6 (5)
Hyponatremia	4 (3)	7 (5)

Data Source: Sponsor's Table 79 in section 14.3.1

Note: The denominator of each percentage is the number of patients who received at least one dose of lanreotide 30 mg PR or lanreotide acetate (N=144 and N=133, respectively).

Note: Patients 801 and 803 reported diarrhea and vomiting, respectively, on the day of the first lanreotide acetate injection. These AEs occurred after the lanreotide acetate injection (known from time since last injection) but are summarized in both the lanreotide 30 mg PR and lanreotide acetate columns although the patient did not experience the AE during treatment with lanreotide 30 mg PR.

### Laboratory Parameters

#### Hematology:

Out-of-range hematology data are summarized for the safety population overall in Table 10.1.6.7

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**Table 10.1.6.4 Number Of Patients Reporting Adverse Events Causing Withdrawal (Safety Population)**

Body System (1) Adverse event	Lanreotide 30mg PR (N=144)	Lanreotide autogel (N=133)
Any adverse event	3 (2%)	1 (<1%)
<b>BODY AS A WHOLE - GENERAL DISORDERS</b>	1 (<1%)	1 (<1%)
HOT FLASHES	1 (<1%)	1 (<1%)
<b>GASTRO-INTESTINAL SYSTEM DISORDERS</b>	1 (<1%)	1 (<1%)
ABDOMINAL PAIN	0	1 (<1%)
DIARRHOEA	0	1 (<1%)
NAUSEA	1 (<1%)	1 (<1%)
TENESMUS	0	1 (<1%)
<b>NEOPLASM</b>	1 (<1%)	0
NEOPLASM NOS	1 (<1%)	0
<b>RESPIRATORY SYSTEM DISORDERS</b>	1 (<1%)	0
HAEMOPTYSIS	1 (<1%)	0

(1) Body system totals are not necessarily the sum of individual adverse events  
 Sponsors Table 80, Vol 164, pg 191

*Treatment Emergent Adverse Events*

During both treatment periods, at least 40% of AEs reported were classified as gastro-intestinal system disorders (42% [N=133] during lanreotide acetate treatment vs. 56% [N=144] during lanreotide 30 mg PR treatment). The most commonly reported AEs during both periods of treatment were diarrhea, abdominal pain, nausea and constipation.

**Table 10.1.6.5 Number Of Patients Reporting AEs By Body System (Safety Population)**

Body System	Lanreotide 30 mg PR N = 144 n (%)	Lanreotide Autogel N = 133 n (%)
Any AE	108 (75)	107 (80)
Gastro-intestinal system disorders	80 (56)	56 (42)
Uncoded term	19 (13)	33 (25)
Metabolic and nutritional disorders	13 (9)	24 (18)
Liver and biliary system disorders	10 (7)	23 (17)
Body as a whole -general disorders	10 (7)	16 (12)
Centr & periph nervous system disorders	13 (9)	10 (8)
Skin and appendages disorders	6 (4)	0 (7)
Respiratory system disorders	8 (6)	8 (6)
Musculo-skeletal system disorders	3 (2)	6 (5)
Psychiatric disorders	3 (2)	5 (4)
Reproductive disorders, female	4 (3)	2 (2)
Secondary terms	2 (1)	4 (3)
Application site disorders	0 (0)	2 (2)
Cardiovascular disorders, general	2 (1)	2 (2)
Endocrine disorders	1 (<1)	2 (2)
Platelet bleeding & clotting disorders	1 (<1)	2 (2)
Red blood cell disorders	2 (1)	3 (2)
Resistance mechanism disorders	0 (0)	2 (2)
Reproductive disorders, male	2 (1)	1 (<1)
Heart rate and rhythm disorders	1 (<1)	1 (<1)
Neoplasm	1 (<1)	1 (<1)
Myo endo pericardial & valve disorders	0 (0)	1 (<1)

Data Source: Sponsor's Table 79 in section 14.3.1

Note: The denominator of each percentage is the number of patients who received at least one dose of lanreotide 30 mg PR or lanreotide acetate (N=144 and N=133, respectively).

The number of patients reporting AEs with an incidence of  $\geq 5\%$  are summarized for the safety population in Table 10.1.6.6.

**Table 10.1.6.6 Number of Patients Reporting AEs with an Incidence  $\geq 5\%$  (Safety Population)**

Adverse Event	Lanreotide 30 mg PR N = 144 n (%)	Lanreotide Autogel N = 133 n (%)
Any AE	108 (75)	107 (80)
Diarhoea	55 (38)	38 (29)
Abdominal pain	31 (22)	23 (17)
Nausea	26 (18)	12 (9)
Constipation	15 (10)	13 (10)
Hyperglycaemia	5 (3)	11 (8)
Headache	0 (0)	5 (4)
Gall bladder sludge	4 (3)	8 (6)
Flatulence	3 (2)	7 (5)
Vomiting	7 (5)	3 (2)
Cholelithiasis	2 (1)	7 (5)
Hyperphosphataemia	4 (3)	6 (5)
Hyponatremia	4 (3)	7 (5)

Data Source: Sponsor's Table 79 in section 14.3.1

Note: The denominator of each percentage is the number of patients who received at least one dose of lanreotide 30 mg PR or lanreotide acetate (N=144 and N=133, respectively).

Note: Patients 801 and 803 reported diarrhea and vomiting, respectively, on the day of the first lanreotide acetate injection. These AEs occurred after the lanreotide acetate injection (known from time since last injection) but are summarized in both the lanreotide 30 mg PR and lanreotide acetate columns although the patient did not experience the AE during treatment with lanreotide 30 mg PR.

*Laboratory Parameters*

**Hematology:**

Out-of-range hematology data are summarized for the safety population overall in Table 10.1.6.7

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**Table 10.1.6.7 Summary of Hematology Data – Number Of Patients With Out-Of-Range Values (Safety Population)**

Parameter	Baseline (Visit R1) N=144 n (%)	End 4 <sup>th</sup> Interval Lanreotide 30 mg PR (Visit R5) N=140 n (%)	End 3 <sup>rd</sup> Interval Lanreotide Autogel (Visit V4) N=132 n (%)
<b>Erythrocytes (10<sup>12</sup>/L)</b>			
Low	27 (20)	28 (21)	27 (23)
Normal	108 (79)	103 (79)	92 (77)
High	1 (<1)	0 (0)	1 (<1)
No. of patients with data	136	131	120
<b>Leucocytes (10<sup>9</sup>/L)</b>			
Low	3 (2)	6 (5)	5 (4)
Normal	129 (94)	122 (93)	109 (89)
High	5 (4)	3 (2)	8 (7)
No. of patients with data	137	131	122
<b>Platelets (10<sup>9</sup>/L)</b>			
Low	6 (4)	8 (6)	3 (2)
Normal	129 (95)	122 (93)	118 (97)
High	1 (<1)	1 (<1)	1 (<1)
No. of patients with data	136	131	122
<b>Haemoglobin (g/dL)</b>			
Low	24 (18)	32 (24)	24 (20)
Normal	112 (82)	99 (76)	97 (80)
High	0 (0)	0 (0)	1 (<1)
No. of patients with data	136	131	122
<b>HbA<sub>1c</sub> (%)</b>			
Low	1 (<1)	1 (<1)	0 (0)
Normal	83 (59)	74 (57)	73 (60)
High	56 (40)	54 (42)	49 (40)
No. of patients with data	140	129	122

Data Source: Sponsor's Table 87 in section 14.3.5

Note: The denominator of each percentage is the number of patients with data.

There were no clinically significant changes in the number of patients with high or low hematology parameters from the end of the fourth interval of lanreotide 30 mg PR to the end of the third interval with lanreotide acetate.

#### Biochemistry

Out-of-range biochemistry data are summarized for the safety population overall in Table 10.1.6.8.

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**Table 10.1.6.8 Summary Of Biochemistry Data – Number Of Patients With Out-Of-Range Values (Safety Population)**

Parameter	Baseline (Visit R1) N=144	End 4 <sup>th</sup> Interval Lanreotide 30 mg PR (Visit R5) N=140	End 3 <sup>rd</sup> Interval Lanreotide Autogel (Visit V4) N=132
Alk. Phosphatases (U/L)			
Low	7 (5)	8 (6)	6 (5)
Normal	124 (87)	122 (88)	115 (88)
High	12 (8)	9 (6)	9 (7)
No. of patients with data	143	139	139
Calcium (mmol/L)			
Low	0 (0)	1 (<1)	1 (<1)
Normal	141 (99)	138 (>99)	128 (98)
High	2 (1)	0 (0)	1 (<1)
No. of patients with data	143	139	139
Creatinine (µmol/L)			
Low	0 (0)	0 (0)	0 (0)
Normal	141 (99)	137 (99)	128 (98)
High	2 (1)	2 (1)	2 (2)
No. of patients with data	143	139	139
Glucose (mmol/L)			
Low	1 (<1)	2 (1)	1 (<1)
Normal	60 (42)	59 (42)	59 (45)
High	82 (57)	78 (56)	70 (54)
No. of patients with data	143	139	139
GOT (AST) (U/L)			
Low	0 (0)	0 (0)	0 (0)
Normal	138 (97)	136 (98)	130 (100)
High	5 (3)	3 (2)	0 (0)
No. of patients with data	143	139	139
GPT (ALT) (U/L)			
Low	0 (0)	0 (0)	0 (0)
Normal	132 (92)	128 (92)	121 (93)
High	11 (8)	11 (8)	9 (7)
No. of patients with data	143	139	139
Phosphorus (mmol/L)			
Low	0 (0)	0 (0)	0 (0)
Normal	131 (92)	125 (90)	120 (92)
High	12 (8)	14 (10)	10 (8)
No. of patients with data	143	139	139
Potassium (mmol/L)			
Low	1 (<1)	2 (1)	0 (0)
Normal	142 (>99)	137 (99)	129 (100)
High	0 (0)	0 (0)	0 (0)
No. of patients with data	143	139	129
Sodium (mmol/L)			
Low	15 (10)	20 (14)	8 (6)
Normal	128 (90)	116 (83)	120 (93)
High	0 (0)	3 (2)	1 (<1)
No. of patients with data	143	139	129
Total Bilirubin (µmol/L)			
Low	0 (0)	0 (0)	0 (0)
Normal	131 (92)	128 (92)	121 (93)
High	12 (8)	11 (8)	9 (7)
No. of patients with data	143	139	139

Data Source: Sponsor's Table 99 in section 14.3.5.

Note: The denominator of each percentage is the number of patients with data.

There were no clinically significant changes in low or high biochemistry parameters from the end of the fourth interval of lanreotide 30 mg PR to the end of the third interval with lanreotide acetate.

Non-specific binding (NSB) lanreotide antibodies:

There were few changes in % NSB of lanreotide antibodies from baseline to the end of the fourth interval of lanreotide 30 mg PR. A decrease in the % NSB of lanreotide antibodies was observed

in 8 (6%; N=140) patients and an increase in the % NSB was observed in 3 (2%, N=140) patients.

There were few changes in % non-specific binding lanreotide antibodies from baseline to the end of the third interval with lanreotide acetate. A decrease in the % NSB of lanreotide antibodies was observed in 19 (15%; N=130) patients and an increase in the % NSB was observed in 2 (1%, N=130) patients.

Laboratory abnormalities reported as AEs

Laboratory abnormalities reported as AEs (including changes in parameters of >50%) are summarized for the safety population in Table 10.1.6.9.

**Table 10.1.6.9 Laboratory Abnormalities Reported As Adverse Events (Safety Population)**

Adverse Event	Lanreotide 30 mg PR N = 144 n (%)	Lanreotide Autogel N = 133 n (%)
Uncoded terms*	19 (13)	33 (25)
Hyperglycaemia	5 (3)	11 (8)
Hyperphosphataemia	4 (3)	6 (5)
Hyponatremia	4 (3)	7 (5)
Hypernatremia	0 (0)	1 (<1)
Phosphatase Alkaline Increased	0 (0)	1 (<1)
Bilirubinaemia	0 (0)	2 (2)
SGOT increased	2 (1)	2 (2)
SGPT increased	2 (1)	1 (<1)

Data Source: Sponsor's Table 79 in section 14.3.1

\*The protocol stated that a laboratory parameter that varied in value by > 50% from one visit to the next was to be reported as an AE. In many cases where this occurred, the investigator had not noted the change in parameter as an AE. The laboratory data was analyzed at the end of the study to identify changes in laboratory parameters of >50%. The changes that were not out-of-range or deemed clinically significant were recorded as AEs and categorized as uncoded terms.

Clinically significant changes were coded by a preferred term.

Note: The denominator of each percentage is the number of patients who received at least one dose of lanreotide 30 mg PR (N=144) or at least one dose of lanreotide acetate (N=133).

The laboratory AEs reported under the body system of uncoded terms were not considered to be clinically significant and were only reported as AEs because of the protocol criterion. Five (3%; N=144) patients reported hyperglycemia during lanreotide 30 mg PR treatment and 11 (8%; N=133) patients reported hyperglycemia during lanreotide acetate treatment. The number of patients reporting all other laboratory abnormalities as AEs were similar during lanreotide 30 mg PR treatment and lanreotide acetate treatment.

#### *Vital Signs*

There were no clinically significant changes in weight, heart rate, systolic and diastolic blood pressures, and physical examination data from baseline to the end of the fourth interval of lanreotide 30 mg PR and to the end of the third interval of lanreotide acetate.

#### *Special Safety Studies*

##### *Gallbladder Ultrasound*

**Table 10.1.6.10 Incidence of Lithiasis and Sludge (Safety Population)**

Parameter	Baseline (Visit R1) N=144 n (%)	End 4 <sup>th</sup> Interval Lanreotide 30 mg PR (Visit R5) N = 140 n (%)	End 3 <sup>rd</sup> Interval Lanreotide Autogel (Visit V4) N = 132 n (%)
No. of patients with data	141	131	122
Lithiasis	40 (28)	36 (27)	41 (34)
Sludge	10 (7)	15 (11)	8 (7)
Either lithiasis or sludge	46 (33)	45 (34)	45 (37)

Data Source: Sponsor's Table 116 in section 14.3.6

Note: The denominator of each percentage is the number of patients with data.

A larger number and percentage of patients had lithiasis at the end of the third interval of lanreotide acetate than compared to at baseline and at the end of the fourth interval of lanreotide 30 mg PR. Nine patients developed lithiasis and lithiasis disappeared in four patients between the fourth interval of lanreotide 30 mg PR and third interval of lanreotide acetate.

**Sponsor's Conclusions:**

**Efficacy:**

The results of the ITT population were similar to the PP population. The results of the PP population are described below. The upper bound 95% confidence interval of the ratio of the geometric means of GH and IGF-1 levels at the end of the fourth interval of lanreotide 30 mg PR and at the end of the third interval of lanreotide acetate were 1.041 and 1.034, respectively. These confidence intervals were lower than the 1.25 limit, demonstrating that lanreotide acetate is no less effective than lanreotide 30 mg PR.

Median GH and median IGF-1 were similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR. Median GH and median IGF-1 levels were highest in the 120 mg lanreotide acetate group and lowest in the 60 mg lanreotide acetate group at the end of the fourth interval of lanreotide 30 mg PR and at the end of the third interval of lanreotide acetate.

The total numbers and percentages of patients with each acromegalic symptom were similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR. Most patients reported acromegalic symptoms that were mild or moderate in severity.

**Safety:**

Overall, a similar percentage of patients reported AEs during the period of lanreotide acetate treatment and during lanreotide 30 mg PR treatment (80% [N=133] vs. 75% [N=144], respectively). During lanreotide acetate treatment and during lanreotide 30 mg PR treatment, at least 40% of AEs reported were classified as gastro-intestinal system disorders (42% [N=133] vs. 56% [N=144], respectively). The most commonly reported AEs during lanreotide acetate treatment and during lanreotide 30 mg PR treatment were diarrhea, abdominal pain, nausea and constipation. The percentages of patients who reported diarrhea, abdominal pain and nausea were 5% to 9% lower during lanreotide acetate treatment [N=133] than during lanreotide 30 mg PR treatment [N=144].

Four (3%; N=144) patients reported SAEs (unrelated to lanreotide) of back pain, neoplasm, bronchitis and hemoptysis during treatment with lanreotide 30 mg PR compared to one (<1%; N=133) patient who reported an SAE (unrelated to lanreotide) of an inflicted injury during treatment with lanreotide acetate.

Two (1%; N=144) patients withdrew during treatment with lanreotide 30 mg PR due the following SAEs (unrelated to lanreotide) of neoplasm and hemoptysis compared to one (<1%; N=133) patient who withdrew during treatment with lanreotide acetate due to drug-related AEs of hot flushes, abdominal pain, diarrhea, nausea and tenesmus.

A higher number and percentage of patients reported indurations at the injection site 30 minutes after the first and third administrations of lanreotide acetate (19% and 14% patients, respectively) than compared to 30 minutes after the fourth administration of lanreotide 30 mg PR (9% patients). There were no clinically significant differences in the percentage of patients who reported pain, redness, itching and indurations at the injection site at the end of the fourth interval of lanreotide 30 mg PR and at the end of the third interval with lanreotide acetate one dosing interval after the injection.

There was a 5% increase in the percentage of patients reporting an AE of hyperglycemia during lanreotide acetate treatment (N=133) compared to during lanreotide 30 mg PR treatment (N=144).

There were no clinically significant differences in hematology, biochemistry, physical examination, weight, heart rate, systolic and diastolic blood pressure results at the end of the fourth interval of lanreotide 30 mg PR and at the end of the third interval with lanreotide acetate.

There were no clinically significant differences in the number and percentage of patients with antidiabetic treatment during treatment with lanreotide 30 mg PR and during treatment with lanreotide acetate.

There was no clinically significant difference in the numbers and percentages of patients with either lithiasis or sludge at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR.

The safety of lanreotide acetate after three injections and lanreotide 30 mg PR after four injections is similar.

**Medical Officer's Conclusions:**

*Efficacy*

Lanreotide acetate is no less effective in maintaining GH and IGF-1 levels than lanreotide 30 mg PR after three dosing intervals of lanreotide acetate compared to four dosing intervals of lanreotide 30 mg PR.

*Safety*

During both treatment periods, at least 40% of AEs reported were classified as gastro-intestinal system disorders (42% [N=133] during lanreotide acetate treatment vs. 56% [N=144] during lanreotide 30 mg PR treatment). The most commonly reported AEs during both periods of treatment were diarrhea (29% in lanreotide acetate), abdominal pain (17%), nausea (9%) and constipation (10%).

There was a 5% increase in the percentage of patients reporting an AE of hyperglycemia during lanreotide acetate treatment (8%, 11/133) compared to during lanreotide 30 mg PR treatment (3%, 5/144).

There was a 4% increase in the percentage of patients reporting an AE of cholelithiasis during lanreotide acetate treatment (5%, 7/133) compared to during lanreotide 30 mg PR treatment (1%, 52/144). Nine patients developed lithiasis and lithiasis disappeared in four patients between the fourth interval of lanreotide 30 mg PR and third interval of lanreotide acetate.

#### **10.1.7 Study Number E-28-52030-710**

##### **Study Title:**

Open, comparative multi-center phase III study evaluating the efficacy of repeated deep subcutaneous administrations of titrated doses of lanreotide acetate (60, 90 or 120 mg) in acromegalic patients previously treated with lanreotide 30 mg PR and with lanreotide acetate at fixed doses

##### **Investigators:**

Thirty investigators participated in the study. The coordinating investigator was Dr. P. Caron of the Service d'endocrinologie, CHU de Rangueil, 31054 Toulouse, France.

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

30 centers from 9 countries (Belgium, Denmark, Finland, France, Germany, Hungary, Poland, Spain and the UK) participated in the study.

##### **Study period:**

Date of first enrollment: 22 December, 1998

Date of last completed: 19 October, 2000

##### **Phase of Development: III**

##### **Publications Based on the Study: None**

##### **Primary Objectives:**

To demonstrate that after 12 repeated deep s.c. administrations of lanreotide acetate (every 28 days) at titrated doses (60, 90 or 120 mg) the biochemical effect on mean growth hormone (GH) level is higher than that observed at the end of the second treatment period in the switching phase III study (E28 52030 709): treatment with lanreotide acetate administered at a fixed dose (values after 3 repeated injections).

**Secondary Objectives:**

To compare these parameters after 12 repeated administrations of lanreotide acetate in this study to those observed at the end of the 2 previous treatments in the preceding study (E28 52030 709) when patients received lanreotide 30 mg PR treatment (values after 4 repeated injections) and lanreotide acetate treatment at a fixed dose (values after 3 repeated injections).

To document the efficacy and safety of lanreotide acetate after 4, 8 and 12 repeated administrations every 28 days, at titrated doses (60, 90 or 120 mg) in terms of:

- reducing serum GH at or below 5 ng/mL and at or below 2.5 ng/mL
- normalization of serum IGF-1
- absence or reduction in clinical signs of acromegaly
- lanreotide serum levels
- GH and IGF-1 serum levels
- safety parameters (local and systemic tolerance, standard hematology and biochemistry, anti-lanreotide antibodies and gall bladder ultrasound, doses of insulin or other treatment in diabetic patients)

**Design:**

Open-label, multi-center study comparing the efficacy and safety of repeated administrations of lanreotide acetate at titrated doses with the 2 treatments (lanreotide 30 mg PR and lanreotide acetate at fixed doses) administered during the preceding study (E28 52030 709).

**Study schema:**

Visit	R1	R5	V1	V4	V16
Study	709	709	709	709/710	710
Treatment	L. 30 mg	L. 30 mg	L. Autogel	L. Autogel	L. Autogel
Injection nb.	1	5	1	4	*

\*: injection n° 15 is administered at visit V15, no injection administered on the last study day.

**Patient Population:**

A total of 130 acromegalic patients were recruited from the 131 patients who completed the previous study (E28 52030 709) at 30 centers in 9 countries. All 130 enrolled patients received at least one injection of lanreotide in the present study and were included in the safety population. Of these patients, 124 patients also had GH or IGF-1 data (intention-to-treat [ITT] population). 88 patients fulfilled the criteria to be included in the per protocol (PP) population.

**Diagnosis and criteria for inclusion:**

Main inclusion criteria from the preceding study included a documented diagnosis of active acromegaly within the previous 5 years (basal GH > 5ng/mL or elevated IGF-1, adjusted for age and sex, or GH level > 2 ng/mL after an oral glucose tolerance test (OGTT) measured after the most recent surgery or radiotherapy) and age ≥18 years. Main exclusion criteria included expected pituitary surgery or radiotherapy during the study period, significant renal or hepatic abnormalities and known hypersensitivity to any of the test materials or related compounds.

**Treatment Groups:**

12 monthly (every 28 days) deep s.c. injections of lanreotide acetate administered at titrated doses (60, 90 or 120 mg) according to the GH and IGF1 individual response.

At the first study visit (visit V4) 49% of patients received lanreotide acetate 60 mg, 32% received 90 mg and 18% received 120 mg. The proportion of patients receiving lanreotide acetate at 60 and 90 mg titrated doses decreased from 49% to 37% and from 32% to 15% respectively from the beginning to the end of the study. The proportion of patients receiving the highest titrated dose of 120 mg increased from 18% to 48% over the course of the study.

The doses at weeks 36, 40 and 44 were adapted according to the biochemical response of the patient assessed at week 32.

Titration criteria:

Patients with mean GH > 2.5 ng/mL:

- Patients receiving lanreotide acetate 60 mg were uptitrated to lanreotide acetate 90 mg every 28 days
- Patients receiving lanreotide acetate 90 mg were uptitrated to lanreotide acetate 120 mg every 28 days
- Patients receiving lanreotide acetate 120 mg remained on lanreotide acetate 120 mg every 28 days

Patients with mean GH  $\geq$  1 ng/mL and  $\leq$  2.5 ng/mL:

- No change

Patients with mean GH < 1 ng/mL and IGF-1 normalized:

- Patients receiving lanreotide acetate 60 mg remained on lanreotide acetate 60 mg every 28 days
- Patients receiving lanreotide acetate 90 mg were down-titrated to lanreotide acetate 60 mg every 28 days
- Patients receiving lanreotide acetate 120 mg were down-titrated to lanreotide acetate 90 mg every 28 days

Patients with mean GH < 1 ng/mL and IGF-1 not normalized:

- No change

Following titration, if the dose of lanreotide acetate was increased, no subsequent decrease of the dose was allowed during the study.

**Duration of Treatment:**

Patients received 12 repeated deep s.c. administrations of lanreotide acetate once every 28 days.

**Endpoints:**

Efficacy:

- Mean serum GH levels (samples at baseline and week 48) (primary endpoint).
- Mean serum IGF-1 levels (samples at baseline and week 48).
- Symptoms of acromegaly (night sweats, headache, asthenia, swelling of extremities and joint pain).
- Serum lanreotide levels.

**Safety:**

Adverse events (AEs), local tolerance, systemic tolerance, standard hematology and biochemistry, anti-lanreotide antibodies, ultrasound of gall bladder and concomitant medication (including anti-diabetic medication).

**Statistical Analyses:**

Primary and secondary efficacy was assessed primarily in the ITT population, although summary tables were also prepared for the PP population. Safety was assessed in all patients who received at least one dose of study medication (safety population).

The primary endpoint, mean GH level, was calculated from 9 serum samples taken over 4 hours for each patient after 12 administrations of lanreotide acetate at titrated doses and after 3 administrations of lanreotide acetate at a fixed dose (end of the previous study). The difference in the log-transformed values at visit V16 and visits V4 and R5 (equivalent to the log of the ratio of the two values) were calculated for each patient and analyzed using an analysis of variance (ANOVA) to test for the presence of a statistically significant difference between regions. The geometric mean ratio and associated 95% two-sided confidence interval were calculated by back transforming the mean and confidence interval from the analysis of the log-transformed difference.

The secondary efficacy endpoints of mean GH (after 12 administrations of lanreotide acetate at a titrated dose compared to lanreotide 30 mg PR treatment) and IGF-1 levels were also analyzed in this way. The other secondary efficacy endpoints (number of patients with mean GH  $\leq 2.5$  ng/mL, number of patients with mean GH  $\leq 5$  ng/mL, number of patients with normalized IGF-1 and the number of patients with mean GH  $\leq 2.5$  ng/mL and normalized IGF-1) were summarized by counts and percentages and analyzed using a McNemar's test.

Safety data was analyzed using descriptive statistics and presented in summary tables. No formal statistical tests were performed on safety data.

**Results:**

**Patient Demographics**

Age ranged from 25 to 77 years, with a median of 53.3 years. There were a comparable number of males and females in the study (63 vs. 67) and the majority of patients were Caucasian (98%). Median time since diagnosis of acromegaly was 8.26 years in the ITT population (n=124). The most common medical history was essential hypertension in 38% of the safety population. 42 subjects (32%) reported calculus of the gallbladder without mention of cholecystitis or obstruction at baseline.

**Patient Disposition**

131 patients completed Study 709 and 130 patients entered Study 710 (Pt 2501 was not recruited on to Study 710). 123/130 (95%) patients completed Study 710. Seven patients (5%) withdrew from the study. Patient 306 withdrew his consent following the AE of cerebral ischemia, patient 1405 died due to sepsis followed by intravascular coagulation, patient 404 had a protocol

deviation (pregnancy), patient 1202 could not attend scheduled visits due to work commitments, patient 2502 was to have radiotherapy and patients 403 and 2405 withdrew due to adverse events (persisting induration at the injection site and severe depression, respectively).

#### Concomitant Medication Use

The most common class of concomitant medication was thyroid hormones which were taken by 38% of patients. Glucocorticoids were taken by approximately 31% of patients and 3-oxoandrogen derivatives were taken by 20%.

#### Drug Exposure

**Table 10.1.7.1 Summary of Exposure to Lanreotide (Safety Population)**

Injection number	Number of patients at visit	Number of patients per lanreotide autogel dose (n (%))		
		60 mg	90 mg	120 mg
4	130	64 (49%)	41 (32%)	23 (18%)
5	128	49 (38%)	42 (33%)	36 (28%)
9	124	48 (39%)	22 (18%)	53 (43%)
13	123	46 (37%)	18 (15%)	59 (48%)

Data Source: Sponsor's Table 122 in Section 14.3.6

Missing data: patients 204 and 1701 at V4 (injection 4), patient 2502 at V5 (injection 5), patient 403 at V9 (injection 9).

#### Primary Efficacy Outcomes

Patients were allocated to the treatment group according to the dose they received at the final visit (V16), independently of any doses they received during the study.

Mean GH level was reduced after 12 repeated administrations of lanreotide acetate at titrated doses (V16) from that observed at the end of the previous study (E28 52030 709) in which patients received lanreotide acetate at fixed doses (V4).

Combined data for all titrated doses of lanreotide acetate showed a reduction in mean GH level from  $3.02 \pm 2.33$  ng/mL at V4 (n=124) to  $2.38 \pm 2.00$  ng/mL at V16 (n=122).

*It is important to note that more patients were on 120 mg at Visit 16 compared to Visit 4. At the first study visit (visit V4) 49% of patients received lanreotide acetate 60 mg, 32% received 90 mg and 18% received 120 mg. At the final study visit (visit V16), 37% of patients received lanreotide acetate 60 mg, 15% received 90 mg and 48% received 120 mg.*

#### Secondary Efficacy Outcomes

##### Change in Mean GH Level from R5 to V16

Mean GH levels were significantly lower after 12 repeated administrations of lanreotide acetate at titrated doses (V16) in the present study than at the end of treatment with lanreotide 30 mg PR (R5) in the previous study (E28 52030 709). A decrease in mean GH level from  $2.82 \pm 2.0$  ng/mL at R5 (n=124) to  $2.38 \pm 2.0$  ng/mL at V16 (n=122) was observed in the ITT population.

##### Change in Mean IGF-1 Level from V4 to V16

Repeated administration of lanreotide acetate at titrated doses was associated with a significant decrease in mean IGF-1 level from V4 to V16 in the ITT population. At V4, the mean IGF-1 level was  $310.4 \pm 153.8$  ng/mL and decreased to  $287.5 \pm 137.1$  ng/mL at V16.

#### Change in Mean IGF-1 Level from R5 to V16

Repeated administration of lanreotide acetate at fixed doses and subsequently titrated doses was associated with a significant decrease in mean IGF-1 level from R5 to V16 in the ITT population. At R5, mean IGF-1 level was  $332.2 \pm 168.2$  ng/mL and decreased to  $287.5 \pm 137.1$  ng/mL at V16.

#### GH $\leq 2.5$ ng/mL, GH $\leq 5.0$ ng/mL and Normalized IGF-1

At V4, 55% of patients had GH levels  $\leq 2.5$  ng/mL. This proportion increased to 68% at the end of treatment (V16). The proportion of patients with GH levels  $\leq 5.0$  ng/mL also increased from 81% at V4 to 93% at V16. The numbers of patients with normalized IGF-1 levels was similar at visit V4 (N=61 (49%)) and at visit V16 (N=62 (50%)). In addition, the number of patients with both GH levels  $\leq 2.5$  ng/mL and normalized IGF-1 were also similar at these two visits (at V4, N=48 (39%), at V16 N=52 (43%)).

**Table 10.1.7.2 Summary of GH Levels  $\leq 2.5$  ng/mL,  $\leq 5.0$  ng/mL and Normalized IGF-1 Levels (ITT Population)**

	End 4 <sup>th</sup> Interval Visit R5 N = 124	End 3 <sup>rd</sup> Interval Visit V4 N = 124	End 7 <sup>th</sup> Interval Visit V8 N = 124	End 11 <sup>th</sup> Interval Visit V12 N = 123	End 15 <sup>th</sup> Interval Visit V16 N = 123
GH $\leq 2.5$ ng/mL	n=124	n=124	n=124	n=123	n=122
Yes	61 (49%)	68 (55%)	75 (60%)	75 (61%)	83 (68%)
No	63 (51%)	56 (45%)	49 (40%)	48 (39%)	39 (32%)
GH $\leq 5.0$ ng/mL	n=124	n=124	n=124	n=123	n=122
Yes	107 (86%)	100 (81%)	106 (85%)	108 (88%)	113 (93%)
No	17 (14%)	24 (19%)	18 (15%)	15 (12%)	9 (7%)
Normalized IGF-1	n=124	n=124	n=124	n=123	n=123
Yes	55 (44%)	61 (49%)	68 (55%)	65 (53%)	62 (50%)
No	69 (56%)	63 (51%)	56 (45%)	58 (47%)	61 (50%)
GH $\leq 2.5$ ng/mL and normalised IGF-1	n=124	n=124	n=124	n=123	n=122
Yes	40 (32%)	48 (39%)	52 (42%)	55 (45%)	52 (43%)
No	84 (68%)	76 (61%)	72 (58%)	68 (55%)	70 (57%)

Data Source: Sponsor's Table 54 in Section 14.2

Treatment with lanreotide acetate at titrated doses was associated with overall improvements in symptoms compared to treatment with lanreotide acetate at fixed doses (V16 versus V4). Improvements were reported by 9% (night sweats), 15% (headache), 16% (asthenia), 17% (swelling of the extremities), and 14% (joint pain) of patients for each of the symptoms and worsening was reported by only 4% (night sweats), 6% (headache), 8% (asthenia), 9% (swelling of the extremities), and 11% (joint pain).

#### *Efficacy Conclusions*

More patients were on 120 mg at Visit 16 compared to Visit 4. At the first study visit (visit V4) 49% of patients received lanreotide acetate 60 mg, 32% received 90 mg and 18% received 120 mg. At the final study visit (visit V16), 37% of patients received lanreotide acetate 60 mg, 15% received 90 mg and 48% received 120 mg.

- Mean GH level was significantly reduced after 12 repeated administration of lanreotide acetate at titrated doses (V16) from that observed at the end of the previous study (E28 52030 709) in which patients received lanreotide acetate at fixed doses (V4).
- Mean GH levels were significantly lower after 12 repeated administration of lanreotide acetate at titrated doses (V16) in the present study than at the end of treatment with lanreotide 30 mg PR (R5) in the previous study (E28 52030 709).
- Reductions in mean GH level were observed with each of the titrated doses of lanreotide (60, 90 and 120 mg).
- Mean IGF-1 level was significantly reduced after 12 repeated administration of lanreotide acetate at titrated doses (V16) from that observed at the end of the previous study (E28 52030 709) in which patients received lanreotide acetate at fixed doses (V4).
- Mean IGF-1 levels were significantly lower after 12 repeated administration of lanreotide acetate at titrated doses (V16) in the present study than at the end of treatment with lanreotide 30 mg PR (R5) in the previous study (E28 52030 709).
- The reductions in mean GH levels associated with lanreotide acetate treatment at titrated doses was accompanied by increases in the proportion of patients who had GH levels  $\leq 2.5$  ng/mL,  $\leq 5.0$  ng/mL and normalized IGF-1 levels.
- Treatment with lanreotide acetate at titrated doses was associated with an improvement in the symptoms of acromegaly including night sweats, headache, asthenia, swelling of extremities and joint pain.

#### Safety Data:

##### *Deaths*

One patient (No. 1405, 48 year-old-female) died during the study due to sepsis followed by intravascular coagulation (not considered to be related to the study drug).

##### *Serious Adverse Events*

Twenty four patients (18%) reported SAEs during the study: 9 patients (19%) that received a final dose of 60 mg, 4 patients (20%) that received a final dose of 90 mg and 11 patients (18%) that received a final dose of 120 mg lanreotide acetate.

The most common SAEs reported during the study were classified as secondary terms, which were surgical intervention (n=6, 5%) and post-operative wound infection (n=1, <1%). These were followed by gastro-intestinal system disorders (5, 4%) which included: diarrhea (n=2, 2%), dysphagia, benign gastro-intestinal neoplasm, intestinal stenosis and peritonitis (all n=1, <1%).

Two SAEs may have a probable relationship to the study medication.

3. A gallstone colic event in a 54-year-old woman which was resolved by surgery. The patient did not discontinue treatment.
4. a 52-year-old women on octreotide therapy in past, had massive cholecystolithiasis prior to study and after 6-months of lanreotide developed aggravated cholelithiasis requiring cholecystectomy. The 6-month lanreotide treatment might have contributed to the cholecystolithiasis-related abdominal symptomatology requiring hospitalization.

**Table 10.1.7.3 Number of Patients Reporting SAEs (Safety Population)**

Serious Adverse Event	Lanreotide Autogel N = 130 n (%)
Any SAE	24 (18%)
Secondary terms	7 (5%)
Gastrointestinal system disorders	5 (4%)
General cardiovascular disorders	2 (2%)
Hearing and vestibular disorders	2 (2%)
Musculo-skeletal system disorders	2 (2%)
Psychiatric disorders	2 (2%)
Vascular (extracardiac) disorders	2 (2%)
General disorders	1 (<1%)
Liver and biliary system disorders	1 (<1%)
Neoplasm	1 (<1%)
Red blood cell disorders	1 (<1%)
Resistance mechanism disorders	1 (<1%)
Urinary system disorders	1 (<1%)

Data Source: Sponsor's Table 89 in Section 14.3.3.1

*Adverse Events that Led to study Withdrawal*

A total of 4 patients reported adverse events that caused their withdrawal from the study. Patient 1405 died; patients 306 and 2405 had serious adverse events with the consequence that the study medication was stopped. Patients 403 and 2405 had non-serious adverse events related to medication that lead to withdrawal.

**Patient 306**

This 73 year old female patient is noted within the protocol compliance section of her CRF as being excluded from clinical study E-28-52030-710 for personal reasons. Reasons for withdrawal are later detailed as due to “consent withdrawal” and not due to an “adverse event”. It should be noted, however, that this patient experienced an SAE (cerebral ischemia) which led to withdrawal of consent.

**Patient 403**

This 52 year old female patient withdrew her consent from clinical study E-28-52030-710 because of persisting injection site indurations. Her reason for withdrawal is detailed therefore as due to the occurrence of an “adverse event”.

**Patient 1405**

This 48 year old female patient died during the study due to sepsis followed by diffuse intravascular coagulation, an incident considered to be unrelated to the study drug. Reasons for her withdrawal are later detailed as due to “other”, namely death, and not recorded as an “adverse event”. However, the fatal SAE is clearly the reason this patient did not complete the study.

**Patient 2405**

Reasons for this 69 year old male patient’s withdrawal from clinical study E-28-52030-710 are detailed as due to the development of symptoms possibly due to severe depression. This was defined as an “adverse event”.

### Treatment Emergent Adverse Events

In the present study, 95% of the patients reported AEs during lanreotide acetate treatment at titrated doses, while in the previous study, 75% during lanreotide 30 mg PR treatment, and 80% during lanreotide acetate treatment at fixed doses.

Gastro-intestinal system disorders were reported by 71 patients (55%), liver and biliary system disorders by 57 patients (44%) and metabolic and nutritional disorders were reported by 55 patients (42%). The following preferred terms for adverse events were reported by 10% or more of patients: diarrhea [43 patients (33%)], abdominal pain [34 patients (26%)], cholelithiasis and hyperglycemia [each 21 patients (16%)], gall bladder sludge [19 patients (15%)], constipation and hyponatremia [each 18 patients (14%)], nausea [15 patients (12%)] and vomiting [13 patients (10%)].

### Laboratory Parameters

#### Hematology

There were no clinically significant changes in the number of patients with high or low values for the hematology parameters assessed during the study (Table 10.1.7.5 and 10.1.7.6). The proportion of patients with high and low values were comparable across treatments with lanreotide 30 mg PR (R1 to R5), lanreotide acetate at fixed doses (R5 to V4) and lanreotide acetate at titrated doses (V4 to V16).

**Table 10.1.7.4 Summary of Hematology Data – Number of Patients with Out-of-Range Values (Safety Population)**

Parameter	Baseline Visit R1 N = 130	End 4 <sup>th</sup> Interval Visit R5 N = 130	End 3 <sup>rd</sup> Interval Visit V4 N = 130	End 15 <sup>th</sup> Interval Visit V16 N = 123
<b>Erythrocytes (10<sup>12</sup>/L)</b>				
Low	26 (21%)	27 (22%)	27 (23%)	24 (20%)
Normal	95 (78%)	95 (78%)	91 (76%)	93 (78%)
High	1 (<1%)	0	1 (<1%)	2 (2%)
No. of patients with data	122 (100%)	122 (100%)	119 (100%)	119 (100%)
<b>Leukocytes (10<sup>9</sup>/L)</b>				
Low	3 (2%)	6 (5%)	5 (4%)	6 (5%)
Normal	115 (93%)	113 (93%)	108 (89%)	107 (89%)
High	5 (4%)	3 (2%)	8 (7%)	7 (6%)
No. of patients with data	123 (100%)	122 (100%)	121 (100%)	120 (100%)
<b>Platelets (10<sup>9</sup>/L)</b>				
Low	5 (4%)	8 (7%)	3 (2%)	7 (6%)
Normal	116 (95%)	113 (93%)	117 (97%)	110 (92%)
High	1 (<1%)	1 (<1%)	1 (<1%)	2 (2%)
No. of patients with data	122 (100%)	122 (100%)	121 (100%)	119 (100%)
<b>Haemoglobin (g/dL)</b>				
Low	21 (17%)	30 (25%)	23 (19%)	25 (21%)
Normal	101 (83%)	92 (75%)	97 (80%)	94 (78%)
High	0	0	1 (<1%)	1 (<1%)
No. of patients with data	122 (100%)	122 (100%)	121 (100%)	120 (100%)
<b>HbA<sub>1c</sub> (%)</b>				
Low	1 (<1%)	1 (<1%)	0	1 (<1%)
Normal	78 (61%)	70 (58%)	72 (60%)	66 (55%)
High	48 (38%)	49 (41%)	49 (40%)	52 (44%)
No. of patients with data	127 (100%)	120 (100%)	121 (100%)	119 (100%)

Data Source: Sponsor's Table 101 in Section 14.3.5

**Table 10.1.7.5 Summary of Hematology Data – Number of Patients with Clinically Significant Values (Safety Population)**

Parameter	Baseline Visit R1 N = 130	End 3 <sup>rd</sup> Interval Visit R5 N = 130	End 3 <sup>rd</sup> Interval Visit V4 N = 130	End 15 <sup>th</sup> Interval Visit V16 N = 123
Low Erythrocytes (10 <sup>12</sup> /L)	0	1 (<1%)	0	0
Low Leukocytes (10 <sup>9</sup> /L)	2 (2%)	1 (<1%)	1 (<1%)	0
High Leukocytes (10 <sup>9</sup> /L)	0	1 (<1%)	1 (<1%)	2 (2%)
Low Platelets (10 <sup>9</sup> /L)	0	1 (<1%)	0	0
Low Haemoglobin (g/dL)	1 (<1%)	0	0	1 (<1%)
High HbA <sub>1c</sub> (%)	1 (<1%)	0	0	0

Data Source: Sponsor's Table 101 in Section 14.3.5

**Biochemistry**

Analysis of biochemistry data showed that the number of patients with out-of-range values and clinically significant values were comparable between treatment with lanreotide 30 mg PR (R1 to R5), lanreotide acetate at fixed doses (R5 to V4) and lanreotide acetate at titrated doses (V4 to V16) (Table 10.1.7.7 and Table 10.1.7.8).

**Table 10.1.7.6 Summary of Biochemistry Data – Number of Patients with Out-of-Range Values (Safety Population)**

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Parameter	Baseline Visit R1 N = 130	End 4 <sup>th</sup> Interval Visit R5 N = 130	End 3 <sup>rd</sup> Interval Visit V4 N = 130	End 15 <sup>th</sup> Interval Visit V16 N = 123
<b>Alk. Phosphatase (U/L)</b>				
Low	6 (5%)	7 (5%)	6 (5%)	3 (2%)
Normal	113 (88%)	115 (89%)	114 (88%)	112 (91%)
High	10 (8%)	7 (5%)	9 (7%)	8 (7%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)
<b>Calcium (mmol/L)</b>				
Low	0	1 (<1%)	1 (<1%)	0
Normal	128 (>99%)	128 (>99%)	127 (98%)	120 (98%)
High	1 (<1%)	0	1 (<1%)	3 (2%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)
<b>Creatinine (µmol/L)</b>				
Low	0	0	0	0
Normal	127 (98%)	127 (98%)	127 (98%)	120 (98%)
High	2 (2%)	2 (2%)	2 (2%)	3 (2%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)
<b>Glucose (mmol/L)</b>				
Low	0	1 (<1%)	1 (<1%)	0
Normal	57 (44%)	55 (43%)	59 (46%)	44 (36%)
High	72 (56%)	73 (57%)	69 (53%)	79 (64%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)
<b>GOT (AST) (U/L)</b>				
Low	0	0	0	0
Normal	125 (97%)	126 (98%)	129 (100%)	118 (96%)
High	4 (3%)	3 (2%)	0	5 (4%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)
<b>GPT (ALT) (U/L)</b>				
Low	0	0	0	0
Normal	119 (92%)	118 (91%)	120 (93%)	115 (93%)
High	10 (8%)	11 (9%)	9 (7%)	8 (7%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)
<b>Phosphorus (mmol/L)</b>				
Low	0	0	0	0
Normal	119 (92%)	117 (91%)	119 (92%)	114 (93%)
High	10 (8%)	12 (9%)	10 (8%)	9 (7%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)
<b>Potassium (mmol/L)</b>				
Low	1 (<1%)	2 (2%)	0	3 (2%)
Normal	128 (>99%)	127 (98%)	128 (100%)	118 (96%)
High	0	0	0	2 (2%)
No. of patients with data	129 (100%)	129 (100%)	128 (100%)	123 (100%)
<b>Sodium (mmol/L)</b>				
Low	13 (10%)	19 (15%)	8 (6%)	9 (7%)
Normal	116 (90%)	107 (83%)	119 (93%)	112 (91%)
High	0	3 (2%)	1 (<1%)	2 (2%)
No. of patients with data	129 (100%)	129 (100%)	128 (100%)	123 (100%)
<b>Total Bilirubin (µmol/L)</b>				
Low	0	0	0	0
Normal	118 (91%)	119 (92%)	120 (93%)	114 (93%)
High	11 (9%)	10 (8%)	9 (7%)	9 (7%)
No. of patients with data	129 (100%)	129 (100%)	129 (100%)	123 (100%)

Data Source: Sponsor's Table 113 in Section 14.3.5

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**Table 10.1.7.7 Summary of Biochemistry Data – Number of Patients with Clinically Significant Values (Safety Population)**

Parameter	Baseline Visit R1 N = 130	End 4 <sup>th</sup> Interval Visit R5 N = 130	End 3 <sup>rd</sup> Interval Visit V4 N = 130	End 15 <sup>th</sup> Interval Visit V16 N = 123
High Creatinine (µmol/L)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Low Glucose (mmol/L)	0	1 (<1%)	1 (<1%)	2 (2%)
High Glucose (mmol/L)	36 (28%)	36 (28%)	34 (26%)	38 (31%)
High GOT (AST) (U/L)	1 (<1%)	2 (2%)	0	0
High GPT (ALT) (U/L)	1 (<1%)	2 (2%)	0	0
High Phosphorus (mmol/L)	9 (7%)	11 (9%)	7 (5%)	7 (6%)
Low Potassium (mmol/L)	1 (<1%)	2 (2%)	0	3 (2%)
High Potassium (mmol/L)	0	0	0	2 (2%)
Low Sodium (mmol/L)	6 (5%)	12 (9%)	4 (3%)	5 (4%)
High Sodium (mmol/L)	0	2 (2%)	1 (<1%)	0
High Total Bilirubin (µmol/L)	3 (2%)	2 (2%)	4 (3%)	3 (2%)

Data Source: Sponsor's Table 113 in Section 14.3.5

#### *Vital Signs*

No clinically significant changes in weight, heart rate, systolic and diastolic blood pressures were observed during the course of the study.

#### *Special Safety Studies*

##### Gall bladder Ultrasound

A substantial proportion of patients had either lithiasis or sludge after treatment with lanreotide acetate (Table 10.1.7.9). The incidence of lithiasis showed a slight increase from baseline levels over the course of treatment with lanreotide acetate. The incidence of lithiasis was the same after treatment with lanreotide 30 mg PR (R5) as it was at baseline (detected in 30% of patients), increased slightly to 34% at V4 after treatment with lanreotide acetate at fixed doses, and increased to 42% at V16 after treatment with lanreotide acetate at titrated doses. The incidence of sludge was 7% of patients at baseline, 11% at R5, 7% at V4 and 12% at V16, the end of study visit. There was also an increase in the proportion of patients with either sludge or lithiasis from 34% at baseline to 51% at V16.

**Table 10.1.7.8 Incidence of Lithiasis and Sludge (Safety Population)**

Parameter	Baseline Visit R1 N = 130	End 4 <sup>th</sup> Interval Visit R5 N = 130	End 3 <sup>rd</sup> Interval Visit V4 N = 130	End 15 <sup>th</sup> Interval Visit V16 N = 123
Lithiasis	39 (30%)	36 (30%)	41 (34%)	47 (42%)
Sludge	9 (7%)	14 (11%)	8 (7%)	14 (12%)
Either lithiasis or sludge	44 (34%)	44 (36%)	45 (37%)	58 (51%)
No. of patients with data	129 (100%)	122 (100%)	122 (100%)	113 (100%)

Data Source: Sponsor's Table 131 in Section 14.3.6

#### **Sponsor's Conclusions:**

Mean GH levels were significantly reduced after 12 repeated administrations of lanreotide acetate at titrated doses. Significant reductions in mean IGF-1 levels were also associated with treatment. Treatment was well tolerated, with a safety profile similar to that reported in the previous study (E28 52030 709). Local tolerance of injection was good, with only very minor changes in the small proportion of patients who reported pain, redness, itching or indurations at the injection site during the study. These data suggest that lanreotide acetate administered at titrated doses is an effective and well tolerated treatment for acromegaly.

**Medical Officer's Conclusions:**

The primary efficacy analysis showed that mean GH and IGF-1 levels were significantly reduced after 12 repeated administrations of lanreotide acetate at titrated doses. The number of patients with both GH levels  $\leq 2.5$  ng/mL and normalized IGF-1 were similar at the beginning and end of Study 710: at V4, N=48 (39%), at V16 N=52 (43%).

More patients were on 120 mg at Visit 16 compared to Visit 4. At the first study visit (visit V4) 49% of patients received lanreotide acetate 60 mg, 32% received 90 mg and 18% received 120 mg. At the final study visit (visit V16), 37% of patients received lanreotide acetate 60 mg, 15% received 90 mg and 48% received 120 mg.

Twenty four patients (18%) reported SAEs during the study; two SAEs may have a probable relationship to the study medication. Two patients had non-serious adverse events related to medication that lead to withdrawal.

Gastro-intestinal system disorders were reported by 71 patients (55%), liver and biliary system disorders by 57 patients (44%) and metabolic and nutritional disorders were reported by 55 patients (42%). The following preferred terms for adverse events were reported by 10% or more of patients: diarrhea [43 patients (33%)], abdominal pain [34 patients (26%)], cholelithiasis and hyperglycemia [each 21 patients (16%)], gall bladder sludge [19 patients (15%)], constipation and hyponatremia [each 18 patients (14%)], nausea [15 patients (12%)] and vomiting [13 patients (10%)].

There were no clinically significant changes in hematology, biochemistry, vital signs or physical examination associated with lanreotide acetate at titrated doses.

Gall bladder ultrasound revealed that the incidence of either lithiasis or sludge was higher after repeated administrations of lanreotide acetate at titrated doses (n=58 (51%)) than at the end of the previous study (n=45 (37%)).

**10.2 Line-by-Line Labeling Review**

The changes proposed have not been discussed with the applicant at the time of this review, so they must be considered preliminary. Deletions to the applicant's proposed language are denoted by strike-through font and additions are denoted by highlighted text.

The image shows several handwritten marks. There are five diagonal slashes arranged in two rows: three in the top row and two in the bottom row. Below these slashes is a single horizontal line.

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       Trade Secret / Confidential

  ✓   Draft Labeling

       Deliberative Process



### 10.3 Additional Studies of Lanreotide

**Table 10.3.1 Clinical studies with lanreotide in acromegalic patients, intrinsic factor studies or studies in healthy subjects**

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

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BA	A-93-52030-149	Single dose PK and BA	Phase I single center open label randomized parallel group	Lanreotide IRF 7 µg/kg (LBCK: JBMI and JBPN solvent) i.v. then deep s.c. injection of either lanreotide Autogel 0.246 mg/mg; 60 mg (LBCL: KBB5) 90 mg (LBCM: KBB3) or 120 mg (LBCN: LBBD) administered into the superior-external quadrant of the buttock.	i.v. route: 30 s.c. route: 38 completed: 38	HS	Ranged from 7 to 16 weeks
BA	E-54-52030-038	Evaluation of linearity of 60, 90, 120 mg; comparative PK. Evaluation of BA and of the interaction between lanreotide Autogel and cyclosporine and Vitamin K. Tolerability	Phase I single center randomized double-blind parallel group with additional drug interaction study	Lanreotide IRF 1 mg (FBNP: GBBF: EBC6, ED01) i.v. then either lanreotide Autogel 0.246 mg/mg; 60 mg (N70051) i.m., 90 mg (N70052) i.m., 120 mg (N70053) i.m. or 0.246 mg/mg; 60 mg s.c. or 0.246 mg/mg; 60 mg (N61007) i.m. or 0.246 mg/mg; 60 mg (N70051) i.m. or s.c.	42	HS	Single dose
BA	E-33-52030-032	Comparative single dose PK, PD and safety. (30 mg s.c. vs. 30 mg i.m.)	Phase I single center randomized double-blind parallel group	Lanreotide IRF 1 mg (NE001) i.v. then either lanreotide Autogel 0.246 mg/mg; 30 mg (N70032), 40 mg (N61006), 60 mg (N61007) s.c. or lanreotide MPF 30 mg i.m.	24	HS	Single dose
BA	E-92-52030-175	Evaluate PK profile including absolute bioavailability and tolerability of both lanreotide IRF and lanreotide MPF	Phase I single center randomized open label cross-over	Lanreotide IRF 7, 21 or 42 µg/kg s.c. or lanreotide IRF 7 µg/kg i.v., then lanreotide MPF 30 mg i.m. (V001 and V002).	12	HS	2 times single dose
BA	E-92-52030-180	Single and repeated dose PK and BA. Therapeutic activity and safety	Multicenter open label non-comparative	Lanreotide IRF 7 µg/kg (A002) i.v. and then lanreotide IRF 7 µg/kg s.c. followed by lanreotide MPF 30 mg i.m. every 14 days to the third month and then every 10 or 14 days from the third month. (B001, CO13, CO18, CO20)	entered: 11 completed: 9	Acro	24-week
BA	E-92-52030-001	Comparative single dose PK and tolerance	Phase I single center open label parallel group	Lanreotide IRF 7 µg/kg (FBGR) i.m. or s.c., then lanreotide MPF 30 mg (EBGF) i.m., lanreotide Autogel 0.246 mg/mg (N70031) or 0.246 mg/mg (N70030) 12.8 mg s.c.	18	HS	2 times single dose separated by 2 day washout

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Regimens; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Healthy subject PK and initial tolerability	E-55-52030-047	Local tolerability study of lanreotide Autogel after single 90, 99 and 120 mg s.c. injection at 3 different sites	Phase I single center non-randomized single blind	Lanreotide Autogel 0.246 mg/kg; 60 mg (GBNF:GBG1), 40 mg (GBNG:GBG2) or 120 mg (GBNE:GBG7) deep s.c. to upper lateral quarter of right buttock, upper arm or right lateral umbilical abdominal wall.	27	HS	Single dose
Healthy subject PK and initial tolerability	E-92-52030-010	PK profile and dose proportionality	Phase I single center randomized crossover (Latin square)	Lanreotide IRF i.v. infusion for 20 minutes: 7, 21 and 42 ug/kg. (DBKF and DBMQ).	11	HS	20 minutes
Healthy subject PK and initial tolerability	E-92-52030-014	Evaluate PK profile and tolerability using multiple doses at three levels	Phase I open label randomized crossover latin square multiple dose	Lanreotide IRF 7, 21, 42 ug/kg single s.c. dose. Lanreotide IRF 7, 21, 42 ug/kg multiple doses (every 8 hrs, 11 doses in total) s.c. (D003).	12	HS	11 times 8 hrs
Healthy subject PK and initial tolerability	E-54-52030-134	Evaluate PK profile at steady state, including metabolism and fecal excretion	Phase I open label parallel group two-dose escalation	Lanreotide IRF low dose (0.7) mg/day s.c. infusion and 0.375 mg after 24 hrs) High dose (3.0 mg/day s.c. infusion for 24 hrs and 1.5 mg s.c. injection and 5.0 mg/day s.c. infusion for four days).	30	HS	3 days
Healthy subject PK and initial tolerability	E-54-52030-057	PK and tolerance	Phase I single center open label non-randomized crossover	Part A: Lanreotide IRF 3 mg (L12B) s.c. Part B: Lanreotide MPF 30 mg (A008) i.m.	Part A: screened: 13 analyzed: 12 Part B: screened: 11 analyzed: 12	HS	7 weeks
Healthy subject PK and initial tolerability	E-54-52030-093	Single dose PK	Phase I single center open label non-comparative	Lanreotide Autogel 40 mg (50066) i.m.	13 PK analysis: n=12	HS	3 weeks
Healthy subject PK and initial tolerability	E-92-52030-035	Comparative PK of single s.c. and i.m. administrations	Phase I single center open label parallel group	Lanreotide Autogel 40 mg (50066) i.m. or 30 mg s.c. or i.m. (N70047 and N70046).	48	HS	11.6 weeks
Healthy subject PK and initial tolerability	E-54-52030-029	Single dose PK	Phase I single center open label non-comparative	Lanreotide MPF 30 mg (E005) i.m.	12	HS	Single dose

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

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Healthy subject PK and initial tolerability	E-94-92030-098	PK of single dose lanreotide i.m.	Phase I single center open label non-randomized	Lanreotide MPF 30 mg (E8D7) i.m.	12	HS	Single dose
Healthy subject PK and initial tolerability	E-92-92030-176	PK of IRF i.v. and PK of MPF i.m. Deconvolution analysis to show the absorption kinetics of MPF	Phase I single center open label crossover	Lanreotide IRF 7 µg/kg i.v. lanreotide MPF 30 mg (A602) i.m.	8	HS	5 weeks
Healthy subject PK and initial tolerability	E-94-92030-086	PK of single doses of two prolonged-release formulations of lanreotide i.m.	Phase I single center open label non-comparative non-randomized parallel	Lanreotide <del>IRF</del> formulation 30 mg (C030) i.m. lanreotide 100-0 formulation 30 mg (C014) i.m.	24	HS	Single dose
Healthy subject PK and initial tolerability	E-92-92030-177/178*	PK of single dose lanreotide i.m.	Phase I single center open label non-randomized	Lanreotide MPF 30 mg (V003 and A003) i.m.	4	HS	Single dose
Healthy subject PK and initial tolerability	E-94-92030-040	PK of single dose lanreotide i.m. and evaluation of clinical and biological safety	Phase I single center open label non-comparative	Lanreotide MPF 60 mg (F005) i.m.	14 PK analysis: n=12	HS	Single dose
Healthy subject PK and initial tolerability	E-28-92030-051	PK and tolerance of single dose lanreotide i.m. and evaluation of secretion of insulin, C-peptide, glucose and glucagon	Phase I single center open label non-comparative	Lanreotide IRF 0.5 mg i.v. then lanreotide MPF 60 mg i.m. (GBH3-G001=MPF 60mg; GBMR = 0.5 g; all supplied to site).	19 PK analysis: n=12	HS	2 times single dose
Healthy subject PK and initial tolerability	E-94-92030-106	PK and safety of single dose of two batches of <del>lanreotide</del> lanreotide	Phase I single center open label non-comparative	Lanreotide MPF 60 mg i.m. 2 and 3 ml suspension. (E042 and E043).	24 12 in each of 2 groups PK analysis: n=11	HS	Single dose
Healthy subject PK and initial tolerability	E-94-92030-092	PK in healthy volunteers after two i.m. injections.	Phase I single center open label non-comparative two dose study	Day 1: Lanreotide MPF 40 mg (D8P2) i.m. Day 28: Lanreotide MPF 40 mg i.m.	13	HS	At least 4 weeks
Healthy subject PK and initial tolerability	E-92-92030-046 / 019	PK of <del>lanreotide</del> formulation	Phase I	Lanreotide 15 mg (N4604) as either i.m. or s.c.	category: 24	HS	Single dose

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

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage; Regimen; (Batch No); Route of Administration	Number of Subject	Healthy Subjects or Diagnostic of Patients	Duration of Treatment
Healthy subject PK and initial tolerability	E-34-32030-082	PK after single dose of prolonged release formulation	Phase I single center open label	Laureotide <del>40 mg</del> 40 mg i.m.	6	HS	Single dose
Healthy subject PK and initial tolerability	E-34-32030-088	PK after two doses of prolonged release formulation	Phase I single center open label non-comparative	Laureotide <del>40 mg</del> 40 mg (D6N1) i.m. 28 day interval then laureotide pumate 40 mg i.m.	22 PK analysis: n=10	HS	12 weeks
Healthy subject PK and initial tolerability	E-34-32030-092	PK after two doses of prolonged release formulation	Phase I single center open label non-randomized multiple dose	Laureotide <del>40 mg</del> 40 mg (D603) i.m. 28 day interval then laureotide pumate 40 mg i.m.	22	HS	12 weeks
Patient PK and initial tolerability	E-28-32030-076	Evaluate PK profile, efficacy and safety	Phase II randomized double blind parallel group	Laureotide Autogel 60 mg (KBEV), 90 mg (KSHS) or 120 mg (KSHR) as deep s.c. in the upper quadrant of the buttock. Fixed doses at 28 day intervals.	18	Acro	16 weeks 27 weeks including screening
Patient PK and initial tolerability	E-92-32030-017	Single dose PK	Multicenter open label parallel group	Laureotide Autogel <del>40 mg</del> 40 mg (N61006) or 60 mg (N61007) as i.m. in the upper quadrant of the buttock.	17	Acro	Single dose
Patient PK and initial tolerability	E-92-32030-096	PK, efficacy and tolerability of laureotide MPF	Multicenter open label single and repeated dose	Laureotide MPF 30 mg i.m. 20 day interval then i.m. injection once every 14 days for 3 months (E01B and E002) equivalent to conditioning batches FBQZ, EBMC and FBES).	18 analyzed: 17	Acro	14.9 weeks
Patient PK and initial tolerability	E-92-32030-179	PK and PD study to evaluate efficacy and safety	Single center open label non-comparative single and repeated dose	Laureotide MPF 30 mg (U001) i.m. (from i.m. injection every 14 days for 3 to 12 months).	PK analysis: n = 7 PD analysis: n = 8	Acro	12 to 30.3 weeks
Intrinsic factor PK	E-92-32030-011	Single dose PK in patients suffering from severe chronic renal insufficiency	Open label comparative parallel group	Laureotide IRF 7 µg/kg (DBKB, D003 and DBJ7) i.v. bolus	25	12 HS 13 patients with renal insufficiency	Single dose
Intrinsic factor PK	E-38-32030-701	PK profile patients suffering from mild to severe hepatic insufficiency	Phase I single center open label parallel group	Laureotide IRF 7 µg/kg i.v. infusion over 20 minutes. (FBL5, EBQ6-E001 and GSDO, FERAF001).	24	12 HS 12 patients with severe hepatic insufficiency	Single dose
Intrinsic factor PK	E-92-32030-013	Evaluate PK profile in patients with hepatic insufficiency	Open label comparative parallel group	Laureotide IRF 7 µg/kg (D003, E001, FBK, FBJW and FBQ6) i.v. infusion over 20 minutes.	29	12 HS 17 patients with hepatic impairment	Single dose

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dose(s); Regimen; (Batch No); Route of Administration	Number of Subject	Healthy Subject or Diagnosis of Patient	Duration of Treatment
Intrinsic factor PK	E-92-32030-013	PK profile in elderly subjects	Comparative parallel group	Lanreotide IRF 7 µg/kg (D003 and E001) i.v. infusion over 20 minutes.	23	HS 13 young 12 elderly	Single dose
Intrinsic factor PK	E-35-32030-146	PK equivalence and tolerance.	Phase I single center randomized double-blind cross-over placebo-controlled	Lanreotide IRF 7 µg/kg (JB17) i.v. infusion over 20 minutes or placebo (JBQS) i.v. infusion over 20 minutes.	29 PK analysis: n = 28 29 PK analysis: n = 27	HS Japanese Caucasian	2 times single dose separated by 14 day washout
Intrinsic factor PK	E-35-32030-182	Absolute BA, PK and tolerance	Phase I single center randomized double-blind crossover	Lanreotide IRF 7 µg/kg i.v. then lanreotide IRF 7, 21, 42 µg/kg s.c. (ΔGSLF and JBQS).	16	HS Japanese	Max 7 weeks
Intrinsic factor PK	E-47-32030-607	PK and safety in hepatically impaired patients	Multi-center open label non-randomized	Lanreotide IRF 100 µg i.v. bolus injection then 48 hrs later, a continuous i.v. infusion of lanreotide 100 µg/h over 24 hrs	14	Hepatically impaired patients	2 times single dose
Healthy subject PD	E-34-32030-132	Evaluate PD effects on nocturnal GH secretion, digestive hormones and TSH	Phase I randomized double-blind placebo-controlled	Group I: Lanreotide IRF in increasing doses of 125, 250, 500 µg s.c. or placebo s.c. Group II: Lanreotide IRF 2000 µg s.c. infusion over 12 hrs or placebo s.c. infusion	16	HS	4 weeks
Healthy subject PD and PK/PD	E-92-32030-173	Evaluate effect on plasma GH and carbohydrate tolerance during orally induced hypoglycemia	Phase I randomized single-blind, placebo-controlled crossover	Lanreotide IRF 1000 µg s.c. or placebo.	6	HS	2.1 weeks
Healthy subject PD and PK/PD	E-92-32030-174	Evaluate effect on plasma GH and carbohydrate tolerance	Phase I randomized double-blind placebo-controlled crossover	Lanreotide IRF s.c. continuous infusion in increasing doses of 1000, 2000 and 3000 µg/24 hrs; or placebo.	8	HS	4 weeks
Healthy subject PD and PK/PD	E-34-32030-133	Compare PK and PD efficacy of two batches of lanreotide IRF	Phase I randomized double-blind placebo-controlled crossover	Lanreotide IRF (two batches) 3 µg/kg s.c. 30 µg/kg s.c. or placebo.	12	HS	Single dose of two batches

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

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Regimen; (Batch No); Route of Administration	Number of Subject	Healthy Subject or Diagnostic of Patients	Duration of Treatment
Healthy subject PD	E-54-52050-133	Evaluate effect on plasma IGF-1, carbohydrate tolerance and digestive hormones during orally induced hyperghrelinemia	Phase I open label placebo-controlled	Placebo s.c. infusion (100µg) over 24 hrs, then lanreotide IRF 2000 µg/24 hrs s.c. infusion (100µg) over 7 days.	6	HS	1.1 weeks
Healthy subject PD	E-47-52050-147	Evaluate effect on intragastric acidity and gallbladder contraction, and plasma concentration of GH, IGF-1, glucose and digestive hormones	Randomized single-blind placebo-controlled crossover	Lanreotide MPF 30 mg i.m. or placebo (B001).	3	HS	12 weeks
Healthy subject PD	E-62-52050-003	Examine effect on renal hemodynamics and concentration of GH, IGF-1, glucagon and insulin	Phase I open label	Lanreotide MPF 30 mg (D011) i.m.	12	HS	Single dose
Healthy subject PD and PK/PD	E-47-52050-134	Evaluate effect of single dose MPF on biliary and pancreatic exocrine secretion	Phase I randomized single-blind cross-over placebo-controlled	Lanreotide MPF 30 mg i.m. or placebo.	3	HS	13 weeks
Healthy subject PD	E-47-52050-403	Investigate vasoconstrictive efficacy on meal-stimulated splanchnic and renal blood flow	Phase I randomized double-blind crossover placebo-controlled	Lanreotide MPF 30 mg i.m. or placebo (C019/B601; B091/B601).	6	HS	3 weeks
Healthy subject PD	E-54-52050-030	Evaluate effect on digestion of liquid meal and rhodanal caecal transit time	Phase I randomized single-blind crossover placebo-controlled	Lanreotide IRF 100 µg bolus i.v. then 100 µg/24 i.v. over 4 hrs. or placebo.	3	HS	24 weeks
Healthy subject PD	E-54-52050-031	Investigate effect on PGE <sub>2</sub> -stimulated jejunal secretion	Phase I open label exploratory	Lanreotide IRF 100 µg i.v. bolus then 100 µg/24 i.v. over 40 minutes.	9	HS	1 day

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Healthy subject PD	E-54-52030-109	Investigate PD effects over time of increasing doses on GH secretion	Phase II randomized single-blind four-way crossover	Saline or lanreotide IRF 250 µg once or twice or thrice per day s.c. (21-164)	8	HS	4 treatment sessions, separated by 1 week washout
Healthy subject PD and PK/PD	E-54-52030-133	Investigate PK and PD effects over time on GH secretion	Phase I randomized single-blind four-way crossover	Saline or lanreotide IRF 750, 1000 or 1250 µg twice per day s.c.	8	HS	4 treatment sessions, separated by 4 day washout
Healthy subject PD	E-54-52030-126	Evaluate effect over time on GH secretion	Phase I crossover	Saline or lanreotide IRF 125, 250 or 500 µg twice per day s.c. (GM 22014, 21-164, 21-633)	assigned: 9 completed: 8	HS	approx. 4 weeks
Healthy subject PD	E-47-52030-108	Evaluate vasoconstrictive efficacy on meal-stimulated splanchnic and renal blood flow	Phase I randomized double-blind crossover placebo-controlled	Lanreotide IRF i.v. infusion (100µg) over 7 hrs: 50, 100, 200µg/h or placebo. (L12C, L3A).	9	HS	4 treatment sessions, separated by 1 week washout
Healthy subject PK	E-92-52030-123	PK of lanreotide IRF versus <del>lanreotide IRF</del> formulation. Safety.	Phase I	Lanreotide IRF 3 mg (L12C/212728) s.c. then lanreotide <del>IRF</del> 3 mg (N36063) i.m.	12	HS	2 treatment sessions, separated by 2 week washout
Healthy subject PD and PK/PD	E-47-52030-103	Vasoconstrictive potency and duration of effect of repeat doses on postprandial hypertension in superior mesenteric artery and portal vein	Phase I single center open label non-randomized	Two lanreotide IRF 60 mg (GH15) i.m. injections 4 weeks apart.	6	HS	2 treatment sessions, separated by 4 weeks
Healthy subject PD and PK/PD	E-47-52030-041	Efficacy of bolus injection versus continuous infusion on postprandial splanchnic blood flow. Safety PK.	Phase I single center randomized double-blind crossover	Lanreotide IRF 300 µg i.v. bolus (with placebo infusion), lanreotide IRF 100 µg/h i.v. infusion over 8 hrs (with placebo injection), Lanreotide IRF 3 mg (FBFL) placebo (EBTI).	15 PK analysis: n = 11	HS	2 single doses on 2 separate days separated by 6 days
Healthy subject PD and PK/PD	E-47-52030-068	Safety and effects on gastric acidity PK	Phase I randomized double-blind placebo-controlled crossover	Lanreotide IRF (L12C) i.v. infusion (100µg) over 24 hrs: 50, 100, 200µg/h or placebo (L3A).	12	HS	4 treatment sessions, separated by 1 week washout
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subject; or Diagnosis of Patients	Duration of Treatment
Healthy subject PK	E-47-52030-503	Effect on VIP-induced jejunal secretion and small intestinal motility	Phase I open, single center, randomized, crossover	Saline or VIP 300 pmol/kg/h i.v. infusion over 300 mins or VIP infusion and lanreotide IRF 200 µg by i.v. infusion over 60 mins (lanreotide, FBEX and L12D, VIP, FVIP201A).	15	HS	44 weeks
Healthy subject PD	E-54-52030-127	Test efficacy as GH suppressant in HS and Acro.	No information available	Lanreotide IRF 250 µg (2 subject), 500 µg (3 subject).	10	HS Acro	Not stated
Efficacy and safety	E-04-52030-012	Open phase I safety and efficacy study of octapeptide on glucose, insulin, ghrelin and growth hormone levels in patients with diabetes mellitus	Phase I open	All patients received Angiotensin 3 mg/day by continuous s.c. infusion for a total of 21 days.	Planned: 20	Diabetes Mellitus	21 days
PD and PK/PD	A-93-52030-055	Investigate effect on volume and composition of exocrine pancreatic secretion	Randomized, double-blind, placebo-controlled, crossover	Lanreotide IRF 0.5 mg s.c. (FBFL) or placebo (EBTI)	8	Protein-pancreatic insufficiency	Single dose
Efficacy and safety	E-54-52030-137	Evaluate effect of lanreotide IRF at increasing doses and via discontinuous and continuous administration, on plasma GH concentrations	Single center placebo-controlled	Part I: Lanreotide IRF 750 µg s.c. (2 injections at 12 hr intervals) or 300 µg s.c. (3 injections at 8 hr intervals) or, 1500 µg/24 hr continuous s.c. infusion over 24 hrs or, placebo s.c. infusion. Part II: Lanreotide IRF - 500 µg/24 hr continuous s.c. infusion or 1000 µg/24 hr continuous s.c. infusion, or 1500 µg/24 hr continuous s.c. infusion over 24 hrs; or placebo s.c. infusion.	Part I: 6 Part II: 4	Acro	6 weeks
Efficacy and safety	E-54-52030-013	Compare efficacy and safety of lanreotide and octreotide	Multicenter open label comparative randomized parallel group	Lanreotide MPF 30 mg i.m.; one injection every 10 days during first month, one injection every 14 days during second month. Thereafter, if GH or IGF-1 levels were inadequately suppressed, every 10 days.	Lanreotide MPF: 20 Octreotide: 18	Acro	24 weeks

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patient	Duration of Treatment
Efficacy and safety	A-93-52030-077	Efficacy, safety and blood levels of lanreotide and possible antibodies	Phase III multicenter open label non-comparative dose duration extension of study E-26-52030-710	Lanscoids Autogel 120 mg, 3 deep s.c. injections administered every 8 weeks. Then injections every 8 weeks (GH $\leq$ 2.5 $\mu$ g/L), every 6 weeks (2.5 < GH $\leq$ 5 $\mu$ g/L) or every 4 weeks (GH > 5 $\mu$ g/L) for 3, 4, or 7 injections, respectively. (JBR6, KBF4, KBR2, KBPH, LABC, and LBDB)	enrolled: 64 completed: 63	Acro	48 - 48 weeks
Efficacy and safety	A-47-52030-704 / E-68-52030-045	Efficacy and safety	Phase II/III multicenter open label	A-47-52030-704: (F005, G018). As study A-47-52030-705 E-68-52030-045: (F005, G005, G018, G023). As study E-68-52030-044.	39	Acro	704: Uyn 16 weeks 704 and 045: Max. of 70 weeks
Efficacy and safety	A-47-52030-705 / E-68-52030-044	Efficacy and safety	Phase II/III multicenter open label E-68-52030-044 extension of study A-47-52030-705	A-47-52030-705: One i.m. injection of lanreotide MPF 30 mg every 14 days. GH and IGF-1 concentration measured before third injection. If GH and/or IGF-1 values not normalized, dosage increased to once every 10 days. However if normalized, patients would receive 3 further injections at 14-day intervals. (F003). E-68-52030-044: Patients continued their A-47-52030-705 dosing schedule. If GH and/or IGF-1 concentrations were not normalized after two further injections, the dosage was increased to 1 injection every 10 days or 7 days for patients on the 14-day and 10-day regimens, respectively. (F003, G005, G028, G018 and G023).	enrolled: 55 completed: 39	Acro	Patients remained in the study until completion of either: 52, 70 weeks of lanreotide 30 mg or until lanreotide was marketed in the USA.
Efficacy and safety	E-34-52030-085	Efficacy and safety.	Phase III multicenter open label non-comparative	Lanscoids MPF 30 mg i.m. every 14 days. If GH > 5 $\mu$ g/mL or IGF-1 concentration above normal after 3 injections, dosing frequency increased to 1 injection every 10 days. (B001, B002, B003, B007, C001, C003, C010; all supplied to site).	118 enrolled and completed	Acro	48 weeks
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patient	Duration of Treatment
Efficacy and safety	E-47-52030-151	Efficacy and safety	Phase II multicenter open label	First 12 weeks: Lanscoids MPF 30 mg i.m. every 14 days. From Week 12: patients who met efficacy criteria continued to receive 1 injection every 14 days. Other patients received 1 injection every 10 days; if control of GH or IGF-1 was not achieved after a further 12 weeks on this dosage, dose frequency increased to once every 7 days. (B005, C001, C019, C020, D007, D011, D017, D021, E002, E004, E007, E010, E012, E016 and F001).	enrolled: 77 completed: 53 (48 weeks) 29 (36 weeks) 3 (168 weeks)	Acro	As long as clinically indicated or until study closure by the sponsor
Efficacy and safety	E-99-52030-503	Efficacy and safety	Phase II multicenter open label non-comparative	Lanscoids 30 mg i.m. every 14 days for 12 weeks. Thereafter, if GH levels normalized, patients continued with same regimen, switching to every 10 days for 12 weeks and thereafter every 7 days if GH levels were not controlled. Patients with GH/IGF-1 serum levels uncontrolled and clinical symptoms not improved after first 12 weeks were withdrawn. (D004, EB0D, EBFP, EBFQ, EBWH, EBLX, EBDR, EBFC, EBFV, EB9G, FB1D, FB1F, FB8E, EBPV, FBPU, EB8H, EBFS, FB9W, FB9X, GB8Q, GB8R, GB8T, GB8J, GB8L, GB8D, GBV, GBV7, EB81 and EB8X).	enrolled: 29 completed: 6	Acro	76 weeks (= 56 weeks)

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 Somatuline® Autogel® (lanreotide acetate) Injection

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subject; or Diagnosis of Patients	Duration of Treatment
Efficacy and safety	E-54-52030-010	Determination of optimum dose	Multicenter open label pilot incremental dose	Lanreotide s.c. continuous infusion: initially 1000 µg/day; after one month if GH levels not sufficiently controlled (>5 ng/mL), and/or if levels of IGF-1 were >400 ng/mL, 1500 µg/day; if GH or IGF-1 levels were uncontrolled after a further month, 2000 µg/day. Patients controlled in the first month with 1000 µg/day but not in the second month could receive 1500 µg/day in the third month.	13	Acro	14 weeks
Efficacy and safety	A-38-52030-260	Efficacy and safety	Phase III open label	Lanreotide MPF 30mg. i.m. every 2 weeks	6 entered and completed	Acro	12 weeks
Efficacy and safety	A-38-52030-303	Efficacy and tolerability	Phase IV single center open label non-comparative	Lanreotide MPF 30 mg i.m. every 14 days, reduced to every 20 days if somatotrophic hormone level reached 10 ng/mL prior to the third injection. (NALSND03)	8 entered and completed	Acro	8-10 weeks
Efficacy and safety	E-54-52030-097	Demonstrate the efficacy and safety of lanreotide 40 mg in acro	Phase II multicenter open label non-comparative	Lanreotide acetate 40 mg i.m. every 28 days, for a total of 3 injections. (E061)	safety: 39	Acro	32 weeks
Efficacy and safety	E-54-52030-123	Assess the efficacy of lanreotide delivery methods: <del>lanreotide</del> MPF formulation)	Phase II comparative	Lanreotide IRF 2 mg/day delivered by <del>lanreotide</del> for 7 days (Scheme A), or Lanreotide MPF 10 mg administered as a single injection every month for 3 months (Scheme B). Patients entered one of two study schemes.	safety: 4 efficacy: 3	Acro	Scheme A: 2 week Scheme B: 8 week
Efficacy and safety	Y-97-52030-093	Assess the efficacy and safety of deep s.c. injection of lanreotide Autogel in patients previously treated with octreotide LAR	Phase III multicenter open label single group comparative	Seven repeated deep s.c. injections of lanreotide Autogel (4 x 90 mg followed by 3 x 60 mg (KBGS, KBFF), 90 mg (KBGT, KBFH) or 120 mg (KBGV, KBFG, LBFG), chosen depending on individual GH levels) at 28-day intervals.	10	Acro	36 weeks
Efficacy and safety	I-48-52030-161*	Efficacy and tolerability	Phase III multicenter open label prospective	Patients that were previously treated with octreotide LAR received a fixed dose of deep s.c. lanreotide Autogel 90 mg every 4 weeks for 12 weeks. Patients then received a fixed dose of lanreotide Autogel 60, 90 or 120 mg every 4 weeks (depending on mean GH and IGF-1 levels) for 12 weeks.	25	Acro	24 weeks
Efficacy and safety	A-92-52030-045	Efficacy and tolerability	Phase III multicenter open label comparative	Lanreotide Autogel 120 mg s.c. every 56, 42 or 28 days for a total of 3, 5 or 5 administrations, respectively. Control group: Prior treatment with commercially available lanreotide (i.e. each patient acted as his/her own control), (HEQP, JBB2, JBJX, JBLX, JBR7, KADF and KBIG).	safety: 97 efficacy: 93	Acro	24 - 30 weeks
Efficacy and safety	Y-97-52030-150	Assessment of the ability of patients with acromegaly or their partners to perform unsupervised lanreotide Autogel injections	Phase IV multicenter open label comparative	Lanreotide Autogel 60 mg, 90 mg or 120 mg every 28 days for up to 40 weeks. In the test group injections were administered s.c. by the patient (or partner) under the supervision of a trained healthcare professional at weeks 4, 8 and 12, and thereafter unsupervised (6 injections). In the control group, all 9 injections were administered by a healthcare professional.	safety: 30 ITT: 30	Acro	Up to 40 weeks

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dose(s); Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and safety	S-48-52030-054	Long-term safety and efficacy	Phase III/III multicenter open label extension of studies: E-88-52030-044 and E-88-52030-045	Lanreotide MPF 30 mg i.m. at intervals of 14, 10 or 7 days. (2100130: G023, G035 and G036).	safety: 63 efficacy: 58	Acro	52 weeks
PK, Efficacy and safety	E-28-52030-714	Efficacy, safety and PK	Phase III multicenter open label non-comparative extension of study E-28-52030-706	Lanreotide MPF 60 mg i.m. at fixed dose every 21 or 28 days for 12 weeks; then every 14, 21 or 28 days on basis of dose titrated GH levels. (G001, G093 and G004).	safety: 15 efficacy: 12	Acro	Max. 48 weeks
Efficacy and safety	A-94-52030-209	To show acro that had participated in a previous study with lanreotide to continue to receive the drug and to collect long-term efficacy and tolerance data	Phase II open label non-comparative extension study	Lanreotide MPF 30 mg at a frequency of 2-3 injections every month. If symptoms, GH and IGF levels were normalized with 3 injections every month, frequency could be reduced to 2 every month. The frequency of injections could be increased to 4 every month if symptoms recurred or IGF or GH levels increased, thereafter if symptoms and GH and IGF levels were not controlled the patient was removed from the study.	8	Acro	Initially for 48 weeks; extended to 84 weeks (max).
Efficacy and safety	E-94-52030-102	Efficacy and safety	Phase II multicenter open label non-comparative extension to study E-94-52030-097	Lanreotide 1-month 40 mg i.m. one injection; thereafter one injection of lanreotide 40 mg or 60 mg, depending on GH levels, every month for 3 months. (EBL2 and EBVQ).	safety: 36 ITT: 36	Acro	15 weeks
Efficacy and safety	E-94-52030-015	Long-term efficacy and safety	Phase II multicenter open label non-comparative extension of studies: E-94-52030-097 and E-94-52030-102	Lanreotide 1-month 40 mg (EBH1, EBL2, FBNA) or 60 mg (EBVQ, EBV8, FBHQ, GBH5, GBRX, EBDD) i.m. every 28 days for 72 weeks (subsequent to sponsor's decision to stop manufacturing the 40 mg dose, patients receiving this dose were either switched to 60 mg or withdrawn).	safety: 27 efficacy: 19	Acro	72 weeks

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Efficacy and safety	E-47-52030-138	Efficacy, safety and definition of a protocol for starting lanreotide therapy	Phase II multicenter open label pilot	Lanreotide MPF 30 mg i.m. for 4 18-week periods at 7-, 16-, 1+ and/or 21-day intervals.	14 efficacy: 2	Acro	120 weeks
Efficacy and safety	A-96-52030-201	Efficacy and safety	Open label non-comparative	Lanreotide MPF 30 mg i.m. every 2 weeks.	11	Acro	12 weeks
PD + efficacy	E-34-52030-170	Pharmacodynamic study of lanreotide MPF after single dose to acro. Assessment of the effects of IGF-I and GH			8	Acro	Single dose
Healthy Subject: PK	E-02-52030-007	Determine the pharmacokinetic profile in healthy subjects of a <del>lanreotide</del> extended release formulation containing either 40 or 60 mg of lanreotide	Phase I open label parallel study (with two groups of healthy subjects)	An immediate release formulation of lanreotide acetate 7mg/kg (E001/F00Q) s.c. Then, after a washout period of at least 2 days, two groups of 12 healthy subjects received 40 mg (N70036) and 60 mg (N70037), respectively of the <del>immediate</del> formulation of lanreotide s.c.	24	HS	2 times single dose
Efficacy and safety	A-96-52030-139	Evaluate the dosing efficacy and safety of lanreotide Autogel in acro previously treated with octreotide LAR, including an extension phase to assess the ability of patients or their partners to administer lanreotide Autogel at home	Phase IV multicenter open label single group	No other information available for this study		Acro	
Efficacy and safety	A-94-52030-163	Evaluate the efficacy and safety of six repeated deep s.c. administrations of lanreotide Autogel 120 mg in acro previously treated with octreotide LAR 10, 20 and 30 mg	Phase III multicenter open label single group comparative	No other information available for this study		Acro	
Efficacy and safety	Y-97-52030-160	Evaluate the efficacy and safety of twelve repeated deep s.c. administrations of lanreotide Autogel in acro previously treated with octreotide s.c. or octreotide LAR 10, 20 or 30 mg	Single center open label comparative	No other information available for this study		Acro	

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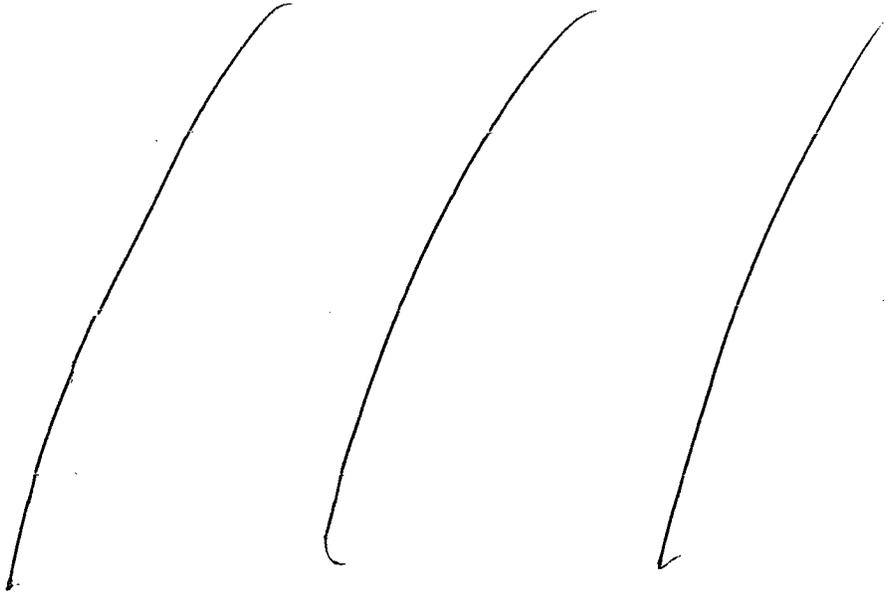
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and safety	A-96-52030-155	Assess the efficacy and safety of lanreotide Autogel (60, 90, 120 mg) administered every 28 days to acro who may or may not have previously received treatment with somatostatin analogs	Phase III, open label, prospective	After an optional 1-month washout phase, patients received a fixed dose of lanreotide Autogel 90 mg every 28 days for a total of 3 administrations, followed by a titrated dose of lanreotide Autogel 60, 90 or 120 mg every 28 days for a total of 3 injections. (MEL5, MBN0 and MBN2).	safety: 10	Acro	24 weeks
Efficacy	A-93-52030-260	Evaluate the efficacy of lanreotide Autogel 120 mg on the control of GH secretion in acro previously treated with octreotide LAR	Phase III, multicenter, open label, non-comparative	Lanreotide Autogel 120 mg deep s.c. in the buttock at a fixed dose every 5 weeks for a total of 4 injections. Doses were then titrated on the basis of mean GH levels, so patients received a further 2 injections at 5- or 8-week intervals or 3 injections at 4-week intervals. (JBR3, KBP5 and LBD0).	safety: 24 ITT: 33	Acro	34-41 weeks
Efficacy and safety	A-94-52030-073	Evaluate the long-term efficacy and safety of repeated deep s.c. administrations of lanreotide Autogel (60, 90 or 120 mg) in acro	Phase III, multicenter, open label, extension of study E-26-52030-710	Twelve lanreotide Autogel injections s.c. to each patient at 28-day intervals. A dose of 60 mg, 90 mg or 120 mg was determined according to the biochemical response of the patient (duration).	safety: 14	Acro	48 weeks
Efficacy and safety	A-92-52030-168	Efficacy, safety and blood levels of lanreotide and possible antibodies	Phase III, open label, dose titration, multicenter, extension of study E-26-52030-710	Lanreotide Autogel 120 mg every 28, 42 or 56 days depending on the GH response of patients during the previous study. Patients previously treated with 90, 90 or 120 mg of lanreotide Autogel every 28 days were administered lanreotide Autogel 120 mg every 56, 48 or 28 days respectively. (JBR3, JBLX, JBR7, KBDF, KB16, KBM9, KBRV, LBF3, LBGF and LBH5).	safety: 20	Acro	31 visits were planned for each patient. Visit dates varied according to dose given.
Tolerability	A-94-52030-072	Evaluate the tolerability of repeated deep s.c. administrations of titrated doses of lanreotide Autogel in acromegalic patients previously treated with individually titrated doses of lanreotide MPF	4 year follow up	Lanreotide MPF 30 mg i.m. every 14, 20 or 7 days for a total of 5 administrations. Patients were then transferred to a regimen where they received 60, 90 or 120 mg (respectively) of lanreotide Autogel every 28 days.	11	Acro	202 week period of lanreotide Autogel.
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety	E-94-52030-094	Evaluate the long term safety of repeated deep s.c. administrations of lanreotide Autogel (60, 90 or 120 mg) at titrated doses	Phase III, multicenter, open label, extension of studies E-26-52030-709 E-26-52030-710 E-94-52030-073	Twelve lanreotide Autogel deep s.c. injections administered to each patient at 28-day intervals. The dose of lanreotide Autogel 60 mg (JBR3), 90 mg (JBR7) or 120 mg (JBR7) was determined according to the biochemical response of the patient (duration).	safety: 14	Acro	48 weeks
Efficacy	A-92-52030-169 study extension of A-92-52030-046	Assess the comparative therapeutic efficacy of lanreotide Autogel, the new somatostatin analog lanreotide's prolonged release form, in acro compared to Somatostatin	Phase III, multicenter, open label, comparative	Patients were treated with the same dose and dosage interval that they followed in the original study. Lanreotide Autogel 120 mg deep s.c. every 28, 42 or 56 days. (JBR3, JBLX, JBR7, KBDF, KB16, KBM9, KBRV, LBF3, LBGF and LBH5).	safety: 84	Acro	16 visits planned 120 mg Doseage; every 7, 10.5 or 14 weeks
Healthy subject PK	E-94-52030-038	Evaluate the kinetics of lanreotide 60 mg after single i.m. injection	Phase I, single center, open label, non-comparative	Lanreotide acetate 60 mg (7BM6) i.m.	safety: 12	HS	Single dose Assessment made for 54 days.
PD	E-47-52030-603	Evaluate the vasoconstrictive potency and duration of the effect of repeated injections of lanreotide "1-month" upon postprandial hyperemia in the superior mesenteric artery and portal vein	Phase I, single center, open label, non-randomized	Two lanreotide 40 mg i.m. 1-month r: a dose repeated by an interval of 28 days	safety: 8	HS	2 treatment sessions separated by 4-week interval. All subjects attended 9 visits.
Efficacy and safety	E-48-52030-002	Assess the effect of administration of lanreotide as an adjuvant treatment to prepare transphenoidal hypophysectomy in acro	Phase IV, open label, non-randomized	Lanreotide MPF 30 mg microspheres (EBS7) i.m. every 10 or 14 days during 4 months	10 analysed for efficacy: 9 for safety: 10	Acro	18 weeks
PK, efficacy and tolerability	E-26-52030-082	PK, efficacy and tolerability	Phase II, single center, open label, non-comparative	Lanreotide MPF 60 mg i.m. every 28 days, total of 3 injections.	safety: 12	Acro	18 weeks

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

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage; Regimen; (Batch No); Route of Administration	Number of Subjects	Healthy Subject or Diagnostic of Patients	Duration of Treatment
Efficacy and safety	A-93-52059-003	Efficacy and safety	Phase II multicenter open label non-comparative prospective	Lanreotide: MPF 30 mg i.m. every 2 weeks for 2 months, other 2 months of totally/partially ineffective treatment. 60 mg every 2 weeks; thereafter, from Month 4, 60 mg every 10 days if still ineffective.	analyzed: 37 safety: 37 PP: 43	Acro	52 weeks treatment phase.

Table 10.3.2. Studies with lanreotide in other indications



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