

Race and Region

There were no US patients in Study 081. Patients in Study 717 were 84% Caucasian, 11% Asian, 4% Black and 2% American Hispanic. Data for ethnicity were not collected in Study 081. There did not appear to be any difference in the percentage of responders between the Caucasian (44.4% responders; 95% CI: 44.7, 66.0) and Asian (36.4% responders; 95% CI: 10.9, 69.2) populations. Since less than 4% of patients were Black and less than 2% were American Hispanic, there were too few patients to make meaningful comparisons for these two groups. There did not appear to be any difference in the percentage of responders between the US (42.1% responders; 95% CI: 26.3, 59.2) and non-US (39.4% responders; 95% CI: 31.0, 48.3) regional subgroups.

6.1.5 Clinical Microbiology

Microbiology issues from _____

_____ Please refer to the review by Dr. Robert Mello regarding microbiology issues with this application.

6.1.6 Efficacy Conclusions

Study 717:

Conclusion

Lanreotide acetate at dose strengths of 60, 90 and 120 mg was statistically significantly more effective than placebo in reducing mean GH and IGF-1 concentrations measured 4 weeks after a single injection. A significantly higher proportion of lanreotide-treated patients (13 of 83, 16%) had mean GH \leq 2.5 ng/mL and normalized IGF-1 at Week 4 as compared to placebo (0 of 25) ($p = 0.033$). A total of 41 (38%) of the 107 lanreotide-treated patients had mean GH \leq 2.5 ng/mL and normalized IGF-1 at Week 16 including 38%, 42% and 35% of patients in the 60, 90 and 120 mg treatment groups, respectively. Analysis of the last value available on study showed 41% of patients had both mean serum GH level \leq 2.5 ng/mL and normalized (age-adjusted) IGF-1 at the end of the study.

For the primary endpoint in study 717, the proportion of patients with a greater than 50% decrease in mean GH from baseline, the results were similar in all patient subpopulations (Naïve, Not treated within 3 month, Previously treated). Similar results were seen for a median reduction in mean GH. For all other efficacy parameters, there was a general trend towards a higher response rate within the previously treated population compared to the naive patient group.

Duration of active treatment in this 52-week study was 364 days indicating that most patients were able to complete the study; the range of treatment duration was 86 to 400 days. The treatment effect was maintained during the duration of the trial. However, in the majority of

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

By the end of the study (LVA), the acromegaly symptoms of headache, perspiration, fatigue, swelling of extremities, and joint pain had improved from baseline or were stable in 88% to 94% of patients. However, the majority of patients were documented as having *None* or *Mild* signs of symptoms of acromegaly at Baseline. No apparent trend was noted for improvement in acromegaly symptoms with increasing lanreotide dose.

Study 081

There were 38 males (60%) and 25 females (40%) aged from 30 to 77 years. The time since diagnosis ranged from 0.2 to 33.3 months. At inclusion, 22 out of 63 patients (35%) had GH ≤ 2.5 ng/mL, while 7 patients (11%) had GH ≤ 1 ng/mL.

At the end of treatment, 24/63 (38%) patients had both normal IGF-1 levels and a GH level of less than or equal to 2.5 ng/mL and 17/63 patients (27%) had both normal IGF-1 levels and a GH level of less than 1 ng/mL. Repeated administration of lanreotide acetate every 4 weeks at a constant dose of 90 mg for 16 weeks followed by a dose titration period to maximize effect (at doses of 60, 90 or 120 mg) was effective in reducing IGF-1 and GH concentrations and in reducing the clinical symptoms of acromegaly.

Study 709:

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.

Study 710:

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 ≤ 2.5 ng/mL and normalized IGF-1 were similar at the beginning and end of Study 710: at 1st visit, N=48 (39%), at end-of-study 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.

Acromegaly symptoms either showed a trend for improvement or remained stable. This study was 'enriched for completers' and combined data on all dose strengths. Nevertheless, these data suggest that lanreotide acetate results in hormonal control comparable to treatment with lanreotide MPF.

Study 150:

This small open-label, non-randomized study suggests that unsupervised self/partner lanreotide acetate injections may present a viable alternative to healthcare professional injections for patients who are suitably motivated and willing. Baseline data indicate that there was a difference between treatment groups in terms of age and weight (Control Group patients were older and heavier), but overall disease control was similar between treatment groups.

In conclusion, Somatuline (lanreotide acetate injection) is an effective treatment for patients with acromegaly to decrease elevated levels of GH and IGF-1. The efficacy of lanreotide acetate was confirmed by demonstrating superiority to placebo in the reduction of GH after 1 month. Lanreotide acetate, at optimized doses for up to 52 weeks, was also effective in controlling most symptoms of acromegaly in the majority of symptomatic patients. The effect of lanreotide acetate on improving co-morbidities such as diabetes and hypertension was not evaluated by the applicant.

Subgroup analysis did not show any significant difference in response to treatment with regard to age, gender, BMI, bodyweight or race. Previous acromegaly treatment with surgery or SSA resulted in increased efficacy after lanreotide acetate. However, lanreotide acetate was shown to be effective in treatment-naïve patients. The presence of antibodies to lanreotide in patients treated with lanreotide acetate was low, did not appear to affect efficacy, and did not increase with long term treatment.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Pooled Lanreotide Acetate Studies in Acromegalic Patients

Safety data were pooled for seven clinical studies of lanreotide acetate 60, 90, or 120 mg administered to acromegalic patients every 28 days by healthcare providers. Studies that were pooled included: Study E28-52030-717, Study 2-47- 52030-721, Study E-28-52030-076, Study E-54-52030-081, Study E-28-52030-709 and its follow-on Study E-28-52030-710, and Study E-88-52030-087 hereafter referred to as Studies 717, 721, 076, 081, 709, 710 and 087, respectively. These seven studies are reviewed separately in detail in Section 10.1. A total of 416 unique patients treated with lanreotide acetate were included in this pooled safety analysis. A total of 23 patients received lanreotide in more than one of these 7 studies. The second study for all 23 patients was Study 721. The patients who re-enrolled had previously participated in Studies 717 (15 patients), 081 (4 patients), and 709/710 (4 patients).

Non-pooled Lanreotide Acetate Studies in Acromegalic Patients

A total of 201 acromegalic patients received lanreotide acetate in 4 non-pooled studies, Study 150, 095, 077 and 046. These studies were not pooled because of differences in study design or dosage of lanreotide acetate compared to the studies that were pooled.

Lanreotide Acetate in Healthy Subjects

A total of 107 healthy subjects received lanreotide acetate in the Phase I studies 149, 038 and 047.

Foreign postmarketing safety data is also reviewed in this section.

7.1.1 Deaths

Pooled Lanreotide Acetate Studies in Acromegalic Patients

There was one death in Study 710. 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).

Non-Pooled Lanreotide Acetate Studies in Acromegalic Patients

There was one death in Study 046. This 72 year old Caucasian female was enrolled in clinical study 046 on 24 February 2000. Acromegaly had originally been diagnosed on 10 September 1991. This patient had a previous medical history which included the presence of hypertension since 1971, dilated hypertensive cardiomyopathy with atrial fibrillation since 1991, recurrent episodes of heart failure, mild renal impairment, hyperbilirubinemia, type 2 diabetes mellitus and breast cancer treated by surgery in — followed by tamoxifen until — (11 years). The patient had been receiving injections of lanreotide 30 mg PR (Somatuline) between 16 October 1997 and 14 February 2000 and on inclusion in clinical study 046 was scheduled to receive a 120 mg dose of lanreotide acetate at 42 day intervals starting on 24 February 2000. Since the beginning of 2000 the patient had hyperbilirubinemia. The patient received her last injection on 5 April 2000. On — the patient was admitted to the emergency unit because of cough and dyspnea. Respiratory infection was suspected. On — the patient presented at hospital with general malaise, nausea, orthopnea and pruritus. An analytical sample on May 16th 2000 showed hepatic disease with AST 159 UI/L, ALT 429 UI/L, alkaline phosphatase 110 UI/L, total bilirubin 5.3 mg/dL and direct bilirubin 3.6 mg/dL. The echocardiogram showed dilated right cavities with severe tricuspid regurgitation. The left ventricle was also dilated with moderate mitral and aortic regurgitation. The heart ejection fraction was of 38%. The patient status deteriorated to cardiovascular shock with disseminated intravascular coagulation on May 21st, 2000. The patient died in hospital on — . Autopsy was not performed.

Lanreotide Acetate in Healthy Subjects

There were no deaths in the 3 Phase I studies.

Deaths in Lanreotide MPF Studies in Acromegalic Patients:

Four deaths were reported in the lanreotide MPF Studies. Patient 000567 (Study 065), a 71-year-old female receiving experienced carotid artery thrombosis and aneurysm and subsequently died. Subject 106 (Study E-54-52030-008), a 39-year-old male was receiving 30 mg lanreotide MPF and died on — . The cause of death was not specified. Subject 603-8 (Study 8-88-52030-054), a 58-year-old male, experienced a fatal myocardial infarction (30 mg lanreotide

MPF). The patient continued to receive a 7 -day regimen prior to death. The 4th death occurred in Study A-93-52030-003, a 46-year-old male subject, was receiving lanreotide MPF (dose not recorded), experienced a severe myocardial infarction and died.

Postmarketing Cases (outside the US):

In total, 18 postmarketing spontaneous reports (PSR) (24 reactions) had an outcome of death.

There were five reports of fatal events in acromegalic patients: MI (2 subjects), cardiopulmonary failure, CVA, and peritoneal carcinoma. Two of these cases were considered to have a relationship to lanreotide treatment. In one case, the death due to myocardial infarction occurred 6 days after the last injection of lanreotide, which may have been given in an excessive dose; however, the patient had other risk factors for myocardial infarction. The second case was a 77-year-old female patient (France) treated with lanreotide at 30 mg 2-weekly for approximately 2 years, having previously been treated with octreotide. She developed upper abdominal pain associated with asthenia, hepatomegaly, ascites, enlargement of the intrahepatic bile duct (dilatation intrahepatic bile duct acquired) and peritoneal carcinoma. She was admitted to hospital and died.

7.1.2 Other Serious Adverse Events

Pooled Lanreotide Acetate Studies in Acromegalic Patients

SAEs in pooled lanreotide acetate studies in acromegalic patients were reported by 15% (61/416) of patients. The SOCs in which SAEs were reported most commonly were surgical and medical procedures (3%), and GI disorders (3%). The only event that was reported as a SAE for ≥ 1 % patients was inguinal hernia, reported by 1 % of patients. SAEs considered related to study drug were: cholecystectomy, diarrhea, pancreatitis, colitis, thrombophlebitis, aortic aneurysm, lethargy, malaise, biliary colic and cholelithiasis. One patient (Patient 000893) experienced lethargy and malaise. A further patient (Patient 000112) experienced pancreatitis and cholelithiasis. Each of the other SAEs considered related was reported by separate patients. Details are in Section 10.1 and are summarized below:

In Study 717, one serious event, pancreatitis associated with gallbladder lithiasis migration, was likely related to study treatment. Patient 717.0002, randomized to receive 60 mg lanreotide, experienced pancreatitis of moderate intensity during open-label treatment with 60 mg at Week 29. The patient recovered within ~3 weeks following cholecystectomy for gallbladder lithiasis.

In Study 081, thirteen patients experienced at least one SAE during the treatment period. All SAEs were unrelated to study treatment as assessed by this reviewer, details are in Section 10.1.2.

In Study 721, a total of 20 serious adverse events were experienced by 15 patients during the study. Six patients experienced six serious adverse events in the lanreotide cohort and nine patients experienced 14 serious adverse events in the octreotide cohort. In the lanreotide cohort, two patients had events (colitis and aortic aneurysm, respectively), that were considered possibly related to treatment by the investigator and in the octreotide cohort, one patient had an event

(biliary colic) that was considered possibly related to treatment by the investigator. Study medication was continued in all three cases and all three patients recovered without sequelae.

In Study 087, 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.

In Study 076, there were no SAEs.

In Study 709, 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 a self-inflicted injury.

In Study 710,

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.

1. A gallstone colic event in a 54-year-old woman which was resolved by surgery. The patient did not discontinue treatment.
2. 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.

Nonpooled Lanreotide Acetate Studies in Acromegalic Patients

In Study 150, at least one SAE was reported by 20% (6/30) of patients. Patient 20 (90 mg), experienced two related SAEs of severe renal colic and severe abdominal pain, each associated with a separate hospitalization. The other SAEs were prostate cancer (60 mg), diverticulitis (120 mg), palpitations, arthralgia and tremor (in a single patient) (90 mg), angina pectoris (60 mg), and pulmonary edema (60 mg).

In Study 046, at least one SAE was reported by 5% (5/97) of patients. One SAE (hepatitis; detailed above) led to death. The other four SAEs were hospitalizations due to scheduled surgery and were considered not related.

In Study 077, at least one SAE was reported by 3% (2/63) patients. Patient 21 (120 mg) experienced severe diarrhea considered probably related to study drug and resulting in hospitalization. The patient later had another SAE (dyspnea due to atrial fibrillation), which was

considered unrelated. Patient 153 experienced hypercortisoluria, considered unrelated to study drug.

In Study 095, at least one SAE was reported by 1 of 12 patients. This patient (Patient 03002) experienced severe respiratory arrest, which prolonged hospitalization after a planned surgical procedure. The adverse event was considered not related to study drug.

Lanreotide Acetate in Healthy Subjects

Two (2%) of healthy subjects reported one SAE each, and both SAEs were considered related to study drug (biliary colic and gallbladder disorder). A 24-year-old Caucasian female subject (Study 149) experienced severe biliary colic 110 days after an injection of 60 mg lanreotide acetate. The AE was considered related to study drug. This was a SAE due to hospitalization of the subject and the SAE resolved after cholecystectomy. The SAE led to withdrawal of the subject from the study. One subject (Study 149) experienced epigastralgia then biliary colic of severe intensity 110 days after the s.c. dose of lanreotide acetate (60 mg). The subject recovered. Another subject (Study 047), experienced cholecystitis of moderate severity (recorded as gallbladder disorder) 53 days after the injection of lanreotide acetate (60 mg). The subject underwent a cholecystectomy and recovered.

Postmarketing Cases (outside the US):

In total, 269 serious adverse reactions were reported through postmarketing surveillance. The most frequently reported serious PMS reports coded to the SOCs, GI disorders (79 serious reactions), General disorders and administration site conditions (42 serious reactions), Nervous system disorders (25 serious reactions) and Hepatobiliary disorders (22 serious reactions).

Within the SOC of GI disorders, the most frequently reported serious PMS reports were GI and abdominal pains, diarrhea, nausea and vomiting symptoms and pancreatitis.

Within the SOC of General disorders and administration site conditions, the most frequently reported serious reactions were injection and infusion reactions and asthenic conditions. Seven (of 11) reactions occurred in patients treated with lanreotide for acromegaly.

Within the SOC, Nervous system disorders, the most frequent serious reactions were disturbances in consciousness not elsewhere categorized, most (5 of 7 cases) of which were reported by patients treated for acromegaly. These reactions comprised loss of consciousness (two reactions) and somnolence, syncope, and syncope vasovagal (one reaction each).

Within the SOC, Hepatobiliary disorders, the most frequent serious reactions were cholecystitis, cholelithiasis and bile duct infections and inflammations.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The pooled analyses of acromegalic patients treated with lanreotide include 684 unique patients (57 patients were included in both pooled lanreotide acetate and MPF studies). End of study records for these pooled sets describing the number of drop-outs and the reason why are provided in Table 7.1.3.1.1.

Table 7.1.3.1.1 End of study record (Reason for withdrawals) based on data provided in the standardized database (All subjects included in Acromegaly and/or Lanreotide Acetate and/or Microparticles clinical studies 717, 721, 076, 081, 709, 710, 087, 044, 705, 045, 704, 151, 501, 065, 149, 038, 047)

Withdrawal reason (1)	Statistic	Acromegaly & Autogel (N= 416)	Acromegaly & MPF(3) (Pivotal) (N= 325)	Healthy Vol. & Spec. Pop. w/ Autogel (N= 119)
Number of Patients Receiving study lanreotide	n	416	325	119
Number of Completers	n(%) (2)	390(93.6%)	163(50.2%)	107(89.9%)
Number of Dropouts After study lanreotide Exposure	n(%)	26(6.3%)	162(49.8%)	12(10.1%)
Adverse Event	n(%)	10(2.4%)	28(8.6%)	2(1.7%)
Insufficient Clinical Response	n(%)	7(1.7%)	57(17.5%)	0(0.0%)
Lost To Follow-Up	n(%)	3(0.7%)	1(0.3%)	0(0.0%)
Consent Withdrawn	n(%)	1(0.2%)	16(4.9%)	10(8.4%)
Other(4)	n(%)	5(1.2%)	78(24.0%)	0(0.0%)

[1] Subjects can have more than 1 reason for withdrawal.

[2] Percentages denominator is the number of patients receiving study lanreotide.

[3] MPF: Microparticles formulations.

[4] Withdrawals for protocol deviation and other reasons have been included in the category 'Other'

Across the pooled lanreotide acetate studies in acromegalic patients, a total of 416 unique patients received lanreotide. A total of 23 patients received lanreotide in more than one of these 7 studies. End of study records for the pooled lanreotide acetate studies are provided by dose (60, 90 and 120 mg) in Table 7.1.3.1.2. Within the pooled analyses, patients are counted in each group of studies, in which they participated, but only once in the overall total for that analysis. As a result patient numbers in the pooled studies may not sum to the total across studies.

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Table 7.1.3.1.2: End of study record (Reason for withdrawals) by dose^[1] including 721 injection date and/or dose data (All patients with Acromegaly in lanreotide acetate studies 721,717,076,081,709,710 and 087)

Withdrawal Reason[2]	Statistic	60 mg (N= 141)	90 mg (N= 91)	120 mg (N=177)	Total (N= 416) [5]
Number of Patients Receiving study lanreotide	n	141	91	177	416
Number of Completers[3]	n(%)	136(96.5 %)	81(89.0 %)	168(94.9 %)	396(93.8 %)
Number of Dropouts After study lanreotide Exposure	n(%)	5(3.5 %)	10(11.0 %)	9(5.1 %)	26(6.3 %)
Adverse Event	n(%)	3(2.1 %)	5(5.5 %)	2(1.1 %)	10(2.4 %)
Insufficient Clinical Response	n(%)	1(0.7 %)	3(3.2 %)	3(1.7 %)	7(1.7 %)
Lost To Follow-Up	n(%)	0(0.0 %)	1(1.1 %)	1(0.6 %)	3(0.7 %)
Consent Withdrawn	n(%)	0(0.0 %)	1(1.1 %)	0(0.0 %)	1(0.2 %)
Other[4]	n(%)	1(0.7 %)	0(0.0 %)	3(1.7 %)	5(1.2 %)

[1] The dose is the dose at time of the withdrawal

[2] Subject can have more than 1 reason for withdrawal

[3] Percentage denominator is the number of patients receiving study lanreotide.

[4] Withdrawals for protocol deviation and other reasons have been included in the category 'Other'

[5] In Study 721, 7 patients were taken into account only for the 'Total' column, since they received 30 mg (patient 000421, 000476), 40 mg (patient 000424, 000332), 42 mg (patient 000498) and 160 mg (patient 000396, 000376).

For study 721 no injection dates were recorded. However, in order to comply with CDISC SDTM implementation guidance the visit dates and the treatment recorded as continuing at that visit were migrated into the exposure domain of the pooled ISS database. These data have been included.

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7.1.3.2 Adverse events associated with dropouts

Pooled Lanreotide Acetate Studies in Acromegalic Patients

Seventeen (4%) of acromegalic patients in the pooled lanreotide acetate studies reported AEs that led to withdrawal. AEs leading to withdrawal, including SAEs, were reported most commonly in the GI disorders SOC, by 1% patients. Within this SOC, individual AEs (PTs) that were considered related to study drug by the investigator and this reviewer were diarrhea (0.5%), abdominal pain (0.5%), nausea (0.2%), vomiting (0.2%), and proctalgia (0.2%). Other AEs leading to withdrawal and considered related to study drug were: dizziness, injection site induration, injection site pain, thrombophlebitis, hot flush, irritability and respiratory failure (each with an incidence of 0.2%). In Study 087, one patient (701-0020, 60 mg lanreotide acetate) had a clinically abnormal 12-lead ECG at the end of the study (compared with a normal ECG at baseline). AEs recorded as a result of this were: "mild nonspecific T wave and transient junctional rhythm abnormalities along with mild sinus bradycardia and occasional premature ventricular contractions". In the same study, a further patient (702-0001, 120 mg lanreotide acetate) had a clinically significant change on echocardiography from baseline to end of study, described as mild worsening of aortic regurgitation and abnormal echo pulmonic regurgitation.

Table 7.1.3.2.1 Adverse Events Resulting in Withdrawal: Acromegalic Patients in Pooled Lanreotide Acetate Studies (721, 081, 717, 076, 087, 709, 710)

Study Number	Subject ID	Sex	Age (years)	MedDRA PT	MEq Dose at Onset	Days Since Last Dose	Duration (days)	Intensity	Relationship			
2-47-52030-721	000416	F	27	Pregnancy	60 mg	Unknown	267	Severe	Not related			
	000430	F	35	Pregnancy	120 mg	Unknown	≥52 (ongoing)	Severe	Not related			
E-54-52030-081	000229	F	76	Rectal haemorrhage	90 mg	Unknown	34	Mild	Not related			
				Thrombophlebitis	90 mg	Unknown	≥42 (ongoing)	Severe	Related			
	000234	M	64	Respiratory failure	90 mg	Unknown	≥56 (ongoing)	Severe	Related			
	000246	F	48	Injection site pain	90 mg	Unknown	<1	Moderate	Related			
	000281	M	30	Abdominal pain	90 mg	Unknown	6	Severe	Related			
			Diarrhoea	90 mg	Unknown	6	Severe	Related				
E-28-52030-709	000618	F	73	Cerebral ischaemia	60 mg	27	≥1 (ongoing)	Moderate	Not related			
E-28-52030-710	000772	F	52	Injection site induration	90 mg	<1	<1	Mild	Related			
	000893	M	69	Lethargy	120 mg	24	≥1 (ongoing)	Severe	Not related			
				Vomiting	120 mg	<1	1	Mild	Related			
	000910	F	48	Disseminated intravascular coagulation	60 mg	4	2	Severe	Not related			
				Sepsis	60 mg	4	2	Severe	Not related			
	001048	F	38	Pregnancy	90 mg	10	≥18 (ongoing)	Mild	Not related			
	001067	M	39	Abdominal pain	60 mg	1	1	Mild	Related			
				Diarrhoea	60 mg	1	6	Mild	Related			
			Hot flush	60 mg	<1	<1	Mild	Related				
			Nausea	60 mg	<1	<1	Mild	Related				
			Proctalgia	60 mg	7	<1	Mild	Related				
E-38-52030-717	000015	F	75	Craniotomy	120 mg	4	14	Severe	Not related			
				Meningioma	120 mg	4	14	Severe	Not related			
				Meningeomas surgery	120 mg	4	14	Severe	Not related			
				Status epilepticus	120 mg	4	14	Severe	Not related			
Study Number	Subject ID	Sex	Age (years)	MedDRA PT	MEq Dose at Onset	Days Since Last Dose	Duration (days)	Intensity	Relationship			
E-28-52030-717 (continued)	000041	F	75	Blood calcium increased	90 mg	18	≥38 (ongoing)	Mild	Not related			
				Cardiomegaly	90 mg	18	≥38 (ongoing)	Mild	Not related			
				Chest wall pain	90 mg	18	10	Mild	Not related			
				Constipation	90 mg	23	≥33 (ongoing)	Mild	Not related			
				Faeces hard	90 mg	37	≥19 (ongoing)	Mild	Not related			
				Fall	90 mg	18	10	Mild	Not related			
				Femur fracture	90 mg	18	5	Severe	Not related			
				Hiatus hernia	90 mg	18	≥38 (ongoing)	Mild	Not related			
				Incision site complication	90 mg	25	≥25 (ongoing)	Moderate	Not related			
				Urinary tract infection	90 mg	25	3	Mild	Not related			
				Urinary tract infection	90 mg	35	7	Moderate	Not related			
				White blood cell count increased	90 mg	18	≥38 (ongoing)	Mild	Not related			
				000102	F	63	Diabetic nephropathy	90 mg	23	≥145 (ongoing)	Severe	Not related
							Diabetic nephropathy	90 mg	<1	≥83 (ongoing)	Severe	Not related
							Oedema peripheral	90 mg	7	≥105 (ongoing)	Mild	Not related
							Proteinuria	90 mg	7	≥105 (ongoing)	Mild	Not related
							Proteinuria	90 mg	<1	≥83 (ongoing)	Severe	Not related
000105	F	68	Thyroid gland cancer	90 mg	14	≥42 (ongoing)	Severe	Not related				
E-48-52030-087	000020	M	68	Dizziness	60 mg	4	<1	Severe	Related			
				Irritability	60 mg	3	33	Moderate	Related			

Source: Sponsor's Table 5.5.17

Non-Pooled Lanreotide Acetate Studies in Acromegalic Patients:

In the four adequate nonpooled lanreotide acetate studies in acromegalic patients (Studies 150, 046, 077 and 095), 1% (2/202) patients reported an AE leading to withdrawal (both in Study 046). One patient reported severe hepatitis (a SAE, causality not specified but possibly due to the patient's previous condition of cardiomyopathy) during treatment with 120 mg lanreotide acetate every 42 days and later died (see section 5.5.6.2 for further details). A different patient was withdrawn following injection site pain of 24 hours duration during treatment with 120 mg lanreotide acetate every 42 days.

Pooled Lanreotide MPF studies in acromegalic patients:

Thirty-six (11%) acromegalic patients in pooled lanreotide MPF studies reported at least one AE, leading to withdrawal. AEs leading to withdrawal were reported most commonly in the GI disorders SOC (4% patients). Individual AEs (PTs) considered related to study drug were diarrhea (3%), abdominal pain (1.5%), vomiting (0.6%), abdominal pain upper, GI pain, nausea, flatulence, gastritis, hemorrhoidal hemorrhage and melena (each with an incidence of 0.3%).

Five patients reported adverse events of pituitary tumor, of which one event was considered serious.

Lanreotide Acetate in Healthy Subjects:

One (0.9%) healthy subject (subject 0000786 in Study 149) experienced a TEAE (biliary colic) leading to withdrawal.

7.1.3.3 Other significant adverse events

See Section 7.1.5.5.

7.1.4 Other Search Strategies

The cardiac safety study is reviewed in Section 7.1.12, Special Safety Studies.

See Section 7.1.5.6 for an analysis of AEs by age, gender, race and concomitant disease.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Safety data from the lanreotide studies included in the clinical development program was based upon standard endpoints, including adverse events (AEs), physical examination findings, clinical laboratory evaluations, vital signs and concomitant medications. Additional safety endpoints have been incorporated into the study designs based on the patient population under study, including gallbladder ultrasound, echocardiograms, electrocardiograms (ECG), questionnaires assessing local and systemic tolerability, and determination of the development of antibodies to lanreotide.

Table 7.1.5.1.1: Overview of Safety Variables Assessed During the Pooled Lanreotide Acetate Studies 717, 721, 076, 081, 709, 710 and 087

Safety Variables	Lanreotide Autogel Study in Acromegalic patients						
	717	721	076	081	709	710 ¹	087
Physical examination	BL, wks 4, 16, 52	BL, month 6, 12	BL, Days 28, 56, 84, 112	BL, wks 4, 8, 12, 16, 28, 32, 48	BL, Day 85	Wks 12, 32	Wks -2 to -1, 0, 48
Vital signs	BL, wks 4, 16, 52	BL, month 6, 12	BL, Days 28, 56, 84, 112	BL, wks 4, 8, 12, 16, 28, 32, 48	BL, Day 85	Wks 12, 32, 48	Wks -2 to -1, 0, 48
ECG	BL, wks 4, 16, 52	BL, month 6, 12	BL, Day 112	Not assessed	Not assessed	Not assessed	Wks -2 to -1, 0, 48
Echocardiogram	BL, wks 16, 52	BL, month 6, 12	BL, Day 112	Not assessed	Not assessed	Not assessed	Wks -2 to -1, 0, 48
Gallbladder ultrasound	BL, wks 16, 52	Not assessed	BL, Day 112	BL, wks 28, 48	BL, Day 85	Wks 12, 32, 48	Wks -2 to -1, 0, 48
Clinical laboratories	BL, wks 4, 16, 52	Not assessed	BL, Day 112	BL, wks 12, 28, 48	BL, Day 85	Wks 12, 32, 48	Wks -2 to -1, 0, 48
Antibodies to lanreotide	BL, wks 4, 16, 36, 52	Not assessed	BL, Day 112	Not assessed	BL, Day 85	Wks 12, 32, 48	Wks -2 to -1, 32, 48
Adverse events	Throughout	Throughout	Throughout	Throughout	Throughout	Throughout	Wks -2 to 48
Local/systemic tolerance	Not assessed	Not assessed	Not assessed	Not assessed	Each injection	Each injection	Not assessed

¹ Follow-up study to 709; baseline evaluations from this study were obtained from Day 85 in Study 709
 BL=baseline line or assessment prior to baseline; wks=weeks

Best Possible Copy

In Study 717 adverse events were assessed at each visit. Information was solicited from patients with regard to any symptoms or unexpected occurrences since the previous visit. The information was gathered using non-leading questions (e.g., “Do you feel different in any way since starting the new treatment/the last assessment?”).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

For the primary and supportive safety data, the assessment of safety was based on those subjects who received at least one dose of lanreotide (either acetate or another formulation). To facilitate an analysis and comparison of data across multiple studies, adverse event (AE) and medical history terms were recoded for all clinical studies using Medical Dictionary of Regulatory Affairs (MedDRA) 7.1 or 8.1. Furthermore, safety data were pooled for all clinical studies of lanreotide acetate 60, 90, or 120 mg administered to acromegalic patients every 28 days by health care providers, where a complete database had been finalized prior to the submission database lock. Studies that were pooled included: Study 721, 717, 076, 081, 087, 709 and its follow-up Study 710. These studies are also reviewed individually, see Section 10.1. This reviewer compared the terms used by the investigator in describing an AE to the preferred term, particularly in cases of AEs leading to dropouts and AEs of particular interest for this class of drug, and these events seem to have been appropriately classified.

7.1.5.3 Incidence of common adverse events

Study 717 included an initial 4-week double-blind, placebo-controlled period, in which patients received a single deep s.c. injection of 60, 90 or 120 mg lanreotide acetate (total N=83) or placebo (N=25). This placebo-controlled aspect of Study 717 provides incidence rates for common adverse events as compared to placebo. A higher percentage of patients receiving lanreotide acetate (60%) compared with placebo (36%) reported ≥ 1 TEAE. Most of the commonly reported TEAEs in this period of the study were reported only by patients receiving lanreotide acetate, indicating that the TEAEs were associated with lanreotide acetate treatment:

diarrhea (31% vs. 0%), abdominal pain (7% vs. 4%); bradycardia (8% vs. 0%), decreased weight (8% vs. 0%) anemia (7% vs. 0%) and flatulence (6% vs. 0%) (for lanreotide acetate vs. placebo treatment groups, respectively).

Table 7.1.5.3.1. Most Commonly ($\geq 5\%$) Reported Treatment-emergent Adverse Events During the Double-blind Phase by Dose as Randomized and Preferred Term (Safety Population, Double-blind Phase)

Preferred Term	Lanreotide 60 mg (N=27)	Lanreotide 90 mg (N=27)	Lanreotide 120 mg (N=29)	All Doses of Lanreotide (N=83)	Placebo (N=25)	Total (N=108)
Diarrhea	3 (11%)	10 (37%)	13 (45%)	26 (31%)	0	26 (24%)
Abdominal Pain	2 (7%)	2 (7%)	2(7%)	6 (7%)	1 (4%)	7 (6%)
Bradycardia	3 (11%)	2 (7%)	2 (7%)	7(8%)	0	7 (6%)
Weight Decrease	2 (7%)	4 (15%)	1 (3%)	7 (8%)	0	7 (6%)
Anemia	1 (4%)	4 (15%)	1 (3%)	6 (7%)	0	6 (6%)
Flatulence	0	2 (7%)	3 (10%)	5 (6%)	0	5 (5%)

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

7.1.5.4 Common adverse event tables

Table 7.1.5.4.1 presents the most common TEAEs that occurred in healthy subjects given lanreotide acetate in the pooled Phase I studies (overall incidence $\geq 5\%$ for any PT or HLT) by MedDRA SOC, HLT and PT. Gastrointestinal disorders were the most common type of TEAE, reported by 71% (76/107) healthy subjects overall who were included in the pooled analysis of Phase I studies. The most commonly reported individual TEAE (PT) was abdominal pain, which was reported by 45/107 (52%) healthy subjects. This was followed by diarrhea (32%), headache (21%) and injection site induration (18%). Other GI disorders reported by $\geq 5\%$ of healthy subjects were abdominal distension (16%), watery stools (16%), vomiting (11%), upper abdominal pain (10%) and nausea (6%).

Table 7.1.5.4.1 Most Common Treatment-Emergent Adverse Events (Incidence $\geq 5\%$ Overall) by MedDRA SOC, HLT and PT: Lanreotide Acetate Phase I Studies (149, 038, 047)

MedDRA SOC HLT PT	Number and Percentage of Healthy Subjects							
	Study 149 ^a (N=38)		Study 038 ^b (N=42)		Study 047 ^c (N=27)		Overall (N=107)	
	n	%	n	%	n	%	n	%
Healthy subjects with ≥ 1 TEAE	36	94.7	30	71.4	23	85.2	89	83.2
Gastrointestinal disorders	36	94.7	18	42.9	22	81.5	76	71.0
<i>Gastrointestinal and abdominal pains (excl oral and throat)</i>	<i>27</i>	<i>71.1</i>	<i>13</i>	<i>31.0</i>	<i>12</i>	<i>44.4</i>	<i>52</i>	<i>48.6</i>
Abdominal pain	21	55.3	13	31.0	11	40.7	45	52.1
Abdominal pain upper	10	26.3	0	0.0	1	3.7	11	10.3
Diarrhoea (excl infective)	30	78.9	3	7.1	1	3.7	34	31.8
Diarrhoea	30	78.9	3	7.1	1	3.7	34	31.8
Flatulence, bloating and distension	17	44.7	0	0.0	3	11.1	20	18.7
Abdominal distension	17	44.7	0	0.0	0	0.0	17	15.9
Faeces abnormal	0	0.0	1	2.4	17	63.0	18	16.8
Stools watery	0	0.0	0	0.0	17	63.0	17	15.9
Nausea and vomiting symptoms	9	23.7	7	16.7	1	3.7	17	15.9
Vomiting	7	18.4	4	9.5	1	3.7	12	11.2
Nausea	2	5.3	4	9.5	0	0.0	6	5.6
General disorders and administration site conditions	19	50.0	5	11.9	0	0.0	24	22.4
<i>Injection and infusion site reactions</i>	<i>19</i>	<i>50.0</i>	<i>0</i>	<i>0.0</i>	<i>0</i>	<i>0.0</i>	<i>19</i>	<i>17.8</i>
Injection site induration	19	50.0	0	0.0	0	0.0	19	17.8
Nervous system disorders	7	18.4	13	31.0	4	14.8	24	22.4
<i>Headaches NEC</i>	<i>7</i>	<i>18.4</i>	<i>11</i>	<i>26.2</i>	<i>4</i>	<i>14.8</i>	<i>22</i>	<i>20.6</i>
Headache	7	18.4	11	26.2	4	14.8	22	20.6
Infections and infestations	1	2.6	4	9.5	2	7.4	7	6.5
Respiratory, thoracic and mediastinal disorders	0	0	6	14.3	0	0	6	5.6
Skin and subcutaneous tissue disorders	0	0	4	9.5	2	7.4	6	5.6

Source: Sponsor Table 5.5.2

a All subjects received one i.v. injection of the immediate-release formulation (IRF) followed by one s.c. injection of 60, 90 or 120 mg lanreotide acetate (0.246 mg/mg) in the buttock.

b All subjects received one i.v. bolus injection followed by either one i.m. injection of 60, 90 or 120 mg lanreotide acetate (N=30, of which N=18 received 0.246 mg/mg) or one para-umbilical s.c. injection of 60 mg lanreotide acetate (N=12, of which N=6 received 0.246 mg/mg).

c All subjects received one s.c. injection of 60, 90 or 120 mg lanreotide acetate (0.246 mg/mg) in the buttock, upper arm or abdominal wall.

Table 7.1.5.4.2 presents the most common TEAEs that occurred in acromegalic patients in pooled lanreotide acetate studies (overall incidence $\geq 5\%$ for any PT or HLT) for Studies 081 and 717 (in which patients had not been treated with medication for acromegaly within 3 months of baseline). Overall data for the seven studies included in the pooled analysis are also presented for comparison.

Table 7.1.5.4.2 TEAEs Occurring in $\geq 5\%$ of Patients in Studies 081 and 717 or Overall Pooled Data

MedDRA SOC HLT PT	081 & 717 ^a (N=170)		Overall ^b (N=416)	
	N	%	N	%
Patients with ≥1 TEAE	157	92.4	356	85.6
Gastrointestinal disorders	121	71.2	235	56.5
<i>Diarrhoea (excl infective)</i>	81	47.6	155	37.3
<i>Diarrhoea</i>	81	47.6	155	37.3
<i>Gastrointestinal and abdominal pains (excl oral and throat)</i>	39	22.9	91	21.9
Abdominal pain	34	20.0	79	19.0
<i>Nausea and vomiting symptoms</i>	20	11.8	61	14.7
Nausea	15	8.8	46	11.1
Vomiting	8	4.7	28	6.7
<i>Faeces abnormal</i>	19	11.2	26	6.3
Loose stools	16	9.4	23	5.5
<i>Gastrointestinal atonic and hypomotility disorders NEC</i>	13	7.6	38	9.1
Constipation	9	5.3	33	7.9
<i>Flatulence, bloating and distension</i>	12	7.1	33	7.9
Flatulence	12	7.1	30	7.2
<i>Gastrointestinal signs and symptoms NEC</i>	10	5.9	15	3.6
Hepatobiliary disorders	53	31.2	99	23.8
<i>Cholecystitis and cholelithiasis</i>	45	26.5	85	20.4
Cholelithiasis	45	26.5	85	20.4
General disorders and administration site conditions	51	30.0	91	21.9
<i>Injection and infusion site reactions</i>	28	16.5	37	8.9
Injection site pain	14	8.2	17	4.1
<i>Asthenic conditions</i>	13	7.6	30	7.2
Fatigue	9	5.3	18	4.3
Musculoskeletal and connective tissue disorders	44	25.9	70	16.8
<i>Joint related signs and symptoms</i>	18	10.6	31	7.5
Arthralgia	17	10.0	30	7.2
<i>Musculoskeletal and connective tissue signs and symptoms NEC</i>	16	9.4	23	5.5
Back pain	9	5.3	13	3.1
Infections and infestations	43	25.3	102	24.5
<i>Upper respiratory tract infections</i>	16	9.4	35	8.4
<i>Urinary tract infections</i>	11	6.5	23	5.5
Urinary tract infection	9	5.3	18	4.3
Investigations	41	24.1	131	31.5
<i>Liver function analyses</i>	3	1.8	53	12.7
<i>Mineral and electrolyte analyses</i>	4	2.4	37	8.9
<i>Physical examination procedures</i>	13	7.6	19	4.6
Weight decreased	12	7.1	16	3.8
<i>Carbohydrate tolerance analyses (incl diabetes)</i>	9	5.3	29	7.0
Nervous system disorders	34	20.0	80	19.2
<i>Headaches NEC</i>	9	5.3	30	7.2
Headache	9	5.3	30	7.2
<i>Neurological signs and symptoms NEC</i>	9	5.3	19	4.6
Cardiac disorders	32	18.8	52	12.5
<i>Supraventricular arrhythmias</i>	16	9.4	18	4.3
Sinus bradycardia	12	7.1	13	3.1
Skin and subcutaneous tissue disorders	27	15.9	51	12.3
<i>Alopecia</i>	13	7.6	18	4.3
Alopecia	9	5.3	13	3.1
Metabolism and nutrition disorders	24	14.1	44	10.6
<i>Diabetes mellitus (incl subtypes)</i>	9	5.3	13	3.1
Vascular disorders	23	13.5	41	9.9
<i>Vascular hypertensive disorders NEC</i>	11	6.5	21	5.0
Hypertension	11	6.5	20	4.8
Renal and urinary disorders	19	11.2	33	7.9
<i>Bladder and urethral symptoms</i>	9	5.3	11	2.6
Blood and lymphatic system disorders	13	7.6	24	5.8
<i>Anaemias NEC</i>	12	7.1	15	3.6
Anaemia	12	7.1	14	3.4
Psychiatric disorders	18	10.6	38	9.1
Respiratory, thoracic and mediastinal disorders	21	12.4	35	8.4
Surgical and medical procedures	15	8.8	27	6.5
Eye disorders	9	5.3	22	5.3
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	12	7.1	22	5.3
Injury, poisoning and procedural complications	9	5.3	19	4.6

Source: Sponsor's Appendix 4 - Statistical Table AE.1.1.1 and Table AE.1.1.2.

a Pooled data for Studies 081 and 717 only, these pivotal efficacy and safety studies had a washout period at baseline.

b Pooled data for Studies 721, 081, 717, 076, 087, 709 and 710.

GI disorders were the most common type of TEAE, reported by 56.5% (235/416) acromegalic patients in the overall pooled lanreotide acetate studies including 71% (121/170) patients from Studies 081 and 717. The most commonly reported individual TEAE preferred terms reported by acromegalic patients in the overall pooled lanreotide acetate studies and patients from Studies 717 and 081 were diarrhea (37% vs. 48%), cholelithiasis (20% vs. 26.5%) and abdominal pain (19% vs. 20%). The incidences of some TEAEs were higher in patients from Studies 717 and 081 than in acromegalic patients in the overall pooled lanreotide acetate studies: diarrhea (48% vs. 37%), cholelithiasis (26.5% vs. 20%), injection site pain (8% vs. 4%), sinus bradycardia (7% vs. 3%) and anemia (7% vs. 3%). These two studies contain a washout period of 3 months prior to baseline. The study design attempted to capture any events such as TEAEs if they re-occur with re-initiation of treatment. The TEAEs reported most commonly by patients who had not received treatment for acromegaly at baseline (in Studies 081 and 717) were similar to the most commonly reported TEAEs in the overall pooled analysis. The incidence of some TEAEs, such as diarrhea, injection site pain and sinus bradycardia, was greater in patients who had not received treatment at baseline.

Diarrhea and other GI disorders (such as abdominal pain, nausea, constipation and flatulence) and cholelithiasis were commonly reported in each study. However, for hyperglycemia, in Studies 710, 717 and 709, the incidence of hyperglycemia was 16%, 9% and 8%, respectively. The overall pooled analysis of TEAEs gives an incidence of 1.2% for this TEAE. There were a higher percentage of patients who had adverse events of increased blood glucose in the pooled analysis (4.8%). This difference in incidence of hyperglycemia between the CSRs and the pooled analysis is due to differences in coding. In some of the CSRs, verbatim terms such as glucose increased or HbA1c increased are coded as hyperglycemia whereas in MedDRA, used for the pooled analysis, they are coded to specific investigations.

The table below presents the most common TEAEs in acromegalic patients in pooled lanreotide acetate studies by dose at AE onset (overall incidence $\geq 10\%$ for any PT or HLT for any dose group or overall). AEs are presented by MedDRA SOC, HLT, PT and the dose of lanreotide acetate at the time of AE onset. The analysis is confounded by the dose titration methodology used in most studies, where patients with more severe disease, or poorer control of GH and IGF-1, frequently titrate to the highest dose. Therefore dose is not an independent variable but is associated with disease severity.

Table 7.1.5.4.3 Most Common Treatment-Emergent Adverse Events (Incidence ≥10%) by MedDRA SOC, HLT, PT and Dose of Lanreotide at Onset of AE: Acromegalic Patients in Pooled Lanreotide Acetate Studies (721, 081, 717, 076, 087, 709, 710)

MedDRA SOC HLT PT	Number and Percentage of Patients							
	60 mg (N=148)		90 mg (N=218)		120 mg (N=194)		Overall (N=413) ^a	
	n	%	N	%	n	%	n	%
Number of patient years	96.15		92.45		129.31		423.66	
Patients with ≥1 TEAE	124	83.8	168	77.1	164	84.5	356	86.2
Gastrointestinal disorders	74	50.0	108	49.5	98	50.5	235	56.9
Diarrhoea (excl infective)	45	30.4	74	33.9	60	30.9	155	37.5
Diarrhoea	45	30.4	74	33.9	60	30.9	155	37.5
Gastrointestinal and abdominal pains (excl oral and throat)	26	17.6	44	20.2	29	14.9	91	22.0
Abdominal pain	24	16.2	41	18.8	23	11.9	79	19.1
Nausea and vomiting symptoms	25	16.9	16	7.3	21	10.8	61	14.8
Nausea	22	14.9	15	6.9	11	5.7	46	11.1
Investigations	54	36.5	39	17.9	52	26.8	131	31.7
Liver function analyses	24	16.2	15	6.9	19	9.8	53	12.8
Infections and infestations	32	21.6	30	13.8	38	19.6	102	24.7
Hepatobiliary disorders	32	21.6	28	12.8	45	23.2	99	24.0
Cholecystitis and cholelithiasis	26	17.6	21	9.6	41	21.1	85	20.6
Cholelithiasis	26	17.6	21	9.6	41	21.1	85	20.6
General disorders and administration site conditions	26	17.6	42	19.3	33	17.0	91	22.0
Nervous system disorders	28	18.9	22	10.1	27	13.9	80	19.4
Musculoskeletal and connective tissue disorders	21	14.2	28	12.8	24	12.4	70	16.9
Cardiac disorders	16	10.8	17	7.8	15	7.7	52	12.6

Source: Sponsor Appendix 4 - Statistical Table AE.1.4

a The dose group population (N=332, all available dosing data, no imputed data)

b The same patient may be present in more than one dose group for any PT if the AE occurred with a different severity at a different dose.

The overall population is the number of patients who received a dose within any dose group (N=416, all available dosing data including imputed data) In Study 721, three patients were excluded from the analysis, because they received 30 mg (Patient 000421), 40 mg (Patient 000424) and 42 mg (Patient 000498).

Additionally, the patient exposure to drug varied across the groups: 96, 92 and 129 patient-years, for the 60 mg, 90 mg and 120 mg groups, respectively. There was an increased incidence for injection and infusion site reactions at higher dose strengths (4.7%, 7.3%, 8.2% patients in the 60 mg, 90 mg and 120 mg groups, respectively).

7.1.5.5 Identifying common and drug-related adverse events

Study 717 (See Section 10.1.1 for details)

In Study 717, the most commonly reported adverse events during lanreotide treatment across all 3 study phases were diarrhea (48%), cholelithiasis (30%), abdominal pain (21%), application site disorders (injection site mass/pain/reaction) (21%), hyperglycemia (includes hyperglycemia, elevated HbA1C, new onset + aggravated DM) (15%), bradycardia (14%), arthralgia (13%),

anemia (12%), alopecia (12%), flatulence (10%), nausea (10%), and hypertension (includes HTN + aggravated HTN) (8%).

The incidence of diarrhea (22%, 29% and 47% for the 60, 90 and 120 mg groups respectively), abdominal pain (11%, 14% and 15%, respectively) and flatulence (4%, 5%, 9%, respectively) increased with lanreotide dose. In addition, the incidence rates of cholelithiasis (17%, 14% and 24%, respectively) and injection site mass (4%, 3% and 11%, respectively) were highest during treatment with 120 mg lanreotide acetate.

The clinically significant changes in hematology or chemistry parameters associated with lanreotide acetate following repeated injections were anemia (12% patients), hyperglycemia (9%), hypoglycemia (4%), increased alkaline phosphatase (3%), hypercholesterolemia (3%) and bilirubinemia (3%). Thyroid function was not monitored during this study.

Lanreotide-treated patients had a decrease in heart rate and concomitant changes in the ECG intervals that follow heart rate. Treatment-emergent adverse events related to ECG assessment and reported in the Heart Rate and Rhythm Disorders body system during the entire study included bradycardia (14%), atrial arrhythmia (2%), atrial fibrillation (2%), heart block (2%), ventricular arrhythmia (<1%) and bundle branch block (<1%).

The cardiac valvular regurgitations seen in this population did not appear to show any clinically meaningful changes over time.

Gallbladder ultrasound revealed that the incidence of new onset of lithiasis and sludge by study end was ~31% of patients with data available at baseline and post-baseline and excluding those who had abnormalities at baseline. Patients whose last dose administered was 120 mg appeared more likely to have new onset of lithiasis and sludge (~20%) compared to patients who received the lower doses of lanreotide acetate ($\leq 10\%$).

In Study 717, of the 98 subjects who had data available at baseline and post-baseline, 17 (17%) had baseline gallstones which persisted throughout the study; 65 (66%) had no gallstones at baseline and end-of-study; 13 (13%) developed new gallstones which persisted; and 3 (3%) developed the occurrence and disappearance of a gallstone during the course of the trial. If the 17 subjects with baseline gallstones are removed from the denominator, there are 13/81 (16%) who developed new gallstones that persisted throughout the course of the study and 16/81 (20%) who developed new gallstones at any time during the study.

Pooled Lanreotide Acetate Studies

Table 7.1.5.5.1 presents the most common treatment-related TEAEs in acromegalic patients in pooled lanreotide acetate studies (incidence $\geq 5\%$ for any PT or HLT). TEAEs are presented by MedDRA SOC, HLT and PT. Related TEAEs are those with a causality to study treatment determined by the clinical investigator that was not classified as unlikely or not related; if causality was not assessable or unknown the TEAE was classified as related.

Table 7.1.5.5.1 Most Common Treatment-Emergent Related Adverse Events (Incidence ≥ 5%) by MedDRA SOC, HLT and PT: Acromegalic Patients in Pooled Lanreotide Acetate Studies (721, 081, 717, 076, 087, 709, 710)

MedDRA SOC HLT PT	Related ^a Number and Percentage of Patients (N=416)	
	N	%
Patients with ≥ 1 related ^a TEAE	290	69.7
Gastrointestinal disorders	214	51.4
<i>Diarrhoea (excl infective)</i>	<i>149</i>	<i>35.8</i>
<i>Diarrhoea</i>	<i>149</i>	<i>35.8</i>
<i>Gastrointestinal and abdominal pains (excl oral and throat)</i>	<i>81</i>	<i>19.5</i>
<i>Abdominal pain</i>	<i>71</i>	<i>17.1</i>
<i>Nausea and vomiting symptoms</i>	<i>46</i>	<i>11.1</i>
<i>Nausea</i>	<i>35</i>	<i>8.4</i>
<i>Gastrointestinal atonic and hypomotility disorders NEC</i>	<i>27</i>	<i>6.5</i>
<i>Constipation</i>	<i>25</i>	<i>6.0</i>
<i>Flatulence, bloating and distension</i>	<i>32</i>	<i>7.7</i>
<i>Flatulence</i>	<i>29</i>	<i>7.0</i>
<i>Faeces abnormal</i>	<i>25</i>	<i>6.0</i>
<i>Loose stools</i>	<i>23</i>	<i>5.5</i>
Hepatobiliary disorders	93	22.4
<i>Cholecystitis and cholelithiasis</i>	<i>84</i>	<i>20.2</i>
<i>Cholelithiasis</i>	<i>84</i>	<i>20.2</i>
General disorders and administration site conditions	68	16.3
<i>Injection and infusion site reactions</i>	<i>35</i>	<i>8.4</i>
Investigations	68	16.3
<i>Liver function analyses</i>	<i>27</i>	<i>6.5</i>
Nervous system disorders	27	6.5
Cardiac disorders	24	5.8
Skin and subcutaneous tissue disorders	24	5.8

Source: Sponsor's Appendix 4 - Statistical Table AE.1.1.1

^a Related TEAEs are those with a causality to study treatment that was not classified as unlikely or not related; if a causality was not assessable or unknown the TEAE was classified as related.

Table 7.1.5.5.1 is similar to Table 7.1.5.5.2 which lists common adverse events attributable to drug but using overall incidence rates rather than investigator's determinations of causality. —
 ———, the rate of an identified adverse reaction should be derived from all reported adverse events of that type in the database used. Determining a rate based on a subset of reported events that individual investigators believe to be causally related to drug exposure is not ideal. Excluding events from the rate calculation based on the judgment of individual investigator introduces bias and inconsistency in rate determinations.

Table 7.1.5.5.2 Most Common Adverse Drug Reactions* (Incidence > 1.0% in Overall Group) Reported in Clinical Studies

System Organ Class	Number and Percentage of Patients			
	Studies 717 & 081 (N = 170)		Overall Pooled Data (N = 416)	
	N	%	N	%
Patients with any Adverse Reactions	157	92	356	86
Gastrointestinal disorders	121	71	235	57
Diarrhea	81	48	155	37
Abdominal pain	34	20	79	19
Abdominal pain upper	4	2	13	3
Nausea	15	9	46	11
Vomiting	8	5	28	7
Constipation	9	5	33	8
Flatulence	12	7	30	7
Abdominal distension	2	1	6	1
Loose stools	16	9	23	6
Abdominal discomfort	8	5	11	3
Dyspepsia	5	3	8	2
Hepatobiliary disorders	53	31	99	24
Cholelithiasis	45	27	85	20
Biliary dilatation	4	2	4	1
General disorders and administration site conditions	51	30	91	22
Injection and infusion site reactions	28	17	37	9
Injection site pain	14	8	17	4
Injection site mass	7	4	7	2
Injection site induration	3	2	4	1
Injection site nodule	2	1	4	1
Injection site pruritus	2	1	4	1
Fatigue	9	5	18	4
Microlithiasis	4	2	9	2
Musculoskeletal and connective tissue disorders	44	26	70	17
Arthralgia	17	10	30	7
Investigations	41	24	131	32
ALT increased	1	1	20	5
Blood bilirubin increased	2	1	14	3
AST abnormal	-	-	11	3
ALT abnormal	-	-	9	2
Blood sodium decreased	-	-	16	4
Blood glucose increased	3	2	20	5
Glycosylated Hemoglobin increased	7	4	9	2
Weight decreased	12	7	16	4
Ultrasound liver	4	2	9	2
Nervous system disorders	34	20	80	19
Headache	9	5	30	7
Dizziness	8	5	18	4
Cardiac disorders	32	19	52	13
Sinus bradycardia	12	7	13	3
Skin and subcutaneous tissue disorders	27	16	51	12
Alopecia	9	5	13	3
Hypotrichosis	5	3	6	1

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

System Organ Class	Number and Percentage of Patients			
	Studies 717 & 081 (N = 170)		Overall-Pooled Data (N = 416)	
	N	%	N	%
Metabolism and nutrition disorders	24	14	44	11
Diabetes	8	5	12	3
Hypoglycemia	4	2	9	2
Vascular disorders	22	13	41	10
Hypertension	11	7	20	5
Psychiatric disorders	18	11	38	9
Depression	5	3	11	3
Blood and lymphatic system disorders	13	8	24	6
Anemia	12	7	14	3
Neoplasm benign, malignant and unspecified	12	7	22	5
Biliary neoplasm	3	2	6	1

*Adverse reactions listed are limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug.

Adverse events of special interest to Lanreotide Acetate include local tolerability, gastrointestinal effects, gallbladder and pancreas effects, glycoregulation, pituitary and thyroid function, sinus bradycardia, hypertension, and anemia.

Local Tolerability

Lanreotide Acetate is a depot formulation injected via a deep s.c. route and some local reactions are expected. Subcutaneous injection of lanreotide acetate in different animal species including rabbits, rats and dogs induced induration at the injection sites. Microscopically, the lesions consisted of the depot of the test item, consistent with the prolonged mechanism of the release of the product, associated with a granulomatous inflammation and/or fibrosis. In the three pooled studies of lanreotide acetate in healthy subjects (Studies 149, 038 and 047), injection site induration was reported as a TEAE in 17.8% (19/107) of subjects.

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Table 7.1.5.5.3 Treatment-Related TEAEs Suggestive of Local Reactions: Acromegalic Patients in Pooled Lanreotide Acetate Studies and Pooled Key MPF Studies

MedDRA SOC <i>HLT</i> PT	Number and Percentage of Patients							
	Pooled Autogel Studies N=416				Pooled Key MPF Studies N=325 ¹			
	Related		Overall		Related		Overall	
	N	%	N	%	N	%	N	%
Patients with ≥1 TEAE	290	69.7	356	85.6	253	77.8	288	88.6
Individual events of interest								
Infections and infestations	8	1.9	102	24.5	11	3.4	81	24.9
<i>Infections NEC</i>	<i>2</i>	<i>0.5</i>	<i>8</i>	<i>1.9</i>	<i>1</i>	<i>0.3</i>	<i>8</i>	<i>2.5</i>
Injection site abscess	1	0.2	1	0.2	0	-	0	-
Injection site infection	1	0.2	1	0.2	0	-	0	-
General disorders and administration site conditions	68	16.3	91	21.9	116	35.7	149	45.8
<i>Injection and infusion site reactions</i>	<i>35</i>	<i>8.4</i>	<i>37</i>	<i>8.9</i>	<i>41</i>	<i>12.6</i>	<i>46</i>	<i>14.2</i>
Injection site pain	17	4.1	17	4.1	28	8.6	31	9.5
Injection site mass	7	1.7	7	1.7	7	2.2	8	2.5
Injection site haemorrhage	2	0.5	4	1.0	8	2.5	9	2.8
Injection site induration	4	1.0	4	1.0	0	-	0	-
Injection site nodule	4	1.0	4	1.0	0	-	0	-
Injection site pruritus	4	1.0	4	1.0	3	0.9	3	0.9
Injection site reaction	2	0.5	2	0.5	1	0.3	1	0.3
Injection site swelling	2	0.5	2	0.5	2	0.6	2	0.6
Injection site irritation	1	0.2	1	0.2	0	-	0	-
Injection site paraesthesia	1	0.2	1	0.2	0	-	0	-
Injection site erythema	0	-	0	-	1	0.3	3	0.9
Injection site stinging	0	-	0	-	1	0.3	1	0.3
Injection site urticaria	0	-	0	-	1	0.3	1	0.3
<i>Implant and catheter site reactions</i>	<i>1</i>	<i>0.2</i>	<i>2</i>	<i>0.5</i>	<i>0</i>	<i>-</i>	<i>0</i>	<i>-</i>
Mechanical complication of implant	1	0.2	1	0.2	0	-	0	-
<i>Mass conditions NEC</i>	<i>2</i>	<i>0.5</i>	<i>3</i>	<i>0.7</i>	<i>2</i>	<i>0.6</i>	<i>4</i>	<i>1.2</i>
Nodule	2	0.5	2	0.5	1	0.3	1	0.3
Mass	0	-	1	0.2	1	0.3	1	0.3
Skin and subcutaneous tissue disorders	24	5.8	51	12.3	62	19.1	83	25.5
<i>Skin neoplasms benign</i>	<i>1</i>	<i>0.2</i>	<i>2</i>	<i>0.5</i>	<i>1</i>	<i>0.3</i>	<i>3</i>	<i>0.9</i>
Dermal cyst	1	0.2	2	0.5	1	0.3	3	0.9

Source: Sponsor's Appendix 4 - Statistical Tables AE 1.1.1; and AE 2.1

¹ One patient from Study 151 (unique patient number 000998) was omitted from the pooled summaries in error

There were three AEs reported which led to withdrawal. Patient 000772 (Study 709/710) reported persistent induration after each of 9 injections of lanreotide. Patient 000246 (Study 081) experienced related injection site pain and Patient 000102 (Study 717) reported unrelated edema. In the pooled lanreotide acetate studies in acromegalic patients, most local reactions at the injection site occurred on the day of injection (median time between last injection before event occurrence and event onset 0.0 days, range 0 to 4 days). The median time between first lanreotide acetate administration and event onset was 74.5 days (range 0 to 319 days), indicating that local reactions continued to occur throughout treatment.

Injection site reactions were variable among the studies and the incidence rate is thus lower when the studies were pooled. In the pivotal efficacy study, Study 717, application site disorders (injection site mass/pain/reaction) occurred in 22 (21%) of patients during lanreotide treatment across all 3 study phases (Table 10.1.1.31). The incidence of application site disorders increased with lanreotide dose occurring in 9%, 11% and 19% of patients during treatment with 60, 90 and 120 mg, respectively. In contrast, in Study 081, application site disorders occurred in 10% of subjects (N=6), including injection site pain in 4 (6%) and injection site mass in 2 (3%). In Study 076, 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.

Table 7.1.5.5.4 presents injection site induration AEs that occurred in patients in pooled lanreotide acetate studies by MedDRA SOC, HLT, PT and dose of lanreotide acetate at the time of presentation with the AE. For most injection site AEs, there was an increasing incidence at higher dose strengths at time of AE onset.

Table 7.1.5.5.4 Injection Site Induration Adverse Events by MedDRA SOC, HLT, PT and Dose at Onset: Pooled Lanreotide Acetate Studies (721, 081, 717, 076, 087, 709, 710)

MedDRA SOC HLT PT	Number and Percentage of Patients							
	60 mg (N=148)		90 mg (N=218)		120 mg (N=194)		Overall (N=413) ^{a,b}	
	n	%	n	%	n	%	n	%
Number of patient years	96.15		92.45		129.31		423.66	
Patients with ≥1 injection site induration AE	2	1.4	6	2.8	11	5.7	20	4.8
General disorders and administration site conditions	2	1.4	6	2.8	11	5.7	19	4.6
Injection and infusion site reactions	2	1.4	6	2.8	11	5.7	19	4.6
Injection site mass	1	0.7	2	0.9	5	2.6	7	1.7
Injection site induration	0	0.0	2	0.9	2	1.0	4	1.0
Injection site nodule	1	0.7	1	0.5	2	1.0	4	1.0
Injection site reaction	0	0.0	1	0.5	0	0.0	2	0.5
Injection site swelling	0	0.0	0	0.0	2	1.0	2	0.5
Injection site irritation	0	0.0	0	0.0	1	0.5	1	0.2
Infections and infestations	0	0.0	0	0.0	1	0.4	1	0.2
Infections NEC	0	0.0	0	0.0	1	0.4	1	0.2
Injection site abscess	0	0.0	0	0.0	1	0.4	1	0.2

Source: Sponsor's Table AE 1.5.1.

^a The same patient may be present in more than one dose group for any PT if the AE occurred on different occasions (dose of onset groups). The overall population is the number of patients who received at least one injection of any dose. In Study 721, three patients were excluded from the analysis, because they received 30 mg (Patient 000421), 40 mg (Patient 000424) and 42 mg (Patient 000498).

^b For study 721 no injection dates were recorded. However, in order to comply with CDISC SDTM implementation guidance the visit dates and the treatment recorded as continuing at that visit were migrated into the exposure domain of the pooled ISS database. These injection data and/or dose data for study 721 have been excluded. However, study 721 is included in the overall column that summarizes across all dose strengths.

Gastrointestinal Effects

In Study 717, GI System Disorders occurred in 72 (67%) of patients across all 3 study phases and increased with dose: 35% at 60 mg, 42% at 90 mg and 62% at 120 mg. The most commonly reported GI adverse events (by preferred term) during lanreotide treatment across all 3 study phases were diarrhea (48%), abdominal pain (21%), flatulence (10%) and nausea (10%). The incidence of diarrhea, abdominal pain and flatulence increased with lanreotide dose.

In Study 081, GI System Disorders occurred in 48 [76%] patients), including diarrhea in 36 (57%) of patients, which was mainly of mild (N=16, 25%) or moderate intensity (N=14, 22%), but six (10%) episodes were severe with one leading to patient withdrawal. Abdominal pain occurred in 17 (27%), nausea in 4 (6%), constipation in 3 (5%), GE reflux in 3 (5%), and vomiting in 1 (2%).

In Study 076, GI System Disorders occurred in 14 (78%) of the 18 patients including diarrhea (8 patients, 44%), flatulence (6, 33%), nausea (4, 22%), abdominal pain (3, 17%), vomiting (3, 17%), constipation (2, 11%) and cholelithiasis (2, 11%).

Gastrointestinal AEs for the pooled studies are summarized by time to onset and duration of event in Table 7.1.5.5.5.

Table 7.1.5.5.5 Time to Onset and Duration of Gastrointestinal AEs (Diarrhea, Abdominal Pain, Nausea) for the Pooled Analysis of Lanreotide Acetate Studies in Acromegaly

	Statistic	Gastrointestinal AEs	
		Related AEs	All AEs
Time between last injection before the event and event onset (days)	n	140	147
	Mean ± SD	2.9 ± 6.2	3.4 ± 7.3
	Median	0.0	0.0
	Range (min, max)	0, 27	0, 29
Time between first study administration and event onset (days)	n	181	188
	Mean ± SD	48.0 ± 74.1	50.3 ± 76.1
	Median	6.0	6.5
	Range (min, max)	0, 362	0, 362
Duration of the event (days)	n	181	188
	Mean ± SD	28.3 ± 66.4	28.7 ± 65.4
	Median	4.0	4.0
	Range (min, max)	1, 393	1, 393

Data source: Sponsor's Appendix 4 - Statistical Table AE1.7.1

Time to onset of gastrointestinal AEs was low, indicating that these AEs appear soon after administration of lanreotide acetate. Most events began on the day of an lanreotide acetate injection (median time to onset 0.0 days for both related AEs and overall). From the last study medication administration, mean time (±SD) to onset was 3.4±7.3 days for all AEs and 2.9±6.2 days for related AEs. The median time to onset from the first study medication administration was also low, at 6.5 days for all AEs and 6.0 days for related AEs, indicating that most gastrointestinal AEs occurred within the first week after the first administration of lanreotide acetate. Although some patients experienced gastrointestinal AEs lasting more than a year (range 1 to 393 days), most resolved in a few days (median 4.0 days for related AEs and for all AEs).

The mean (SD) cumulative dose at adverse event onset was 241.0 (237.6) mg, with a median of 120 mg. Mean (SD) duration of exposure was 379.7 (131.2) days, with a median of 365.0 days. The GI AE profiles from other clinical studies of lanreotide acetate in Acromegaly were consistent with those observed in the pooled lanreotide acetate studies. Four lanreotide acetate studies (total patients: n=426) included specific solicited questions on gastrointestinal tolerability as part of the assessment of safety and tolerability, Studies 046, 077, 709 and 710. Study 709 showed that gastrointestinal effects were very similar for both the MPF and lanreotide acetate formulations. In the follow-up Study 710 lanreotide acetate was generally better tolerated with regard to GI effects than the MPF formulation had been in Study 709. Results from Studies 046 and 077 were consistent with these findings and with the GI AE profile.

Lanreotide has pharmacological effects on the GI function and so adverse effects affecting the GI tract are anticipated. Gastrointestinal AEs are more commonly reported soon after the start of treatment. GI AEs were reported within 7 days by more than half of the 188 patients where data of injection and date of onset were available in the pooled lanreotide acetate studies. It is not known if the reduction in new reports with time is due to a decrease of AEs over time or a reduction in reporting by patients.

Postmarketing data indicate that disorders related to the gastrointestinal tract were the most frequent reactions reported, see Section 7.1.17 for further details. The adverse effect profile from the postmarketing data is consistent with data from the clinical studies.

Gallbladder and Pancreas Effects

In Study 717, gallbladder ultrasound revealed that the incidence of new onset of lithiasis and sludge by study end was ~31% of patients with data available at baseline and post-baseline and excluding those who had abnormalities at baseline. Patients whose last dose administered was 120 mg appeared more likely to have new onset of lithiasis and sludge (~20%) compared to patients who received the lower doses of lanreotide acetate ($\leq 10\%$). Of the 98 subjects who had data available at baseline and post-baseline, 17 (17%) had baseline gallstones which persisted throughout the study; 65 (66%) had no gallstones at baseline and end-of-study; 13 (13%) developed new gallstones which persisted; and 3 (3%) developed the occurrence and disappearance of a gallstone during the course of the trial. If the 17 subjects with baseline gallstones are removed from the denominator, there are 13/81 (16%) who developed new gallstones that persisted throughout the course of the study and 16/81 (20%) who developed new gallstones at any time during the study.

In Study 081, of the patients who did not have gallstones or a cholecystectomy at baseline, eight out of 36 (22%) had a new gallstone at the last evaluation.

In Study 087, one out of 6 patients (17%) developed the new onset of cholelithiasis. Gallbladder ultrasound examination was performed at multiple timepoints for the majority of studies in acromegalic patients due to the known increased incidence of cholelithiasis predicted by the pharmacology of SSAs. Table 7.1.5.5.6 presents the number and percentage of patients with a shift in presence or absence of gallstones and sludge in gallbladder ultrasound findings, from baseline to LVA in Studies 721, 717, 081 and 076.

Table 7.1.5.5.6 Number (%) of patients with a shift in presence or absence of gallstones or gallbladder sludge from baseline to LVA : Pooled Lanreotide Acetate studies (721, 717, 081 and 076)

	Shift from baseline to LVA			
	Absent to present	Absent to absent	Present to present	Present to absent
Gallstones (N=167) ¹	20 (12.0%)	118 (70.7%)	29 (17.4%)	0
Sludge (N=167) ¹	20 (12.0%)	130 (77.8%)	5 (3.0%)	12 (7.2%)

N=167 denotes the total number of assessed patients for gallstones and sludge in pooled studies 721, 717, 081, 076.
 Source: Sponsor's Table GS.1.1.

Twelve percent (20/167) of patients who did not have gallstones at baseline had formation of gallstones at LVA; similarly 20/167 (12%) moved from an absence to presence of sludge from baseline to LVA. AEs associated with gallbladder function were usually mild and did not lead to withdrawal; 29 (17.4%) of these acromegalic patients were found with gallstones already present at baseline.

In the pooled lanreotide acetate studies, cholecystitis and cholelithiasis AEs were reported by 20% (85/416) patients and were considered related to study drug in all but one patient. Gallbladder AEs are summarized by time to onset and duration of event in Table 7.1.5.5.7.

Table 7.1.5.5.7. Time to Onset and Duration of Gallbladder AEs (Cholelithiasis and Gallbladder Sludge) for the Pooled Analysis of Lanreotide Acetate Studies in Acromegaly

	Statistic	Gallbladder AEs	
		Related AEs	All AEs
Time between last injection before the event and event onset (days)	n	69	70
	Mean ± SD	11.0 ± 13.4	10.5 ± 13.3
	Median	1.0	0.0
	Range (min, max)	0, 35	0, 35
Time between first study administration and event onset (days)	n	81	82
	Mean ± SD	217.3 ± 116.0	215.4 ± 115.9
	Median	196.0	196.0
	Range (min, max)	0, 425	0, 425
Duration of the event (days)	n	81	82
	Mean ± SD	96.4 ± 108.3	98.3 ± 109.8
	Median	30.0	30.0
	Range (min, max)	1, 393	1, 393

Data source: Sponsor's Table AE1.7.2

Gallbladder AEs occurred throughout the treatment period, between 0 and 425 days after first lanreotide acetate administration, with mean and median values approximately in the middle of the range (around 200 days after first lanreotide acetate administration). The median AE duration was 30.0 days (for both related AEs and overall), however some events lasted longer (up to 393 days) giving a mean duration (±SD) of 98.3±109.8 days for all AEs and 96.4±108.3 days for related AEs. There were three SAEs concerning the gallbladder or pancreas that was considered related to study medication, as follows:

In Study 709/710, a 52-year-old female patient, presented with a SAE of treatment-related, mild biliary colic that recovered

In Study 709/710, a 51-year-old female patient, presented with a SAE of treatment-related, moderate cholecystectomy.

In Study 717, a 67-year-old male patient, presented with a SAE of treatment-related, moderate pancreatitis from a migrated gallstone. This event was treated by cholecystectomy and recovered. No patients in the pooled studies with lanreotide acetate in acromegaly withdrew from the study due to adverse events

The assessments of the gallbladder and pancreas in clinical studies of lanreotide acetate and other formulations showed evidence consistent with the known propensity of SSAs to reduce gallbladder motility. It appears that the occurrence of cholelithiasis is related to dose and time on treatment. Few patients developed acute symptoms requiring cholecystectomy. Cases of pancreatitis occurred in patients rarely but were serious. Although increases in LFTs were noted they were mostly nonserious. LFT increases reported as serious were usually related to reported clinical events.

Postmarketing data confirmed cholelithiasis as the most commonly occurring AE related to the gallbladder, see Section 7.1.17. There were also postmarketing cases of pancreatitis in non-acromegaly indications, which were less frequent, but included one fatal case that was considered related to study drug. The occurrence of cholelithiasis may be related to dose strength and/or time on lanreotide treatment. Overall, the occurrence of new gallstones or sludge did not exceed the expected rate for this known side effect of somatostatin analog treatment. Because of the possible effects of lanreotide on the gallbladder, patients may need to be monitored periodically.

Glycoregulation

In Study 717, of the 79 patients with no recorded history of diabetes mellitus at baseline, four patients (5%) experienced AEs of diabetes during the study. Of the 27 patients with active diabetes mellitus at baseline, nine (33%) had some form of AE after initiation of study drug that could be attributed to the worsening of diabetes mellitus or disturbances of glucose homeostasis.

In the pooled lanreotide acetate studies, glycoregulation TEAEs were reported by 14% (47/332) patients and were considered related to study drug in 7% (24/332) patients. AEs associated with glycoregulation (hypoglycemia, hyperglycemia, diabetes) occurred throughout the lanreotide acetate treatment period (range 0 to 425 days after first lanreotide acetate administration), with a median time to onset of 172.0 days and a mean time to onset (\pm SD) of 188.0 ± 130.2 days for all AEs. Duration of the event ranged from 1 to 365 days, with a mean (\pm SD) of 75.9 ± 107.8 days. The mean (SD) cumulative dose at adverse event onset was 640.5 (461.4) mg, with a median of 600.0 mg. Mean (SD) duration of exposure was 373.0 (72.0) days, with a median of 419.0 days. TEAEs relating to glycoregulation from the pooled studies are summarized in Table 7.1.5.5.7 below.

Table 7.1.5.5.8. Treatment-Related TEAEs Concerning Glycoregulation: Acromegalic Patients in Pooled Lanreotide Acetate Studies and Pooled Key MPF Studies

MedDRA SOC HLT PT	Number and Percentage of Patients							
	Pooled Autogel Studies N=416				Pooled Key MPF Studies N=325 ¹			
	Related		Overall		Related		Overall	
	N	%	N	%	N	%	N	%
Patient with ≥1 TEAE	290	69.7	356	85.6	253	77.8	288	88.6
Individual Events of Interest								
Investigations	68	16.3	131	31.5	38	11.7	76	23.4
<i>Carbohydrate tolerance analyses (incl diabetes)</i>	<i>15</i>	<i>3.6</i>	<i>29</i>	<i>7.0</i>	<i>7</i>	<i>2.2</i>	<i>11</i>	<i>3.4</i>
Blood glucose increased	8	1.9	20	4.8	4	1.2	7	2.2
Glycosylated haemoglobin increased	5	1.2	9	2.2	2	0.6	4	1.2
Blood glucose abnormal	1	0.2	1	0.2	0	0	0	0
Blood glucose decreased	0	0	0	0	3	0.9	3	0.9
<i>Gastrointestinal, pancreatic and APUD hormone analysis</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>2</i>	<i>0.6</i>
Insulin C-peptide decreased	0	0	0	0	0	0	1	0.3
Insulin C-peptide increased	0	0	0	0	0	0	1	0.3
Metabolism and nutrition disorders	18	4.3	44	10.6	20	6.2	31	9.5
<i>Diabetes mellitus (incl subtypes)</i>	<i>3</i>	<i>0.7</i>	<i>13</i>	<i>3.1</i>	<i>6</i>	<i>1.8</i>	<i>8</i>	<i>2.5</i>
Diabetes mellitus non-insulin-dependent	0	0	0	0	3	0.9	4	1.2
Diabetes mellitus	3	0.7	12	2.9	2	0.6	3	0.9
Diabetes mellitus inadequate control	0	0	2	0.5	1	0.3	1	0.3
<i>Hypoglycaemic conditions NEC</i>	<i>5</i>	<i>1.2</i>	<i>9</i>	<i>2.2</i>	<i>6</i>	<i>1.8</i>	<i>6</i>	<i>1.8</i>
Hypoglycaemia	5	1.2	9	2.2	6	1.8	6	1.8
<i>Hyperglycaemic conditions NEC</i>	<i>2</i>	<i>0.5</i>	<i>5</i>	<i>1.2</i>	<i>1</i>	<i>0.3</i>	<i>4</i>	<i>1.2</i>
Hyperglycaemia	2	0.5	5	1.2	1	0.3	4	1.2
Glucose tolerance impaired	1	0.2	1	0.2	0	0	0	0
Endocrine disorders	1	0.2	7	1.7	1	0.3	8	2.5
<i>Posterior pituitary disorders</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0.2</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
Diabetes insipidus	0	0	1	0.2	0	0	0	0

Source: Sponsor's Appendix 4 - Statistical Tables AE 1.1.1 and AE 2.1

¹ One patient from Study 151 (unique patient number 000998) was omitted from the pooled summaries in error

Neither the lanreotide acetate nor lanreotide MPF studies included oral glucose tolerance tests or measurements of serum insulin, so the effect of treatment on glycoregulation must be assessed from the surveillance of adverse events in patients with measurements of blood glucose and HbA1c. In the pooled studies, within the HLT of Carbohydrate tolerance analyses (including diabetes), TEAEs were reported by 7% and 3% of patients treated with lanreotide acetate and lanreotide MPF respectively. There were patients with high glycosylated hemoglobin both at baseline (29% [31/107] patients) and at LVA (33% [35/107] patients). Blood glucose shifted from high to normal in 8% (13/170) and from normal to high in 12% (21/170) patients. The incidence of patients with high fasting glucose decreased from baseline (28% [5/18] patients) to LVA (11% [2/18] patients) and was normalized in 22% (4/18) patients.

Within the HLT of Diabetes mellitus (including subtypes) 3% and 2.5% of patients reported TEAEs with lanreotide acetate and MPF, respectively. In those studies in which shifts from normal to abnormal fasting blood glucose was reported, results were generally consistent with

adverse event reports of hyperglycemia. Hypoglycemia was also reported as an adverse event, but less frequently than hyperglycemia. Treatment-emergent hyperglycemia was reported in up to 16% of patients across the lanreotide acetate studies, with no clear evidence of dose-dependent emergence. In Study 710, hyperglycemia was reported in 13%, 15% and 19% of patients receiving 60, 90 and 120 mg, respectively, and in 7%, 6% and 4%, of patients receiving 60, 90 and 120 mg, respectively, in Study 717. In study 717, 9% of subjects developed hyperglycemia and 4% developed hypoglycemia by changes in chemistry parameters. Thus, glycoregulation in patients treated with lanreotide acetate is altered and adjustments in anti-diabetic medication may be necessary.

Thyroid and Pituitary Function

In studies with lanreotide acetate, the impact of treatment on the size of the pituitary gland was evaluated formally using MRI/CT in two studies (Studies 717 and 077). These studies recruited 107 and 63 patients and had treatment periods of 48 and 52 weeks, respectively.

In pivotal efficacy Study 717, pituitary MRI/CT findings were reported at Weeks 16 and 52 or at the time of early withdrawal from the study. A total of 91/107 (85%) patients had a pituitary tumor that could be imaged at baseline, including 93%, 83% and 81% randomized to receive 60, 90 and 120 mg lanreotide acetate respectively. By Week 16 (the end of the double/single-blind phase), changes from baseline considered clinically significant by the investigator were reported for 5 (5%) of the 104 patients for whom change from baseline data were available, including 2, 2 and 1 patients in the 60, 90 and 120 mg treatment groups respectively. At the end of the study (last visit evaluation) changes from baseline considered clinically significant by the investigator were reported for 2 (2%) of the 105 patients for whom data was available. Benign pituitary neoplasm was reported as an adverse event in 2 patients during the study.

TSH and free T4 were not evaluated in most studies. In Study 717, a total of 23 patients (21.3%) reported prior or concomitant thyroid therapy at screening. Twenty-one of these patients (19.4%) had received some form of thyroid hormones, and three (2.8%) had received other thyroid therapy; one patient received both. Seventeen of the above patients were still receiving thyroid hormones at study entry; three of whom had their regimens altered after administration of lanreotide acetate. Medication and dose remained unchanged throughout the study for 14 of 17 the patients who were receiving thyroid therapy at baseline. A further four patients began new thyroid hormone therapy during the study.

In supportive efficacy Study 077, the effect of lanreotide acetate 120 mg on the pituitary gland was assessed in de novo patients (i.e. no previous surgery) by pituitary MRI/CT. MRI was performed at baseline and at the final study visit. The tumor size decreased from baseline to the final visit in the overall, ITT population, from 15.9 ± 10.5 to 13.2 ± 8.3 in the sagittal diameter, from 22.8 ± 24.1 to 18.8 ± 14.7 in the antero-posterior diameter and from 17.0 ± 13.5 to 15.6 ± 11.2 in the coronal diameter. In patients with both baseline and final visit measurements, the median prolactin level decreased from 13.4 ng/mL at baseline to 10.2 ng/mL at the end of treatment. Two patients developed thyrotoxicosis in this study but no further details are available.

Cardiac Function

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

In Study 717, lanreotide-treated patients had a decrease in heart rate and concomitant changes in the ECG intervals that follow heart rate. During the double-blind placebo-controlled phase (weeks 0 to 4), bradycardia was reported in 8% of the lanreotide patients as compared to 0% of the placebo-treated patients. Treatment-emergent adverse events related to ECG assessment and reported in the Heart Rate and Rhythm Disorders body system during the entire study included bradycardia (14%), atrial arrhythmia (2%), atrial fibrillation (2%), heart block (2%), ventricular arrhythmia (<1%) and bundle branch block (<1%). The adverse event of hypertension, which included hypertension and aggravated hypertension, was 8%.

Anemia

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

7.1.5.6 Additional analyses and explorations

Gender

Table 7.1.5.6.1 presents the most common TEAEs in acromegalic patients in pooled lanreotide acetate studies by gender (overall incidence \geq 10% for any PT or HLT and for either gender or overall). TEAEs are presented by MedDRA SOC, HLT, PT and gender.

Table 7.1.5.6.1 Most Common Treatment-Emergent Adverse Events (Incidence ≥10%) by MedDRA SOC, HLT, PT and Gender: Acromegalic Patients in Pooled Lanreotide Acetate Studies (721, 081, 717, 076, 087, 709, 710)

MedDRA SOC HLT PT	Number and Percentage of Patients					
	Male (N=205)		Female (N=211)		Overall (N=416)	
	N	%	N	%	N	%
Patients with ≥1 TEAE	178	86.8	178	84.4	356	85.6
Gastrointestinal disorders	117	57.1	118	55.9	235	56.5
<i>Diarrhoea (excl infective)</i>	84	41.0	71	33.6	155	37.3
Diarrhoea	84	41.0	71	33.6	155	37.3
<i>Gastrointestinal and abdominal pains (excl oral and throat)</i>	43	21.0	48	22.7	91	21.9
Abdominal pain	41	20.0	38	18.0	79	19.0
<i>Nausea and vomiting symptoms</i>	18	8.8	43	20.4	61	14.7
Nausea	12	5.9	34	16.1	46	11.1
<i>Gastrointestinal atonic and hypomotility disorders NEC</i>	9	4.4	29	13.7	38	9.1
Constipation	8	3.9	25	11.8	33	7.9
Investigations	59	28.8	72	34.1	131	31.5
<i>Liver function analyses</i>	28	13.7	25	11.8	53	12.7
<i>Mineral and electrolyte analyses</i>	16	7.8	21	10.0	37	8.9
Infections and infestations	48	23.4	54	25.6	102	24.5
Hepatobiliary disorders	59	28.8	40	19.0	99	23.8
<i>Cholecystitis and cholelithiasis</i>	53	25.9	32	15.2	85	20.4
Cholelithiasis	53	25.9	32	15.2	85	20.4
General disorders and administration site conditions	39	19.0	52	24.6	91	21.9
<i>Injection and infusion site reactions</i>	16	7.8	21	10.0	37	8.9
Musculoskeletal and connective tissue disorders	24	11.7	46	21.8	70	16.8
<i>Joint related signs and symptoms</i>	8	3.9	23	10.9	31	7.5
Arthralgia	7	3.4	23	10.9	30	7.2
Nervous system disorders	34	16.6	46	21.8	80	19.2
Cardiac disorders	27	13.2	25	11.8	52	12.5
Skin and subcutaneous tissue disorders	19	9.3	32	15.2	51	12.3
Metabolism and nutrition disorders	11	5.4	33	15.6	44	10.6
Vascular disorders	18	8.8	23	10.9	41	9.9
Psychiatric disorders	16	7.8	22	10.4	38	9.1

Source: Sponsor Appendix 4-Stats Table AES.1.1

The percentage of males and females who reported ≥ 1 TEAE was similar: 178/205 (87%) and 178/211 (84%), respectively. The most commonly reported TEAE, diarrhea, was reported by a larger percentage of males (41%) than females (34%). Loose stools were also reported by a larger percentage of males (8%) than females (3%). However, some other GI disorders, such as nausea and constipation, were each reported by a larger percentage of females (nausea 16%, constipation 12%) than males (nausea 6%, constipation 4%). Cholelithiasis was reported by a larger percentage of males (26%) than females (15%). Urinary tract infections, arthralgia, and alopecia were all reported by a larger (>5%) percentage of females than males. A notably larger

percentage of females (16%) reported TEAEs in the metabolism and nutrition disorders SOC compared with males (5%). The most common HLT within this SOC, diabetes mellitus (including subtypes), had a slightly higher incidence in females (5%) compared with males (2%). For other individual PTs, the difference between males and females was < 5%.

Age Groups

Overall, for the most commonly occurring TEAEs in the pooled analysis, diarrhea, abdominal pain and cholelithiasis, there was no apparent trend for increasing incidence with age. However, for other TEAEs, there was an increased incidence in the higher age groups (66-74 years and ≥ 75 years). Interpretation of the data should be done with caution due to the imbalance in the number of patients per age group and the difficulty of placing the data in context of extent of exposure.

For GI disorders overall, there was a tendency for increasing incidence with age to 74 years. This was reflected in the individual PTs nausea, vomiting, constipation, flatulence, loose stools and hiatus hernia, for which the incidence was highest in the 66-74 years or ≥ 75 years groups. However, for diarrhea and abdominal pain, the highest incidence was in the 40-65 years and < 40 years groups, respectively.

For investigations overall, there was also an increasing incidence with age, reflected in the HLTs mineral and electrolyte analyses and physical examination procedures (including decreased weight). For liver function analyses, a similar percentage of patients (15 and 17%) were reported in the 40-65 years and the ≥ 75 years groups, respectively.

Similarly, for general disorders and administration site conditions, there was an increasing incidence with age. The highest incidence occurred in the ≥ 75 years group for injection and infusion site reactions (including injection site pain and mass), asthenic conditions (including fatigue) and pain and discomfort (including chest pain).

The highest incidence occurred in one of the two highest age groups in the following TEAEs: urinary tract infections, neurological signs and symptoms (including dizziness), supraventricular arrhythmias (including sinus bradycardia), alopecias, hyperglycemic conditions (hyperglycemia and impaired glucose tolerance), vascular hypertensive disorders (including hypertension), disturbances in initiating and maintaining sleep (including insomnia), and inner ear signs and symptoms. In addition, the incidence of diabetes mellitus was increased in the two higher age groups (7% and 6%) compared with the two younger groups (0% and 3%).

There was no apparent age-related trend for cholelithiasis, with the lowest incidence in the ≥ 75 years group. However, the incidence of biliary dilatation was notably higher in the ≥ 75 years group (17%) compared with the other three age groups (< 1% in each).

Race

In the pooled Lanreotide Acetate studies there were 22 non-Caucasian subjects and 394 Caucasians subjects. The most commonly occurring TEAEs in non-Caucasian patients were GI disorders, reported by 15 (68%) patients. Within this SOC, the highest incidence was recorded for diarrhea (41%) and loose stools (23%). The number of non-Caucasian subjects was small but

the pattern of TEAEs seen in the non-Caucasian population was consistent with that seen in the overall safety analysis.

Table 7.1.5.6.2 Most Common Treatment-Emergent Adverse Events (Incidence ≥ 10% NonCaucasian) by MedDRA SOC, HLT, PT and Race: Acromegalic Patients in Pooled Lanreotide Acetate Studies (721, 081, 717, 076, 087, 709, 710)

MedDRA SOC HLT PT	Number and Percentage of Patients			
	NonCaucasian ^a N=22		Overall ^b N=416	
	N	%	N	%
Patients with ≥1 TEAE	19	86.4	356	85.6
Gastrointestinal disorders	15	68.2	235	56.5
<i>Diarrhoea (excl infective)</i>	9	40.9	155	37.3
Diarrhoea	9	40.9	155	37.3
<i>Faeces abnormal</i>	5	22.7	26	6.3
Loose stools	5	22.7	23	5.5
<i>Nausea and vomiting symptoms</i>	5	22.7	61	14.7
Nausea	5	22.7	46	11.1
<i>Gastrointestinal and abdominal pains (exc. oral and throat)</i>	3	13.6	91	21.9
Abdominal pain	3	13.6	79	19.0
General disorders and administration site conditions	10	45.5	91	21.9
<i>Injection and infusion site reactions</i>	3	13.6	37	8.9
Injection site mass	3	13.6	7	1.7
<i>Asthenic conditions</i>	3	13.6	30	7.2
<i>Pain and discomfort NEC</i>	3	13.6	14	3.4
Investigations	9	40.9	131	31.5
<i>Physical examination procedures</i>	4	18.2	19	4.6
Weight decreased	4	18.2	16	3.8
Nervous system disorders	7	31.8	80	19.2
Infections and infestations	6	27.3	102	24.5
<i>Upper respiratory tract infections</i>	3	13.6	35	8.4
Metabolism and nutrition disorders	6	27.3	44	10.6
Cardiac disorders	5	22.7	52	12.5
<i>Supraventricular arrhythmias</i>	3	13.6	18	4.3
Sinus bradycardia	3	13.6	13	3.1
Musculoskeletal and connective tissue disorders	5	22.7	70	16.8
<i>Joint related signs and symptoms</i>	3	13.6	31	7.5
Arthralgia	3	13.6	30	7.2
Respiratory, thoracic and mediastinal disorders	5	22.7	35	8.4
Skin and subcutaneous disorders	4	18.2	51	12.3
Blood and lymphatic system disorders	3	13.6	24	5.8
<i>Anaemias NEC</i>	3	13.6	15	3.6
Anaemia	3	13.6	14	3.4
Hepatobiliary disorders	3	13.6	99	23.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	13.6	22	5.3
<i>Hepatobiliary neoplasms malignancy unspecified</i>	3	13.6	6	1.4
Biliary neoplasm	3	13.6	6	1.4
Psychiatric disorders	3	13.6	38	9.1

Source: Sponsor's Appendix 5 - Statistical Listing ISS.1.1, Table BL.1.1, Table AE.1.1.1

^a Pooled data for patients with a race other than Caucasian or missing.

^b Pooled data for Studies 721, 081, 717, 076, 087, 709 and 710 (all races). Note that Study 081 did not capture race information.

Overall N applies to all seven studies included in the pooled analysis of patients with acromegaly who received lanreotide acetate. Percentages are calculated with this as denominator.

Concomitant Illness

Diabetes Status

In the pooled Lanreotide Acetate studies there were 131 diabetic subjects and 285 non-diabetic subjects. GI disorders were reported by a higher percentage of diabetic patients than non-diabetic patients (63% versus 54%), and the higher incidence in diabetic patients was reflected in many of the individual TEAEs in this SOC, including diarrhea, abdominal pain, nausea, vomiting, constipation and flatulence. As expected, there was a difference between the two groups for carbohydrate tolerance analyses (13% vs. 4%) and diabetes mellitus (9% vs. 0.4%). There was also a higher incidence of arthralgia (11.5% vs. 5%).

Hepatic Function Status

In the pooled Lanreotide Acetate studies there were 23 subjects with impaired hepatic function and 393 subjects with no documented impaired hepatic function. The 23 patients designated hepatically-impaired in the ISS comprise 13 patients in Study E-28-52030-709, six patients in Study E-28-52030-717, four patients in Study 2-47-52030-721 and three patients in Study E-54-52030-081. None of these studies made all of the assessments required (e.g. bilirubin, albumin, ascites) to enable calculation of Child-Pugh scores. As with the race analyses, the imbalance between the groups and the small number of patients should be taken into consideration when interpreting the data. GI disorders were reported by more patients with impaired hepatic function than patients with no impaired hepatic function (65% vs. 56%). The higher incidence in patients with impaired hepatic function was reflected in all of the individual TEAEs in this SOC reported by $\geq 10\%$ patients, including diarrhea, abdominal pain, nausea, vomiting, constipation and flatulence. The most notable differences between the groups (hepatically impaired patients vs. patients with no documented impaired hepatic function) appeared to be in the PT abdominal pain (39% [9/23] vs. 18% [70/393]) and the HLT dyspeptic signs and symptoms (13% [2/23] vs. 2% [6/393]). There was generally an increased incidence of TEAEs in patients with impaired hepatic function compared with patients with no documented impaired hepatic function. As expected, liver function analyses were more common in hepatically impaired patients. The incidence of cholelithiasis was similar between groups although other hepatobiliary disorders were more common in patients with hepatic impairment. Renal and urinary disorders were also more common in patients with documented hepatic impairment at 30.4% (7/23) compared to 6.6% (26/393).

7.1.6 Less Common Adverse Events

Less common TEAEs with an incidence $<5\%$ by MedDRA SOC term for acromegalic patients in pooled Lanreotide Acetate studies (721, 081, 717, 076, 087, 709, 710) with 416 patients total include the following:

Injury, poisoning and procedural complications:	19 (4.6%)
Reproductive system and breast disorders:	15 (3.6%)
Endocrine disorders:	7 (1.7%)

Congenital, familial and genetic disorders:	3 (0.7%)
Pregnancy, puerperium and perinatal conditions	3 (0.7%)
Social circumstances:	3 (0.7%)
Immune system disorders:	1 (0.2%)

7.1.7 Laboratory Findings

Safety evaluations from the lanreotide acetate studies in acromegalic patients included clinical laboratory data (hematology and clinical chemistry), vital signs (systolic and diastolic blood pressure and heart rate), and gallbladder ultrasound findings. Summary data were pooled for Studies 717, 081, 076 and 721 where possible (Study 721 did not include hematology or clinical chemistry evaluations).

7.1.7.1 Overview of laboratory testing in the development program

In Study 717, hematology and biochemistry clinical laboratory tests were obtained at screening (visit 1) and weeks 4, 16 and 52 (end of study) corresponding to visits 4, 10 and 19 and submitted to the central laboratory for analysis. In Study 717, the clinically significant changes in hematology or chemistry parameters associated with lanreotide acetate following repeated injections were anemia (~12% patients), hyperglycemia (9%), hypoglycemia (4%), increased alkaline phosphatase (3%), hypercholesterolemia (3%) and bilirubinemia (3%). Thyroid function was not monitored during the course of this trial. For the pooled studies, the schedule of testing is summarized in Table 7.1.5.1.1 and is described in detail for each individual study in Section 10.1.

The frequency of assessments is appropriate to capture laboratory abnormalities and AEs in order to provide adequate safety data for the review of lanreotide.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory data were pooled for clinical studies of lanreotide acetate 60, 90, or 120 mg administered to acromegalic patients every 28 days by healthcare providers for Studies 717, 076, and 081. Hematology, biochemistry and urinalysis data were not collected for Study 721. Lab and U/S studies were done at Week 0 and end-of-study (Week 48) only for the 11 subjects in Study 087. Laboratory data for each of the 7 studies comprising the safety database is detailed in Section 10.1.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Hematology

The table below presents pooled summary statistics for hematology values (baseline, LVA and change from baseline to LVA), for acromegalic patients in lanreotide acetate Studies 717, 081 and 076.

Table 7.1.7.3.1.1 Summary of Hematology Parameter Values at Baseline, LVA and Change from Baseline: Acromegalic Patients in Lanreotide Acetate Studies (717, 081 and 076)

	Baseline	LVA	Change from baseline to LVA
Glycosylated Hemoglobin A1c (%TL HB) (N=107) [1]			
Measured n (%)	107 (100%)	107 (100%)	107 (100%)
Missing n (%)	0	0	0
Median (Min, Max)	6.00 (4.0, 15.0)	6.10 (3.9, 13.3)	0.10 (-7.8, 1.7)
Mean±SD	6.35 (1.62)	6.30 (1.12)	-0.05 (1.10)
Hematocrit (%) (N=188)			
Measured n (%)	185 (98.4%)	187 (99.5%)	185 (98.4%)
Missing n (%)	3 (1.6%)	1 (0.5%)	3 (1.6%)
Median (Min, Max)	0.400 (0.27, 0.49)	0.390 (0.27, 0.50)	0.000 (-0.11, 0.11)
Mean±SD	0.397 (0.040)	0.392 (0.041)	-0.005 (0.033)
Hemoglobin (mmol/L) (N=188)			
Measured n (%)	185 (98.4%)	187 (99.5%)	185 (98.4%)
Missing n (%)	3 (1.6%)	1 (0.5%)	3 (1.6%)
Median (Min, Max)	8.250 (4.90, 10.12)	8.070 (5.03, 10.12)	-0.060 (-2.04, 1.74)
Mean±SD	8.194 (0.857)	8.106 (0.865)	-0.094 (0.606)
Platelets (10⁹/L) (N=188)			
Measured n (%)	184 (97.9%)	187 (99.5%)	184 (97.9%)
Missing n (%)	4 (2.1%)	1 (0.5%)	4 (2.1%)
Median (Min, Max)	232.0 (38, 437)	236 (39, 537)	6.0 (-202, 214)
Mean±SD	234.3 (57.8)	242.5 (67.2)	7.5 (47.7)
Red Blood Cell Count (10¹²/L) (N=188)			
Measured n (%)	185 (98.4%)	187 (99.5%)	185 (98.4%)
Missing n (%)	3 (1.6%)	1 (0.5%)	3 (1.6%)
Median (Min, Max)	4.390 (3.10, 5.51)	4.300 (3.09, 5.40)	-0.040 (-1.25, 1.24)
Mean±SD	4.373 (0.420)	4.311 (0.443)	-0.065 (0.342)
White Blood Cell Count (10⁹/L) (N=188)			
Measured n (%)	185 (98.4%)	187 (99.5%)	185 (98.4%)
Missing n (%)	3 (1.6%)	1 (0.5%)	3 (1.6%)
Median (Min, Max)	5.300 (2.10, 13.00)	5.700 (1.90, 15.40)	0.400 (-3.10, 6.50)
Mean±SD	5.619 (1.642)	6.052 (1.931)	0.440 (1.427)

[1] Glycosylated Hemoglobin A1c was only requested in Study E-28-52030-717
 Source: Sponsor's Appendix 4 - Statistical Table LAB.1.1.3.

Mean and median hematology parameters (hematocrit, hemoglobin, red blood cell count) decreased slightly from baseline to LVA. The mean (±SD) white blood cell count increased

slightly from 5.62 (± 1.64) 10%L at baseline to 6.05 (± 1.93) 10%L at LVA. These changes are not clinically meaningful.

Chemistry

The table below presents pooled summary statistics for clinical chemistry values (baseline, LVA and change from baseline to LVA), for acromegalic patients in lanreotide acetate Studies 717, 081 and 076.

Table 7.1.7.3.1.2. Summary of Clinical Chemistry Parameter Values at Baseline, LVA and Change from Baseline: Acromegalic Patients in Lanreotide Acetate Studies (717, 081 and 076)

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	Baseline	LVA	Change from baseline to LVA
Albumin (g/L) (N=18)^[1]			
Measured n (%)	18 (100%)	18 (100%)	18 (100%)
Missing n (%)	0	0	0
Median (Min, Max)	42.0 (38, 47)	42.5 (36, 48)	-2.0 (-9, 7)
Mean±SD	42.3 (2.8)	41.6 (3.3)	-0.7 (4.2)
Alkaline Phosphatase (U/L) (N=188)			
Measured n (%)	184 (97.9%)	188 (100%)	184 (97.9%)
Missing n (%)	4 (2.1%)	0	4 (2.1%)
Median (Min, Max)	67.0 (28, 230)	65.0 (23, 205)	-1.5 (-126, 44)
Mean±SD	75.7 (32.3)	72.8 (29.1)	-3.7 (23.0)
ALT (U/L) (N=188)			
N measured	184 (97.9%)	188 (100%)	184 (97.9%)
Missing n (%)	4 (2.1%)	0	4 (2.1%)
Median (Min, Max)	16.0 (3, 78)	16.0 (4, 73)	1.0 (-64, 56)
Mean±SD	18.7 (12.1)	19.2 (11.7)	0.5 (13.1)
AST (U/L) (N=188)			
Measured n (%)	184 (97.9%)	188 (100%)	184 (97.9%)
Missing n (%)	4 (2.1%)	0	4 (2.1%)
Median (Min, Max)	17.0 (9, 57)	19.0 (6, 51)	1.0 (-30, 28)
Mean±SD	18.9 (7.4)	20.0 (6.9)	1.1 (7.6)
Total Bilirubin (µmol/L) (N=188)			
Measured n (%)	184 (97.9%)	187 (99.5%)	183 (97.3%)
Missing n (%)	4 (2.1%)	1 (0.5%)	5 (2.7%)
Median (Min, Max)	10.260 (3.42, 59.85)	10.000 (3.42, 56.43)	0.000 (-25.65, 34.20)
Mean±SD	11.344 (6.471)	11.926 (6.885)	0.603 (5.107)
Gamma GT (U/L) (N=18)^[1]			
Measured n (%)	18 (100%)	17 (94.4%)	17 (94.4%)
Missing n (%)	0	1 (5.6%)	1 (5.6%)
Median (Min, Max)	16.500 (8.00, 41.00)	15.000 (11.00, 81.00)	0.000 (-12.00, 40.00)
Mean±SD	18.000 (8.100)	21.400 (17.200)	2.8 (11.00)
Creatine (µmol/L) (N=188)			
Measured n (%)	184 (97.9%)	188 (100%)	184 (97.9%)
Missing n (%)	4 (2.1%)	0	4 (2.1%)
Median (Min, Max)	68.500 (26.52, 146.00)	70.720 (26.52, 153.00)	1.000 (-44.20, 53.04)
Mean±SD	67.065 (17.875)	70.074 (18.877)	3.452 (11.291)
Glucose (mmol/L) (N=170)^[2]			
Measured n (%)	170 (100%)	170 (100%)	170 (100%)
Missing n (%)	0	0	0
Median (Min, Max)	5.890 (4.20, 34.25)	6.100 (4.00, 15.76)	0.110 (-18.49, 3.27)
Mean±SD	6.576 (2.901)	6.398 (1.549)	-0.178 (2.134)
Fasting Glucose* (mmol/L) (N=18)^[1]			
Measured n (%)	18 (100%)	17 (94.4%)	17 (94.4%)
Missing n (%)	0	1 (5.6%)	1 (5.6%)
Median (Min, Max)	5.110 (3.61, 23.54)	4.830 (3.66, 16.76)	-0.220 (-17.49, 1.05)
Mean±SD	7.599 (6.091)	5.515 (2.991)	-1.581 (4.332)
Calcium (mmol/L) (N=125)^[3]			
Measured n (%)	125 (100%)	125 (100%)	125 (100%)
Missing n (%)	0	0	0
Median (Min, Max)	2.350 (2.02, 2.79)	2.320 (1.92, 2.69)	-0.050 (-0.42, 0.37)
Mean±SD	2.366 (0.125)	2.317 (0.118)	-0.049 (0.123)

	Baseline	LVA	Change from baseline to LVA
Phosphate (mmol/L) (N=125) ^[1]			
Measured n (%)	122 (97.6%)	125 (100%)	122 (97.6%)
Missing n (%)	3 (2.4%)	0	3 (2.4%)
Median (Min, Max)	1.30 (0.9, 1.9)	1.30 (0.8, 1.8)	-0.10 (-0.5, 0.4)
Mean±SD	1.35 (0.2)	1.29 (0.17)	-0.06 (0.18)
Potassium (mmol/L) (N=125) ^[2]			
Measured n (%)	122 (97.6%)	125 (100%)	122 (97.6%)
Missing n (%)	3 (2.4%)	0	3 (2.4%)
Median (Min, Max)	4.20 (3.4, 5.4)	4.30 (3.4, 6.4)	0.00 (-1.7, 2.0)
Mean±SD	4.24 (0.38)	4.28 (0.43)	0.05 (0.46)
Sodium (mmol/L) (N=125) ^[3]			
Measured n (%)	125 (100%)	125 (100%)	125 (100%)
Missing n (%)	0	0	0
Median (Min, Max)	141.0 (129, 148)	141.0 (123, 148)	0.0 (-10, 9)
Mean±SD	140.9 (2.9)	140.7 (3.2)	-0.2 (2.9)

[1] Albumin, Gamma GT and Fasting Glucose were only requested in Study E-28-52030-076

[2] Glucose was only requested for studies E-28-52030-717 and E-54-52030-081

[3] Calcium, Phosphate, Potassium and Sodium were only requested in studies E-28-52030-076 and E-28-52030-717

*Blood glucose is only designated "fasting blood glucose" if specifically reported as such

Source: Sponsor's Appendix 4 - Statistical Table LAB.1.2.3

Mean (±SD) Gamma GT increased from 18.0 (±8.1) to 21.4 (±17.2) with a corresponding increase in the SD and the maximum values. However, as only 18 patients were assessed for Gamma GT this increase in the mean value mostly reflects the increase in the maximum observed value from 41 to 81 (in patient 001- 0012). See Section 7.1.7.3.2 for details of this patient.

Mean (±SD) fasting glucose decreased from 7.6 (±6.1) mmol/L at baseline to 5.5 (±3.0) mmol/L at LVA. The maximum values and SD were reduced, however, there was no corresponding change in median values. This result should be interpreted with caution as only 18 patients had their glucose results labeled as "fasting blood glucose".

There were no clinically meaningful changes from baseline to LVA in the other mean and median pooled clinical chemistry data from acromegalic patients in lanreotide acetate Studies 717, 081 and 076.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Hematology

The table below presents the shift of hematology parameters from baseline to LVA, for acromegalic patients in lanreotide acetate Studies 717, 081 and 076. These shift tables define low and high values with reference to the normal ranges of the laboratories who conducted the original analyses.

Table 7.1.7.3.2.1 Number (%) Patients with a Shift in Hematology Parameter Values From Baseline to LVA: Acromegalic Patients in Lanreotide Acetate Studies (717, 081 and 076)

Glycosylated Hemoglobin A1c (% TL HB) (N=107) [1]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	0	0	0	0
Normal	0	67 (62.6%)	9 (8.4%)	76 (71.0%)	0
High	0	5 (4.7%)	26 (24.3%)	31 (29.0%)	0
Total Evaluated	0	72 (67.3%)	35 (32.7%)	107 (100%)	0
Missing	0	0	0	0	0
Hematocrit (%) (N=187)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	24 (12.8%)	11 (5.9%)	0	35 (18.6%)	0
Normal	27 (14.4%)	105 (55.9%)	0	132 (70.2%)	0
High	0	0	18 (9.6%)	18 (9.6%)	0
Total Evaluated	51 (27.1%)	118 (62.8%)	18 (9.6%)	185 (98.4%)	1 (0.5%)
Missing	0	2 (1.1%)	0	2 (1.1%)	0
Hemoglobin (mmol/L) (N=187)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	32 (17.0%)	13 (6.9%)	0	45 (23.9%)	0
Normal	22 (11.7%)	118 (62.8%)	0	140 (74.5%)	0
High	0	0	0	0	0
Total Evaluated	54 (28.7%)	133 (70.7%)	0	185 (98.4%)	1 (0.5%)
Missing	0	2 (1.1%)	0	2 (1.1%)	0
Platelets (10 ⁹ /L) (N=187)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	1 (0.5%)	4 (2.1%)	0	5 (2.7%)	0
Normal	6 (3.2%)	169 (89.9%)	2 (1.1%)	177 (94.1%)	0
High	0	1 (0.5%)	1 (0.5%)	2 (1.1%)	0
Total Evaluated	7 (3.7%)	177 (94.1%)	3 (1.6%)	184 (97.9%)	1 (0.5%)
Missing	0	3 (1.6%)	0	3 (1.6%)	0
Red Blood Cells Count (10 ¹² /L) (N=187)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	29 (15.4%)	15 (8.0%)	0	44 (23.4%)	0
Normal	19 (10.1%)	121 (64.4%)	0	140 (74.5%)	0
High	0	1 (0.5%)	0	1 (0.5%)	0
Total Evaluated	48 (25.5%)	139 (73.9%)	0	187 (98.4%)	1 (0.5%)
Missing	0	2 (1.1%)	0	2 (1.1%)	0
White Blood Cells Count (10 ⁹ /L) (N=187)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	4 (2.1%)	11 (5.9%)	0	15 (8.0%)	0
Normal	8 (4.3%)	154 (81.9%)	6 (3.2%)	168 (89.4%)	0
High	0	0	2 (1.1%)	2 (1.1%)	0
Total Evaluated	12 (6.4%)	167 (88.8%)	8 (4.3%)	183 (98.4%)	1 (0.5%)
Missing	0	2 (1.1%)	0	2 (1.1%)	0

[1] Glycosylated Hemoglobin IC was only requested in Study E-28-52030-717
 Source: Sponsor's Appendix 4 - Statistical Table LAB.1.3

High glycosylated hemoglobin was present in some patients at baseline (31/107 [29%]) and at LVA (31/107 [29%]). Shifts from normal to high were seen in 9/107 (8.4%) patients and from high to normal in 5/107 (4.7%) of patients. The analysis of glycosylated hemoglobin A1C was only assessed in Study 717.

Hematocrit was stable in 147/187 (78.6%) patients. Low hematocrit was present in 35/187 patients at baseline (18.6%). In 11 (5.9%) patients, low hematocrit normalized by LVA. However, normal hematocrit became below normal by LVA in 27 (14.4%) of patients.

Hemoglobin was stable in 150/187 patients (80.2%). Low hemoglobin was present in 45 (23.9%) of patients at baseline. In 13 (6.9%) patients, low hemoglobin had normalized by LVA. However, a further 22 (11.7%) patients with normal baseline hemoglobin had developed low hemoglobin at LVA.

For red blood cell count a low count was present at baseline (23% [44/188] patients) and LVA (25.5% [48/188] patients), with 15 patients normalizing and 19 patients developing low red blood cell count.

Platelets and white blood cell counts remained within the normal range for most of the patients.

Analyses of shifts in hematology parameters showed slightly more patients developing low hematocrit (14.4%) or hemoglobin (11.7%) compared to those where low baseline values resolved (5.9% and 6.9%, respectively). Throughout treatment hematocrit and hemoglobin levels remained below normal in 12.8% and 17% of patients, respectively. The overall pattern of changes in hematology parameters is reflected by the individual clinically significant laboratory values reported as AEs by the investigator such as the rate of anemia of 7.1% in Studies 717 and 081 combined and 3.4% in the overall pooled lanreotide acetate studies (see Table 7.1.5.4.3).

Chemistry

The table below presents the shift of clinical chemistry parameters from baseline to LVA, for acromegalic patients in lanreotide acetate Studies 717, 081 and 076. These shift tables define low and high values with reference to the normal ranges of the laboratories who conducted the original analyses.

Table 7.1.7.3.2.2 Number (%) of Patients With a Shift in Clinical Chemistry Parameter Values From Baseline To LVA: Acromegalic Patients in Lanreotide Acetate Studies (717, 081 and 076)

Albumin (g/L) (N=18) [U]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	0	0	0	0
Normal	0	18 (100%)	0	18 (100%)	0
High	0	0	0	0	0
Total Evaluated	0	18 (100%)	0	18 (100%)	0
Missing	0	0	0	0	0

Alkaline Phosphatase (U/L) (N=188)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	9 (4.8%)	6 (3.2%)	0	15 (8.0%)	0
Normal	6 (3.2%)	142 (75.5%)	4 (2.1%)	152 (80.9%)	0
High	0	8 (4.3%)	9 (4.8%)	17 (9.0%)	0
Total Evaluated	15 (8.0%)	159 (84.6%)	14 (7.4%)	184 (97.9%)	0
Missing	0	3 (1.6%)	1 (0.5%)	17 (9.0%)	0

ALT (U/L) (N=188)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	1 (0.5%)	0	1 (0.5%)	0
Normal	1 (0.5%)	165 (87.8%)	7 (3.7%)	173 (92.0%)	0
High	0	8 (4.3%)	2 (1.1%)	10 (5.3%)	0
Total Evaluated	1 (0.5%)	178 (94.7%)	9 (4.8%)	184 (97.9%)	0
Missing	0	4 (2.1%)	0	4 (2.1%)	0

AST (U/L) (N=188)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	0	0	0	0
Normal	0	177 (94.1%)	2 (1.1%)	179 (95.2%)	0
High	0	4 (2.1%)	1 (0.5%)	5 (2.7%)	0
Total Evaluated	0	185 (98.4%)	3 (1.6%)	184 (97.9)	0
Missing	0	4 (2.1%)	0	4 (2.1%)	0

Total Bilirubin (µmol/L) (N=188)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	0	0	0	0
Normal	0	163 (86.7%)	5 (2.7%)	168 (89.4%)	1 (0.5%)
High	0	4 (2.1%)	11 (5.9%)	15 (8.0%)	0
Total Evaluated	0	171 (91.0%)	16 (8.3%)	183 (97.3%)	1 (0.5%)
Missing	0	4 (2.1%)	0	4 (2.1%)	0

Creatinine (µmol/L) (N=188)					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	9 (4.8%)	10 (5.3%)	0	19 (10.1%)	0
Normal	7 (3.7%)	147 (78.2%)	4 (2.1%)	158 (84.0%)	0
High	0	2 (1.1%)	5 (2.7%)	7 (3.7%)	0
Total Evaluated	17 (9.0%)	162 (86.2%)	9 (4.8%)	184 (97.9%)	0
Missing	1 (0.5%)	3 (1.6%)	0	4 (2.1%)	0

Gamma GT (U/L) (N=18) [1]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	0	0	0	0
Normal	0	15 (83.3%)	1 (5.6%)	16 (88.9%)	1 (5.6%)
High	0	0	1 (5.6%)	1 (5.6%)	0
Total Evaluated	0	15 (83.3%)	2 (11.1%)	17 (94.4%)	1 (5.6%)
Missing	0	0	0	0	0
Glucose (mmol/L) (N=170) [2]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	0	0	0	0
Normal	0	99 (58.2%)	21 (12.4%)	120 (70.6%)	0
High	0	13 (7.6%)	37 (21.8%)	50 (29.4%)	0
Total Evaluated	0	112 (65.9%)	58 (34.1%)	170 (100%)	0
Missing	0	0	0	0	0
Fasting Glucose*(mmol/L) (N=18) [1]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	2 (11.1%)	0	2 (11.1%)	0
Normal	1 (5.6%)	8 (44.4%)	1 (5.6%)	10 (55.6%)	0
High	0	4 (22.2%)	4 (22.2%)	5 (27.8%)	1 (5.6%)
Total Evaluated	1 (5.6%)	14 (77.8%)	2 (11.1%)	17 (94.4%)	1 (5.6%)
Missing	0	0	0	0	0
Calcium (mmol/L) (N=125) [3]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	2 (1.6%)	0	2 (1.6%)	0
Normal	2 (1.6%)	113 (90.4%)	2 (1.6%)	117 (93.6%)	0
High	0	5 (4.0%)	1 (0.8%)	6 (4.8%)	0
Total Evaluated	2 (1.6%)	120 (96.0%)	3 (2.4%)	125 (100%)	0
Missing	0	0	0	0	0
Phosphate (mmol/L) (N=125) [3]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	0	0	0	0
Normal	0	78 (62.4%)	8 (6.4%)	86 (68.8%)	0
High	0	23 (18.4%)	13 (10.4%)	36 (28.8%)	0
Total Evaluated	0	102 (81.6%)	23 (18.4%)	122 (97.6%)	0
Missing	0	1 (0.8%)	2 (1.6%)	3 (2.4%)	0
Potassium (mmol/L) (N=125) [3]					
LVA					
Baseline	Low	Normal	High	Total Evaluated	Missing
Low	0	1 (0.8%)	0	1 (0.8%)	0
Normal	1 (0.8%)	113 (92.0%)	2 (1.6%)	118 (94.4%)	0
High	0	3 (2.4%)	0	3 (2.4%)	0
Total Evaluated	1 (0.8%)	122 (97.6%)	2 (1.6%)	122 (97.6%)	0
Missing	0	3 (2.4%)	0	3 (2.4%)	0

Sodium (mmol/L) (N=125) [3]					
Baseline	LVA			Total Evaluated	Missing
	Low	Normal	High		
Low	2 (1.6%)	3 (2.4%)	0	5 (4.0%)	0
Normal	2 (1.6%)	113 (90.4)	2 (1.6%)	117 (93.6%)	0
High	0	2 (1.6%)	1 (0.8%)	3 (2.4%)	0
Total Evaluated	4 (3.2%)	118 (94.4%)	3 (2.4%)	125 (100%)	0
Missing	0	0	0	0	0

[1] Albumin, Gamma GT and Fasting Glucose* were only requested in Study E-28-52030-076

[2] Glucose was only requested in studies E-28-52030-717 and E-54-52030-081

[3] Calcium, Phosphate, Potassium and Sodium were only requested in studies E-28-52030-076 and E-28-52030-717

*Blood glucose is only designated "fasting blood glucose" if it was specifically reported as such.

Source: Appendix 4 - Statistical Table LAB.1.4.

Albumin, alkaline phosphatase, ALT, AST, bilirubin, creatinine, calcium, potassium and sodium values were normal for most acromegalic patients at baseline and LVA. There were no clinically meaningful shifts from baseline to LVA in the incidence of patients with normal or abnormal values for these parameters.

Shifts in Gamma GT were seen in one patient (001-0007), where Gamma GT became elevated from baseline to LVA. However, the actual shift was from 32 to 35 U/L. The change in the maximum value from 41 to 81 U/L occurred in a separate patient (001-0012). This 35-year-old female with a history (taken on 18 Jan 2002) of allergic rhinitis, hypertension and diabetes mellitus had abnormal baseline and fasting glucose (16.15 mmol/L), gallbladder microstones, GGT (41 U/L) and AP (132 U/L). On 01 Apr 2002 the patient presented with mild abdominal pain, considered possibly related to treatment that resolved 2 days later. On Day 56 (08 Apr 2002), physical examination identified onychomycosis, and fungal dermatitis of the trunk on Day 84 (06 May 2002). This was treated with topical ketoconazole from Day 57 (09 Apr 2002), ongoing at last assessment.

There were a high number of patients with high blood glucose at baseline (29% [50/170] patients) and at LVA (34% [58/170] patients). Blood glucose shifted from high to normal in 8% (13/170) and from normal to high in 12% (21/170) patients. The incidence of patients with high fasting glucose decreased from baseline (28% [5/18] patients) to LVA (11% [2/18] patients) and was normalized in 22% (4/18) patients. The potential for effect of lanreotide on glycoregulation is discussed further in section 7.1.5.5. The incidence of high phosphate decreased from 29% (36/125) patients at baseline to 18% (23/125) patients at LVA. Elevated phosphate levels at baseline were normalized at LVA in 18% (23/125) patients.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

In Study 717, there were no dropouts for laboratory abnormalities. There was one marked outlier for a hematology abnormality of anemia which was assessed as severe in intensity. Patient 731.0006 experienced severe anemia at weeks 45 and 51 during treatment with 120 mg; the former event was reported as resolved within 15 days and the latter within 1 day. The patient's hematocrit and hemoglobin were 0.274 and 5.7 mmol/L at week 51; both in the very low range. There was one marked outlier for a chemistry abnormality of hypoglycemia which was assessed

as severe in intensity. Patient 712.0001 experienced severe hypoglycemia on Study Day 84 (Week 12) during treatment with 120 mg that was judged to be unrelated to study treatment; glucose value was not reported at that time. The event was reported as resolved within 1 day.

In Studies 081, 087, 076, 709 and 710, there were no marked outliers or dropouts for laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

See Section 7.4.2, Explorations for Predictive Factors

7.1.7.5 Special assessments

None

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The approach used by the applicant in monitoring vital signs was similar among the different studies and was adequate to capture variations in vital signs that could represent issues of safety.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital sign data were pooled for clinical studies of lanreotide acetate 60, 90, or 120 mg administered to acromegalic patients every 28 days by healthcare providers for Studies 721, 717, 076, and 081. Vital sign data for each of the 7 studies comprising the safety database is detailed in Section 10.1.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 *Analyses focused on measures of central tendencies*

The table below presents summary statistics for diastolic blood pressure, systolic blood pressure and heart rate values (baseline, LVA and change from baseline to LVA) for acromegalic patients in lanreotide acetate Studies 721, 717, 081 and 076.

Table 7.1.8.3.1.1 Summary of Vital Signs Parameter Values at Baseline, LVA and Change From Baseline: Acromegalic Patients in Lanreotide Acetate Studies (721, 717, 081 and 076)

	Baseline	LVA	Change from baseline to LVA
Heart Rate (bpm) (N=276)			
Measured n (%)	274 (99.3%)	273 (98.9%)	271 (98.2%)
Missing n (%)	2 (0.7%)	3 (1.1%)	5 (1.8%)
Median (Min, Max)	72.0 (43, 174)	68.0 (39, 105)	-4.0 (-102, 36)
Mean±SD	72.5 (12.3)	68.4 (11.4)	-4.2 (12.7)
Diastolic BP (mmHg) (N=276)			
Measured n (%)	274 (99.3%)	272 (98.6%)	270 (97.8%)
Missing n (%)	2 (0.7%)	4 (1.4%)	6 (2.2%)
Median (Min, Max)	80.0 (41, 120)	80.0 (48, 119)	0.0 (-40, 40)
Mean±SD	80.2 (11.4)	80.0 (10.6)	0.0 (11.3)
Systolic BP (mmHg) (N=276)			
N measured	274 (99.3%)	272 (98.6%)	270 (97.8%)
Missing n (%)	2 (0.7%)	4 (1.4%)	6 (2.2%)
Median (Min, Max)	130.0 (95, 178)	130.0 (96, 199)	0.0 (-41, 40)
Mean±SD	131.0 (17.4)	129.7 (16.5)	-1.2 (14.7)

Source: Appendix 4 - Statistical Table VS.1.1.

There was no evidence in clinical studies with long term lanreotide treatment to suggest a change in the central tendency of the population for blood pressure, although approximately 5-7% of subjects in the pooled safety studies developed the adverse event of hypertension/ hypertension aggravated. Additionally, there was a modest reduction in mean (~4 bpm) and median heart rate. This is reflected in the relatively frequent observation of sinus bradycardia or bradycardia as an AE.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Please refer to Section 10.1 for individual study review. There were no shifts from normal to abnormal in the analyses of vital signs in the Pooled Population that were clinically meaningful.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

In Study 717, five patients had 6 vital signs abnormalities reported as severe in intensity (3 reports of hypertension aggravated and one report each of bradycardia, hypertension and weight decrease), see Section 10.1. No subjects discontinued due to vital signs abnormalities.

7.1.8.3.4 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results.

7.1.9.1.1 Preclinical results

Cardiovascular effects of intravenous administered lanreotide were assessed in anesthetized rats in Study No. 145-275. Lanreotide produced small, transient hypotensive responses immediately after injection. No changes on ECG were recorded at the tested doses. Lanreotide did not affect the blood pressure response to epinephrine, norepinephrine, isoprenaline or acetylcholine. Cardiovascular effects were assessed in anesthetized dogs in two studies. Lanreotide caused no significant changes in blood pressure or venous or arterial flow. The high dose (80 µg/kg) caused a transient bradycardia which persisted for about one minute but this effect was not observed after the low dose (20 µg/kg). Lanreotide produced no changes in ECG nor were there changes in blood gases or pH.

The effect of lanreotide was evaluated *in vitro* on the Human Ether-a-go-go Related Gene (HERG) tail current recorded from HEK-293 cells stably transfected with HERG-1 cDNA (Study No. 20030464PEHP). Lanreotide was tested at 10⁻⁵ M. E-4031, a drug known to cause torsade de pointes that is a strong blocker of the HERG current, was used at 10⁻⁷ M as a positive control. Lanreotide produced no statistically significant inhibition of HERG tail current.

The effect of lanreotide was assessed *in vitro* on cardiac action potential in isolated canine Purkinje fibers (Study No. 20040085PECM). Lanreotide had no statistically significant effect on action potential parameters under either normal (1 Hz) or low (0.33 Hz) stimulation rates. Neither early nor delayed after-depolarization was observed at any concentration.

The *in vivo* QT study was conducted in conscious dogs receiving placebo, and subsequently lanreotide i.v. infusion (1 mg/kg, 3 mg/kg and 10 mg/kg over 24 h) at 1 week intervals (Study No. 20030465PCC). Blood pressure, heart rate and ECG were assessed in all animals monitored by telemetry. The study showed no statistically significant change in arterial blood pressure, heart rate, QRS complex duration or QT interval corrected for heart rate using Bazett's (QTcB) and Fridericia's (QTcF) formulas or Sarma's method.

7.1.9.1.2 Interpretation of ECG

In all three studies (721, 717, and 076), ECGs were performed at the same visits as echocardiograms (baseline, Month 6 and Month 12 in Study 721; baseline, Month 4 and Month 12 in Study 717; and baseline and Month 4 in Study 076). In Study 721 the central ECG review was blinded. In Studies 717 and 076, a central analysis of ECGs was conducted retrospectively. Blinding to treatment was not possible as all but one patient in these studies received lanreotide, the remaining patient had received placebo in the double blind phase of Study 717, but withdrew

from Study 717 before receiving lanreotide. In all three studies, ECG assessments included standard comments on normal/abnormal, rhythm, arrhythmia, conduction, morphology and myocardial infarction. Observations of the ST segment, T wave and U wave were also recorded, with measurements of RR, PR, QT and QTc intervals, QRS width and heart rate.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The primary source of cardiac safety information is Study 721 and two other clinical Studies (717 and 076) with lanreotide acetate in acromegaly. In these 3 studies, centralized echocardiogram and ECG assessments were included as safety objectives. The other pooled lanreotide acetate studies in acromegalic patients provide supportive cardiac safety data. This set comprises four other phase III/IV clinical studies with lanreotide acetate: Studies 081, 709 and its follow-up Study 710, and 087, which enrolled screen failures from Study 717. Only cardiac AEs could be included in pooled analyses for these studies, which included 207 patients.

7.1.9.3 Standard analyses and explorations of ECG data

In reviewing the ECG data from these studies, prolongation of QTc to a value greater than 500 ms and prolongation by more than 60 ms were designated as clinically notable findings.

7.1.9.3.1 *Analyses focused on measures of central tendency*

In Study 721, ECG measurements (heart rate and mean QRS, QTcB, QTcF, QT, PR and RR intervals) were comparable between the lanreotide and octreotide cohorts at baseline and at Months 6 and 12. The incidence of ECG abnormalities (mainly conduction defects such as first degree atrioventricular block and left anterior hemiblock) was similar in the lanreotide cohort throughout treatment with 22% at baseline, 28% at Month 6 and 23% at Month 12. In the octreotide cohort, the incidence was 18% at baseline, 21% at Month 6 and 13% at Month 12.

Changes from baseline to LVA in mean ECG measurements in the pooled population from lanreotide acetate cardiac studies were small and comparable with those in lanreotide patients in Study 721, as shown in Table 7.1.9.3.1.1 below. There appears to be a small reduction in mean heart rate during treatment with lanreotide acetate.

Table 7.1.9.3.1.1. Changes from Baseline to LVA in ECG Parameters, Pooled Lanreotide Acetate Cardiac Studies and Study 721 (Safety Populations)

Parameter	Lanreotide Autogel Patients in Pooled Autogel Cardiac Studies N=217				Lanreotide Autogel Patients in Study 721 N=107			
	Baseline		Change from Baseline at LVA		Baseline		Change from Baseline at Month 12	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Heart rate (bpm)	212	70.8 (14.4)	212	-5.7 (12.4)	102	65.9 (13.5)	91	-2.1 (9.6)
PR mean (ms)	208	159.4 (24.4)	208	5.1 (16.2)	99	166.1 (24.0)	88	0.5 (15.3)
QRS mean (ms)	212	92.1 (17.7)	212	-0.4 (11.3)	102	90.1 (17.5)	91	-4.0 (12.4)
QTcB mean (ms)	212	406.1 (26.1)	212	-3.1 (24.1)	102	404.2 (24.4)	90	-4.3 (20.7)
QTcF mean (ms)	212	396.3 (24.4)	212	2.4 (21.4)	102	399.9 (22.9)	90	-2.3 (17.8)
QT mean (ms)	ND	ND	ND	ND	102	390.5 (36.9)	91	1.4 (25.4)
RR mean (ms)	212	882.6 (177.0)	212	76.0 (153.8)	102	946.8 (182.4)	91	22.9 (138.4)

Source: Sponsor's CSR 721: Table 25 (change from baseline data), and Appendix 3: Tables ECG1.1 to 1.6 (baseline data). SD = standard deviation; LVA = last value available; ND = analysis not done
 15 patients received lanreotide in both Study 721 and Study 717 and are counted only once in the total

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

In Study 717 there was one patient (7010001) with a maximum post baseline value of 556 ms (QTcB) and 542 ms (QTcF) and corresponding prolongations of 124 ms (QTcB) and 104 ms (QTcF). Although two other patients had prolongations of more than 60 ms, their last values remained nonetheless below 500 ms.

Table 7.1.9.3.2. Lanreotide Treated Patients in Lanreotide Acetate Cardiac Studies with Notable QT Interval Prolongations

Study/patient number	Timepoint	QTcB (ms)	QTcF (ms)
717/7010001	Visit 3	432	438
	Visit 19	556	542
	Change	124	104
717/7130003	Visit 3	351	327
	Visit 19	413	394
	Change	62	67
717/7310006	Visit 3	369	351
	Visit 19	457	393
	Change	88	42

Source: Sponsor CSR 717: Appendix 16.1.10.

Patient 717/7010001: QT Interval Prolongation

This 78 year old female entered Study 717 in May 2000. Relevant history included cardiomegaly, angina pectoris, heart failure, hypokalemia, hypocalcemia, hypomagnesemia, hypertension; coronary artery bypass surgery and aortic valvular replacement one year before the baseline visit, LVH, atrial hypertrophy and right bundle branch block during — and sinus bradycardia (45 bpm at inclusion). Concomitant medications included digoxin, furosemide, losartan, amlodipine, nitroglycerine, thyroxine, and supplements of potassium and magnesium. Approximately five months after first dose of study lanreotide, severe bradycardia (25 bpm) was identified during echocardiography and she was diagnosed with third degree AV block requiring insertion of a permanent pacemaker. This SAE was considered by the

investigator as severe and not related to study medication. The patient was maintained in the study and completed the open label titration phase on 06 June 2001 (last dose received on 09 May 2001: lanreotide acetate 120 mg).

Patient 717/7130003: QT Interval Prolongation

This 55 year old female entered Study 717 in February 2001. Relevant history included: diabetes mellitus, hypertension and hypothyroidism. She was taking multiple medications for manic depressive psychosis and was receiving thyroid replacement therapy. She had palpitations reported as an AE during the study, assessed as not related to the study drug. The patient was hospitalized in _____ for recurrent depression. The patient was maintained in the study and completed the open label dose titration phase on 13 May 2002 (last dose received on 12 April 2002: lanreotide acetate 90 mg).

Patient 717/7310006: QT Interval Prolongation

This 63 year old male entered Study 717 in August 2001. Relevant history included severe mitral valvular insufficiency. Concomitant medications included furosemide and enalapril for prophylaxis against cardiac failure and valproic acid for epilepsy. On _____, he complained of chest pain and was hospitalized due to anemia on the same day. On admission hemoglobin was 5.7 mmol/L (normal: 8.5 to 11 mmol/L). ECG showed lateral ischemia. He was transfused with two packs of red cells. Sigmoid polyps were found during a colonoscopy performed to locate the source of anemia. A surgery was planned and he recovered without sequelae on _____. The patient completed the open label dose titration phase on _____ (last dose received on _____ lanreotide acetate 120 mg). On the day of completion of the study (_____) the patient was hospitalized for serious atrial fibrillation and a recurrence of serious anemia; digoxin was initiated. He recovered from the anemia or _____ but had not yet recovered from the atrial fibrillation.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

In Study 717, one patient with a normal baseline ECG experienced severe atrial fibrillation at Week 51. This patient had severe mitral insufficiency at baseline and would thus be at risk to develop AFib secondary to this pre-existing cardiac condition. There were no marked outliers or subjects discontinued from the other 6 studies due to ECG abnormalities.

7.1.9.4 Additional analyses and explorations

Cardiac AEs/SAEs

Treatment related cardiac AEs in the pooled population of studies 721, 717 and 076 affected 12.9% of 217 patients. The most frequent were sinus bradycardia (5.5%, or 7.0% when combined with 'bradycardia'), and hypertension (2.3%). No other treatment related cardiac AE was reported by more than 2% of patients. Treatment related cardiac events were mostly mild (21 patients) or moderate (six patients).

Treatment related cardiac AEs in the pooled population of Studies 081, 087 and 709/710 affected seven patients (3.4% of 207). The most frequent were hypertension and chest pain (two patients

each). In Study 087, one patient with a normal ECG at baseline had an abnormal ECG evaluation at the end of study: mild non-specific T wave and transient junctional rhythm abnormalities with mild sinus bradycardia and occasional premature ventricular contractions; all assessed as possibly related to study treatment.

7.1.9.5 Conclusions

The ECG data from the pooled population in the three primary cardiac studies were consistent with those from Study 721. In particular, neither the summary statistics nor the extreme values indicate an association between treatment with lanreotide acetate and clinically significant prolongation of the QTc interval. The ECG data overall does show decreases in mean HR (~4 bpm) but no other ECG findings of clinical concern.

7.1.10 Immunogenicity

Lanreotide is a small peptide with a low molecular weight (1096.34 for lanreotide free base) below the approximate 10000 minimum for antigenicity independently of any haptenic function. Lanreotide, being a small molecule, is unlikely to generate an immune response. No increased risk of infections or immune disorders has been observed.

In the long term carcinogenicity studies, 3.6% and 2.2% of the treated mice and rats, respectively, showed values of nonspecific binding (NSB), in the lanreotide assay, that were higher than 30%, indicating the presence of antibodies. Results using specific anti-IgG antibodies indicate that antibodies in treated animals with NSB>30% were specific antibody to lanreotide. NSB values between 10 and 30%, suggesting a slight immunological response, were obtained in 6.9% of mice and 3.3% of rats. In the 26-week toxicity study with lanreotide acetate in dogs, 2 of the 18 treated animals had a NSB value higher than 30% (11.1%).

A competitive inhibition radioimmunoassay (RIA) methodology was used to determine lanreotide concentrations in serum from patients treated with lanreotide acetate in seven studies (717, 076, 077, 150, 709, 710 and 046). The percentage of patients with NSB <10% ranged from 82 to 94%, and those with NSB 10 to 30% ranged from 5 to 14%. The percentage of patients with putative antibodies where NSB was >30% at any timepoint after treatment with lanreotide acetate was low (<1 to 4% patients, in all studies except for the small Study 076 where incidence was 1/18 patients), and was similar for somatostatin analog (SSA) naïve and lanreotide pretreated patients. In summary, data from long term clinical studies with lanreotide acetate indicate that antibody formation was reported in only a small number of patients and no effects on efficacy or safety were observed.

7.1.11 Human Carcinogenicity

The review of the lanreotide clinical studies did not reveal an increase risk of neoplasia. Please see Dr. Yao's toxicology review for a complete discussion of the applicant's carcinogenicity program.

7.1.12 Special Safety Studies

7.1.12.1 Cardiac Safety Study (detailed review of Study 721 is in Section 10.1.3)

An assessment of cardiac safety was requested by the Food and Drug Administration due to concerns raised

The applicant had explored the potential cardiac benefit of lanreotide by the assessment of cardiac function of some patients in several studies. In one study (Study A-47-52030-705) there was a numerical increase in cardiac valvular regurgitation, however in none of the studies presented was cardiac function assessed as a primary criterion.

To address these concerns the applicant has:

- conducted a cardiac safety study in patients with acromegaly (Study 2-47-52030-721, final protocol submitted to IND #53,993 in April 2003);
- performed a central analysis of the echocardiograms and electrocardiograms performed in the lanreotide acetate acromegaly Studies 721, 717 and 076;
- reviewed findings pertinent to cardiac safety from nonclinical lanreotide studies; lanreotide acetate and other formulation clinical studies in acromegalic patients or healthy volunteers; and cardiac reactions spontaneously reported to the sponsor.

In Study 721, each patient had an echocardiogram performed at baseline, Month 6 and Month 12. A central, blind review of the echocardiograms was performed by two independent cardiologists at the core laboratory. Discrepant readings were resolved by consensus. The cardiologists were blind to the cohort group of the echocardiograms they reviewed, and were also blind to the sequence of each echocardiogram (i.e. baseline, Month 6 or Month 12). Echocardiograms from both normal subjects and patients with severe valvular regurgitation were collected to serve as negative and positive controls. Control echocardiograms were included at random among the echocardiograms collected from the study patients. In Studies 717 and 076, central analyses of echocardiograms were conducted retrospectively. Echocardiograms were performed at baseline, Month 4 and Month 12 in Study 717 and at baseline and Month 4 (end of study) in Study 076. Reading and analysis were performed centrally by two independent cardiologists in the same central organization and according to the same procedures as in Study 721. The severity of valvular regurgitation was determined using a qualitative scale of trace/physiologic, mild, moderate, or severe. Additional details are given in reviews of each study in Section 10.1.

Cardiac chamber measurements

Echocardiographic cardiac chamber measurements, including baseline values, and absolute values and change from baseline for minimum and maximum post baseline values, and for LVA suggested no change in central tendency for cardiac dimensions or mass during treatment with lanreotide acetate in these studies. For approximately 80% of all patients within the pooled study population, dose was titrated according to clinical need and therefore patients with more severe disease received higher doses of lanreotide. The sponsor's analysis across the range of doses received (60, 90 or 120 mg per month) did not show any evidence of a relationship between changes in any parameter and dose of lanreotide acetate.

Doppler Assessments

Echocardiographic doppler assessments, including baseline values, and absolute values and change from baseline for minimum and maximum post baseline values, and for LVA, provided no evidence of a clinically significant change in any of the Doppler assessments during treatment with lanreotide acetate in these studies.

Volumes and Function

Analyses of end diastolic volume, end systolic volume and ejection fraction showed no evidence of any significant change in the pooled population during treatment with lanreotide acetate. The data were consistent across the three studies and there was no evidence to suggest a clinically significant difference across the dose range of 60, 90 or 120 mg per month in the effect of lanreotide acetate on end systolic volume, end diastolic volume or ejection fraction.

Valvular Regurgitation

In Study 721, the incidence of mild or moderate regurgitation in any heart valve was comparable in the lanreotide and octreotide cohorts at baseline (39% and 37%, respectively) and at Month 12 (40% and 37%, respectively) for the ITT matched population. At baseline, the incidence of mild or moderate mitral valvular regurgitation was high in both cohorts (21% in the lanreotide group and 12% in the octreotide group) and remained similar at Month 12 (26% in the lanreotide group and 13% in the octreotide group). The incidence of mild or moderate regurgitation in the aortic, tricuspid, and pulmonic valves was similar in each cohort at baseline and Month 12. Analysis of the primary endpoint indicated that there was no statistically significant difference between the two cohorts in the risk of developing new or worsening valvular regurgitation in any valve at 12 months.

Valvular regurgitation data summarized in Table 7.1.12.1 for the 3 pooled studies show that baseline data were available for the mitral and aortic valves in ~ 85% of cases, for the tricuspid valve in 80% of cases, and for the pulmonic valve in only 50% of cases. Most echocardiograms showed no valvular regurgitation or only a physiologic degree of regurgitation both at baseline and at LVA. Severe valvular regurgitation was rare (0% to 1.0%) and was no more frequent at LVA than at baseline. Moderate valvular regurgitation was also infrequent (1.0% to 3.8%) and the rate at LVA was similar to or lower than that at baseline in all except the pulmonic valve (3.8% at LVA, 1.0% at baseline). However, this may be confounded by the higher number of evaluable patients at LVA. Mild valvular regurgitation was more frequent at baseline (11.4% to 15.7%) than moderate or severe regurgitation. Mild regurgitation was also slightly more frequent at LVA than at baseline in the case of the mitral, aortic and pulmonic valves; slightly less frequent in the case of the tricuspid valve.

Table 7.1.12.1.1 Valvular Regurgitation Status at Baseline and LVA from Central Reading of Echocardiograms in Lanreotide Treated Patients in Lanreotide Acetate Cardiac Studies 721, 717, and 076.

	None	Physiologic	Mild	Moderate	Severe	Missing
Mitral valve						
Baseline (n=210)	56 (26.7%)	84 (40.0%)	33 (15.7%)	8 (3.8%)	0	29 (13.8%)
LVA (n=210)	86 (41.0%)	64 (30.5%)	37 (17.6%)	8 (3.8%)	0	15 (7.1%)
Aortic valve						
Baseline (n=210)	128 (61.0%)	26 (12.4%)	19 (9.0%)	6 (2.9%)	2 (1.0%)	29 (13.8%)
LVA (n=210)	137 (65.2%)	24 (11.4%)	25 (11.9%)	7 (3.3%)	2 (1.0%)	15 (7.1%)
Tricuspid valve						
Baseline (n=210)	40 (19.0%)	90 (42.9%)	31 (14.8%)	6 (2.9%)	1 (0.5%)	42 (20.0%)
LVA (n=210)	37 (17.6%)	123 (58.6%)	25 (11.9%)	2 (1.0%)	0	23 (11.0%)
Pulmonic valve						
Baseline (n=210)	42 (20.0%)	40 (19.0%)	24 (11.4%)	2 (1.0%)	0	102 (48.6%)
LVA (n=210)	63 (30.0%)	43 (20.5%)	28 (13.3%)	8 (3.8%)	0	68 (32.4%)

Source: Sponsor's Appendix 3: Tables E 1.4.1.1 to E 1.4.1.4.

15 patients received lanreotide in both Study 721 and Study 717 and are counted only once in the total.

There was no evidence to suggest any difference in the incidence of any grade of valvular regurgitation across the dose range of 60, 90 or 120 mg per month. The sponsor's subgroup analyses show no evidence of a relation between change in overall regurgitation status and age group (<40, 40 to 65, 66 to 74, and ≥75 years). Subgroup analysis by duration of acromegaly suggested that worsening regurgitation could be more common with a longer duration of acromegaly as reflected by a greater prevalence within the <5 years group (8 patients, 9.2%), than in the 1 to 5 years (0 patients) or <1 year (1 patient, 2.6%) groups. However, these data should be interpreted with caution given the unequal size of the exposure categories.

The table below shows an overview of the shifts in valvular regurgitation from baseline to LVA with octreotide from Study 721 and Lanreotide Acetate from the pooled analysis of cardiac studies 721, 717, and 076.

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Table 7.1.12.1.2 Comparison of Shifts in Valvular Regurgitation with Octreotide in Study 721 and Lanreotide Acetate in the Pooled Analysis of Cardiac Studies

Shift from baseline to Month 12:	Mitral		Aortic		Tricuspid		Pulmonic	
	Lan N=181	Oct N=82	Lan N=181	Oct N=82	Lan N=165	Oct N=82	Lan N=97	Oct N=82
Worsening:								
None to physiologic	14 (8%)	5 (6%)	7 (4%)	2 (2%)	22 (13%)	4 (5%)	8 (8%)	0
None to mild	1 (1%)	0	3 (2%)	0	1 (1%)	0	2 (2%)	0
None to moderate	0	0	0	0	0	0	1 (1%)	0
Physiologic to mild	15 (8%)	4 (5%)	5 (3%)	0	6 (4%)	2 (2%)	7 (7%)	3 (4%)
Physiologic to moderate	1 (1%)	0	0	0	0	0	2 (2%)	
Mild to moderate	3 (2%)	1 (1%)	1 (1%)	0	0	0	3 (3%)	0
Moderate to severe	0	0	1 (1%)	0	0	0	0	0
No change	92 (51%)	42 (51%)	149 (82%)	59 (72%)	101 (61%)	35 (43%)	54 (56%)	12 (15%)
Improvement:								
Severe to mild	0	0	1 (1%)	0	1 (1%)	0	0	0
Moderate to mild	4 (2%)	0	0	0	4 (2%)	0	2 (2%)	0
Moderate to physiologic	1 (1%)	1 (1%)	0	1 (1%)	0	0	0	0
Moderate to none	1 (1%)	0	0	0	0	0	0	0
Mild to physiologic	13 (7%)	4 (5%)	3 (2%)	0	15 (9%)	2 (2%)	6 (6%)	4 (5%)
Mild to none	2 (1%)	0	1 (1%)	0	3 (2%)	0	2 (2%)	0
Physiologic to none	34 (19%)	5 (6%)	10 (6%)	3 (4%)	12 (7%)	4 (5%)	10 (10%)	1 (1%)
Not evaluable		13 (16%)		10 (12%)		28 (34%)		54 (66%)

Source: Sponsor's ICSS Table 14 and CSR 2-47-52030-721: Table 14.3.4.6.1.

15 patients received lanreotide in both Study 721 and Study 717 and are counted only once in the total

Note: Study 721, the ITT matched population for octreotide comprised 82 patients, but shifts in valvular regurgitation were missing for 7 of the 82 patients and are not included in this table

Physiol = Physiologic, Lan = lanreotide; Oct = octreotide;

Thus, a majority of patients had no change in regurgitation in any valve. The pattern of shifts (improvement and worsening) in valvular regurgitation during treatment in this pooled population of lanreotide patients was similar to that in octreotide patients in Study 721. Severe valvular regurgitation was rare (<1%), and shifts from normal regurgitation (none or physiologic) in any valve to mild or moderate regurgitation were infrequent and were accompanied by a similar number of improvements.

Conclusion

In Study 721, twenty-eight (34%) of lanreotide-treated patients and 27 (33%) of octreotide-treated patients developed new or worsening valvular regurgitation. The incidence of valvular regurgitation that was mild or greater in any valve was 48 (58%) at baseline for lanreotide and 54 (65%) at 12 months. Increases in events were seen for the mitral valve 17 (21%) at baseline to 21 (26%) at 12 months; aortic valve with 8 (10%) at baseline and 9 (11%) at 12 months and the pulmonic valve with 10 (12%) at baseline and 12 (14%) at 12 months. The tricuspid valve had 13 (15%) of mild or greater regurgitation at baseline which decreased to 12 (14%) at 12 months.

The incidence of valvular regurgitation that was mild or greater in any valve was 46 (55%) at baseline for octreotide and 45 (54%) at 12 months. Increases in events were seen for the mitral valve 10 (12%) at baseline to 11 (13%) at 12 months. Aortic valve regurgitation remained stable with 9 (11%) at baseline and at 12 months. The tricuspid valve had 12 (14%) of mild or greater regurgitation at baseline which decreased to 11 (13%) at 12 months and the pulmonic valve was 15 (18%) at baseline and 14 (17%) at 12 months.

In Study 721 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. It is important to note that 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.

In the pooled analysis of centrally read echocardiographs (Studies 721, 717 and 076, n=217), lanreotide was not associated with any change in central tendency for cardiac dimensions or mass, or for end systolic volume and ejection fraction and there was no evidence of any clinically significant change in Doppler assessments during treatment.

During treatment with lanreotide, the majority of patients had no change in regurgitation in any valve. The pattern of shifts (improvement and worsening) in valvular regurgitation during treatment in this pooled population of lanreotide patients was comparable to that in octreotide patients in Study 721. Severe valvular regurgitation was rare (<1%), and shifts from normal regurgitation (none or physiologic) in any valve to mild or moderate regurgitation were infrequent.

Thus, echocardiographic evaluations did not demonstrate a significant difference in the risk of developing new or worsening valvular regurgitation or significant regurgitation after 12 months between patients treated with lanreotide and those treated with octreotide.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

GH and IGF-1 levels increase after withdrawal of lanreotide, as expected. This would be expected to correlate with an increase in the symptoms of acromegaly. Two studies with washout phases were examined for evidence of withdrawal effects, no relevant effects were observed. However, none of the studies in the clinical development program have investigated this effect. There was a single report of a treatment emergent adverse event related to withdrawal of lanreotide. A 21-year-old patient treated with lanreotide and bromocriptine for acromegaly with panhypopituitarism and diabetes mellitus was found to be pregnant. Lanreotide and bromocriptine were withdrawn and she experienced headache, visual field defect and syncopal episode later in pregnancy. The patient recovered without sequelae.

In the absence of euphoria or other CNS-related effects the abuse potential of lanreotide acetate is considered to be low. Lanreotide acetate is a product that is designed to be given parentally and intermittently and physician consultation is required to obtain the dose titration that is necessary for the optimal effect of the product. There were no postmarketing reports or published data related to potential drug abuse.

7.1.14 Human Reproduction and Pregnancy Data

There are 13 known cases related to pregnancy, 12 concerning women who had received lanreotide treatment at the time of gestation and one concerning one of the newborn. Of the five pregnancies occurring in clinical trials, one is known to have resulted in a normal birth, one caesarean birth of a healthy child, one therapeutic abortion and two were miscarriages (after which the patients recovered without sequelae). Of the seven postmarketing cases of pregnancies one is known to have resulted in a normal birth, one caesarean birth of a healthy child, 2 patients elected to undergo induced abortion and in one case the outcome of the pregnancy was not recorded. Another newborn exposed in utero was reported with vomiting (not serious), recurrent hypoglycemia (serious) and thrombocytopenia (not serious). The baby was treated with glucose infusion and then orally and recovered without sequelae. The seventh case of pregnancy was ended by caesarean delivery at 31 weeks due to fetal growth retardation and oligohydramnios. However, the effect of lanreotide on this gestation is considered is not known as the patient had confounding co-existent medical condition (extension of her adenoma treated by hydrocortisone and levothyroxine).

With regard to potential reduction of oral contraceptive efficacy, none of the postmarketing cases of pregnancy was due to oral contraceptive failure.

7.1.15 Assessment of Effect on Growth

The youngest subjects enrolled in the Phase 3 studies were 18 years old, and therefore no effect of lanreotide on linear growth can be inferred from these studies. Furthermore, acromegaly is a rare disease of adults. GH-secreting pituitary adenomas are extremely rare in children and constitute a separate clinical entity of pituitary gigantism. Experience with lanreotide acetate in the pediatric population is limited and the sponsor has applied for a pediatric waiver.

7.1.16 Overdose Experience

In the majority of clinical trials, lanreotide was administered by trained staff in a clinical setting and only one case of accidental overdose was recorded. The only recorded case of overdose occurred in Study E-47-52030-607, a phase I pharmacokinetic study in nonacromegalic but hepatically impaired patients. Patient 367001, a 61 year old male, received a continuous infusion of 100 µg lanreotide over 15 minutes rather than the planned hour. Thus, he was technically overdosed although he had received the same 100 µg dose as a bolus on the previous day. He complained of nausea and thoracic pain during the infusion. The adverse event resolved the same day. The subject had a history of benign neoplasm of the colon (colon polyps) and Type IIa

diabetes mellitus. On the same day as the infusion, this patient also had severe convulsions (seriousness unknown) and a diagnosis of epilepsy was made (first diagnosis). It was reported that possibly signs and symptoms of epilepsy had occurred prior to the study, but no diagnosis had been made. The convulsions were not reported as serious and were considered to be unrelated to treatment. The patient was treated with phenytoin.

The applicant reports one unconfirmed report of significant overdose. Although the dose stated in the source documents is unclear, it appears that case 20519990038 may have received lanreotide MPF, 30 mg daily in place of every 7 to 14 days for a 2-month period. No reactions were reported during this period and this was not reported as an adverse event. Six days after his last dose, on _____ he fell ill and died; autopsy indicated that the cause of death was myocardial infarction, considered related by the reporter.

7.1.17 Postmarketing Experience

The postmarketing spontaneous reports (PMS) reporting period (11 years; 1995 to 2005) covers approximately 35,000 patient-years of exposure to all formulations of lanreotide over all indications. The highest postmarketing exposure to lanreotide is to lanreotide MPF at >17,200 patient-years, exposure to lanreotide acetate was estimated by the sponsor to be >13,900 patient-years, and the remaining >3,900 patient-years comprised other formulations approved in limited geographical areas, and compassionate use sales. PMS reports of 322 reactions were collected from patients treated with lanreotide for acromegaly. The overall number of PMS reports was 614. Of these, 269 were serious and 345 non-serious. In Table 7.1.17.1, the most frequent PMS reports (at least 1 per 1,000 years of exposure, that is, at least 35 reactions) are summarized. The profile of PMS reports was consistent with that observed for treatment-related adverse events in the clinical studies.

Table 7.1.17.1 PMS Reports Occurring at ≥ 1 per 1,000 Patient-Years of Exposure or ≥ 35 Reactions Overall, N (Reporting Ratio %)

Indication MedDRA SOC	Acromegaly 322		Total 614		
	HLT PT	PT	Serious	Nonserious	Total
Total PMS Reports	143 (44.4)	179 (55.6)	269 (43.8)	345 (56.2)	614 (100)
Gastrointestinal disorders	50 (35.0)	45 (25.1)	79 (29.3)	99 (28.7)	178 (29.0)
Gastrointestinal & abdominal pains (excl oral & throat)	14 (9.8)	9 (5.0)	19 (7.1)	26 (7.5)	45 (7.3)
Abdominal pain	9 (6.3)	9 (5.0)	13 (4.8)	22 (6.4)	35 (5.7)
Diarrhoea (excl infective)	12 (8.4)	10 (5.6)	17 (6.3)	27 (7.8)	44 (7.2)
Diarrhoea	12 (8.4)	10 (5.6)	17 (6.3)	27 (7.8)	44 (7.2)
General disorders & administration site conditions	15 (10.5)	59 (33.0)	42 (15.6)	115 (33.3)	157 (25.6)
Injection & infusion site reactions	2 (1.4)	39 (21.8)	13 (4.8)	71 (20.6)	84 (13.7)
Injection site nodule	1 (0.7)	27 (15.1)	5 (1.9)	43 (12.5)	48 (7.8)
Skin & subcutaneous tissue disorders	7 (4.9)	20 (11.2)	16 (5.9)	33 (9.6)	49 (8.0)
Nervous system disorders	14 (9.8)	14 (7.8)	25 (9.3)	21 (6.1)	46 (7.5)

Source: Sponsor's Appendix 4 - Statistical Table AE 8.1

The denominator used for serious/not serious is the total number of serious and not serious PMS reports within that indication; the denominator used for each serious (or not serious) SOC, HLT and PT is the number of serious (or not serious) PMS reports within that indication.

Deaths

In total, 18 PMS reports (24 reactions) had an outcome of death. There were five reports of fatal events in acromegalic patients. Three of these were considered not related to lanreotide treatment. The two cases considered to have a relationship to lanreotide treatment were reports 20519990038 and 10E19970103. In case 20519990038 the death due to myocardial infarction occurred 6 days after the last injection of lanreotide, which may have been given in an excessive dose (lanreotide MPF, 30 mg daily instead of every 7 to 14 days for a 2-month period); however, the patient had other risk factors for myocardial infarction. Case 10E19970103 is a 77-year-old female patient (France) who was treated with lanreotide at 30 mg 2-weekly for approximately 2 years, having previously been treated with octreotide. She developed abdominal pain associated with asthenia, hepatomegaly, ascites, enlargement of the intrahepatic bile duct and peritoneal carcinoma. She was admitted to hospital and died.

Other Serious Adverse Events

In total, 269 serious adverse reactions were reported through postmarketing surveillance. In Table 7.1.17.2, the most frequent serious PMS reports (at least 1 per 5,000 patient-years of exposure or at least 7 reactions) are summarized by indication for use of lanreotide in order of decreasing frequency by SOC, HLT, and PT. The profile of PMS reports was consistent with that observed for treatment-related adverse events in the clinical studies.

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Table 7.1.17.2 Serious PMS Reports Occurring at > 1 per 5,000 Years of Exposure or > 7 Reactions Overall N (reporting ratio %)

Indication	Acromegaly	Not specified	Other	Total
Number of adverse reactions	322	24	268	614
Number of serious adverse reactions	143 (44.4)	13 (54.2)	113 (42.2)	269 (43.8)
MedDRA SOC				
HLT				
PT				
Gastrointestinal disorders	50 (15.5)	2 (8.3)	27 (10.1)	79 (12.9)
<i>Gastrointestinal & abdominal pains (excl oral & throat)</i>	14 (4.3)	1 (4.2)	4 (1.5)	19 (3.1)
Abdominal pain	9 (2.8)	1 (4.2)	3 (1.1)	13 (2.1)
Abdominal pain upper	5 (1.6)		1 (0.4)	6 (1.0)
<i>Diarrhoea (excl infective)</i>	12 (3.7)		5 (1.9)	17 (2.8)
Diarrhoea	12 (3.7)		5 (1.9)	17 (2.8)
<i>Nausea & vomiting symptoms</i>	11 (3.4)		3 (1.1)	14 (2.3)
Vomiting	8 (2.5)		2 (0.7)	10 (1.6)
<i>Acute & chronic pancreatitis</i>	4 (1.2)		5 (1.9)	9 (1.5)
General disorders & administration site conditions	15 (4.7)	4 (16.7)	23 (8.6)	42 (6.8)
<i>Injection & infusion site reactions</i>	2 (0.6)	2 (8.3)	9 (3.4)	13 (2.1)
<i>Asthenic conditions</i>	7 (2.2)		4 (1.5)	11 (1.8)
Malaise	5 (1.6)		4 (1.5)	9 (1.5)
Skin & subcutaneous tissue disorders	7 (2.2)	1 (4.2)	8 (3.0)	16 (2.6)
Nervous system disorders	14 (4.3)	2 (8.3)	9 (3.4)	25 (4.1)
<i>Disturbances in consciousness NEC</i>	5 (1.6)		2 (0.7)	7 (1.1)
Hepatobiliary disorders	14 (4.3)		8 (3.0)	22 (3.6)
<i>Cholecystitis & cholelithiasis</i>	6 (1.9)		4 (1.5)	10 (1.6)
Cholelithiasis	5 (1.6)		3 (1.1)	8 (1.3)
Investigations	7 (2.2)	1 (4.2)	4 (1.5)	12 (2.0)
Musculoskeletal & connective tissue disorders	2 (0.6)		6 (2.3)	8 (1.3)
Cardiac disorders	9 (2.8)		2 (0.7)	11 (1.8)
Metabolism & nutrition disorders	6 (1.9)		3 (1.1)	9 (1.5)
Infections & infestations	2 (0.6)	1 (4.2)	5 (1.9)	8 (1.3)

Source: Sponsor's Appendix 4 - Statistical Table AE 8.1

The denominator used for serious/not serious is the total number of serious and not serious reactions within that indication; the denominator used for each serious SOC, HLT and PT is the number of serious reactions within that indication.

Four reports appeared to have a close temporal relationship to dosing with lanreotide. A 68-year-old acromegalic woman (10E19980098) who had been treated with lanreotide for several months without any problem experienced malaise, bradycardia and short loss of consciousness 48 hours after an administration of lanreotide MPF 30 mg. The symptoms recurred systematically thereafter, about 48 hours after the injections of lanreotide. A 61-year-old acromegalic woman (10E20020140) who had been treated with lanreotide 30 mg and octreotide SR 30 mg for several months without any problem experienced abdominal pain and nausea and one episode of malaise with a short loss of consciousness 48 hours after receiving her first injection of lanreotide acetate 90 mg. A 40-year-old female acromegalic patient (10E2002055) who had had an unremarkable first post injection period of lanreotide acetate 90 mg, experienced malaise, severe asthenia, excessive sweating, chest pain, dyspnea, palpitation and local reaction at injection site including edema, erythema and pruritus the day after being administered with her second monthly injection. A 55-year-old acromegalic male patient (10720020490) who had been

treated with lanreotide MPF 30 mg for about 3 years complained of cold sweats, dizziness, malaise and sleepiness 30 minutes after a lanreotide injection. The symptoms recurred after reintroduction of the treatment 17 months later.

Postmarketing Safety Aspects of Particular Interest:

Hypersensitivity

The sponsor reviewed PMS reports for possible cases of acute hypersensitivity. There were 13 cases identified, seven in patients treated for acromegaly and six in patients treated for other conditions. Five cases were serious: angioneurotic edema and tongue edema requiring hospitalization; generalized cutaneous allergic reaction with edema, urticaria and erythema that was considered significantly disabling; oral pruritus and cheilitis, where the patient requested hospitalization for the next lanreotide injection as a precautionary measure; bullous skin eruptions associated with swelling, severe leukocytoclastic vasculitis; dermatitis bullous; peripheral edema, 2 hours after the first injection recovering after treatment with hydrocortisone and antihistamines and after lanreotide was discontinued; and dermatitis exfoliative, chest pain, constipation, myalgia, face edema and eye pain two days after the first dose, continuing until shortly after lanreotide was discontinued at 3 months. The remaining 8 nonserious cases comprised three with angioneurotic and/or oral edema, three with skin and subcutaneous tissue reactions and two with nonspecific systemic symptoms. In two cases, the adverse event occurred following the first administration of lanreotide to a patient previously treated with octreotide. Seven cases occurred in patients treated with lanreotide for acromegaly; one was in a patient treated for another indication.

Local Tolerability

Reactions related to injection sites were reported frequently. There were 84 injection and infusion site reactions, and a further 5 injection site abscesses. The majority was nonserious; of the total, 19 were considered serious. The most frequent PMS report related to injection sites was injection site nodules, comprising 48 of the injection site reactions reported. Injection site pain was also reported in a total of 15 reactions.

Gastrointestinal Effects

Reactions coded to the System Organ Class, GI disorders, were the most frequent AEs reported. A total of 178 reactions were reported of which 79 were considered serious. The most frequently reported AEs relevant to gastrointestinal disorders were diarrhea (7.2%), abdominal pain (5.7%), vomiting (2.9%), nausea (2.4%) and constipation (1.6%). These occurred with similar frequency in patients treated for acromegaly and for other indications. Amongst patients treated with lanreotide for acromegaly, a high proportion of the serious GI disorders reported were manifestations of other conditions including pancreatitis, gallbladder disorders, peritoneal carcinoma and hypoglycemia. These AEs appear typical of those reported during clinical trials.

Gallbladder

In total, 27 reactions were coded to the SOC hepatobiliary disorders, of which 22 were serious. In addition, three reactions (three serious) were coded to the HLT biliary tract and gallbladder therapeutic procedures; all of these were co-manifestations in cases with other reactions coded to

the SOC of hepatobiliary disorders. The number of nonserious cases related to cholestasis or biliary disorders was higher in patients treated for acromegaly (12 unique cases) than in those treated for other or unspecified conditions (five unique cases).

Pancreas

In total, nine cases of pancreatitis have been reported of which one was fatal. All adverse events were considered related and serious. Four cases occurred in patients treated with lanreotide for acromegaly; five were in patients treated for other indications.

Glycoregulation

Five adverse events were reported in four patients treated for acromegaly. Two patients with no previous report of diabetes mellitus had adverse events related to hypoglycemia (10E20030467; 10E20040111, hypoglycemia in a neonate delivered after an exposed pregnancy, treatment with lanreotide had been discontinued some months prior to delivery). Two patients had adverse events related to hyperglycemia (10E19950082, a patient with no previous history of diabetes mellitus presented with hyperglycemia; and 21220030055, a patient with a known history of diabetes mellitus presented with diabetes mellitus inadequate control and ketoacidosis). All adverse events were considered serious but the patients recovered after appropriate treatment, with sequelae in one case. In addition, case 23320050106, involved a patient with diabetes who was advised diet and exercise because of changes in his blood glucose and glycosylated hemoglobin.

There were seven adverse events associated with glycoregulation, of which four were considered serious, occurred in patients treated for other indications. Four adverse events were considered related to hypoglycemia and three were considered related to hyperglycemia. In total, 12 postmarketing cases relevant to glycoregulation were listed in 11 patients.

Thyroid Function

A small number of postmarketing reports related to patients for whom lanreotide had been prescribed for thyroid disease, in particular thyroid eye disease or thyroid cancer, off-label indications. In patients with acromegaly there were no postmarketing reports of treatment-emergent adverse events related to thyroid function.

Cardiac Effects

Lanreotide has been marketed since 1995 and the total postmarketing exposure estimated from 1995 to 2005 is ~ 35,000 patient-years for all formulations and dose strengths combined. During this postmarketing time period, 35 cardiac adverse reactions have been reported (in any indication). Of the 35 cardiac adverse reactions, 20 were reported in acromegalic patients. Cardiac adverse reactions reported in more than one patient being treated for acromegaly were: bradycardia and sinus bradycardia, palpitations, hypertension, and edema. One further report of edema was from use of lanreotide for treatment of an unknown indication. Among these cardiac adverse reactions, several were serious including bradycardia, sinus bradycardia, palpitations and edema. In other indications there were three reports of peripheral edema, two each of hypotension, chest pain and chest discomfort and one case of palpitation, cyanosis, bradycardia, circulatory collapse and chest wall pain. Among these cardiac adverse reactions, several were

serious including chest pain, peripheral edema, hypotension, cyanosis, bradycardia, circulatory collapse and chest wall pain. The overall incidence of cardiac serious adverse reactions in any indication was 25 cases. Overall, the profile of cardiac adverse reactions was consistent with that observed for the treatment-related adverse events in the clinical studies.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary safety data used in conducting this review are:

Phase I, lanreotide acetate studies conducted in healthy subjects,

Study Number	Formulation	Purpose
A-93-52030-149	Proposed Formulation for Marketing	Definitive Safety
E-54-52030-038	Proposed Formulation for Marketing	Definitive Safety
E-55-52030-047	Proposed Formulation for Marketing	Definitive Safety

Pooled acetate studies in acromegalic patients (7 studies)

Study Number	Formulation	Purpose
E-28-52030-717 ^{1,2}	Proposed Formulation for Marketing	Definitive Efficacy / Safety
E-54-52030-081 ¹	Proposed Formulation for Marketing	Definitive Efficacy / Safety
E-28-52030-076 ²	Proposed Formulation for Marketing	Definitive Pharmacokinetics
E-88-52030-087	Proposed Formulation for Marketing	Definitive Safety
E-28-52030-709	Proposed Formulation for Marketing	Definitive Safety
E-28-52030-710	Proposed Formulation for Marketing	Definitive Safety
2-47-52030-721 ²	Proposed Formulation for Marketing and Commercial Microparticle Formulation in Europe	Definitive Cardiac Safety

1: Studies 717 and 081 are the pivotal efficacy studies and are also summarized separately for AEs

2: Studies 721, 717 and 074 are the lanreotide acetate cardiac safety studies and are summarized separately for cardiac AEs

The remaining lanreotide acetate studies in acromegalic patients were not pooled and were viewed as supportive studies only.

Study Number	Formulation	Purpose
Y-97-52030-150	Proposed Formulation for Marketing	Supportive Safety and Self Administration
A-92-52030-046	Proposed Formulation for Marketing	Supportive Safety
E-93-52030-077	Proposed Formulation for Marketing	Supportive Safety
Y-97-52030-095	Proposed Formulation for Marketing	Supportive Safety

7.2.1.1 Study type and design/patient enumeration

The tables in Section 4.2, Tables of Clinical Studies, provides a comprehensive list of all clinical studies conducted in the development of lanreotide and those studies which comprise the evaluation of safety and efficacy.

7.2.1.2 Demographics

Lanreotide Acetate Studies in Healthy Subjects

Fifty-four Caucasian subjects (27 male and 27 female) were enrolled in Study 149. The mean age of subjects in this study was 28 ± 6.3 years (range 21 to 37 years). Forty-two Caucasian subjects (21 male and 21 female) were enrolled in Study 038 and the mean subject age for this study was 25 ± 5 years (range 21 to 45 years). Twenty-seven subjects, all male Caucasians, were enrolled in Study 047. The mean subject age for this study was 26.2 ± 5.3 years (range 18 to 40 years).

Lanreotide Acetate Studies in Acromegalic Patients

Table 7.2.1.2.1 summarizes the demographic characteristics of the 416 acromegalic patients who participated in the pooled lanreotide acetate studies.

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Table 7.2.1.2.1 Patient Demographics: Acromegalic Patients in Pooled Lanreotide Acetate Studies (717, 721, 076, 081, 709, 710 and 087)

Demographic characteristic	Male (N=205)	Female (N=211)	Total (N=416) ¹
Race			
Caucasian N (%)	153 (74.6%)	176 (83.4%)	329 (79.1%)
Black N (%)	3 (1.5%)	7 (3.3%)	10 (2.4%)
Asian N (%)	8 (3.9%)	3 (1.4%)	11 (2.6%)
American Hispanic N (%)	2 (1.0%)	0 (0.0%)	2 (0.5%)
Other N (%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Not requested N (%)	38 (18.5%)	25 (11.8%)	63 (15.1%)
Age (years) at entry			
Mean±SD	50.8 ± 12.8	54.5 ± 12.7	52.7 ± 12.9
Median (range)	52.0 (19,80)	54.0 (23,84)	53.0 (19,84)
<40 N (%)	43 (21.0%)	26 (12.3%)	69 (16.6%)
40 to 65 N (%)	134 (65.4%)	141 (66.8%)	275 (66.1%)
66 to 74 N (%)	24 (11.7%)	30 (14.2%)	54 (13.0%)
≥75 N (%)	4 (2.0%)	14 (6.6%)	18 (4.3%)
Region			
US N (%)	30 (14.6%)	19 (9.0%)	49 (11.8%)
NonUS N (%)	175 (85.4%)	192 (91.0%)	367 (88.2%)
Height¹ (cm)			
Mean ± SD	178.00 ± 9.00	163.20 ± 7.20	170.00 ± 11.00
Median (range)	177.40 (152.4, 206.0)	162.00 (147.0, 180.3)	170.00 (147.0, 206.0)
Weight (kg)			
Mean ± SD	91.80 ± 16.20	75.60 ± 15.00	83.40 ± 17.60
Median (range)	89.60 (57.2, 141.0)	74.80 (41.0, 124.4)	81.00 (41.0, 141.0)
<75 N (%)	13 (6.3%)	70 (33.2%)	83 (20.0%)
75 to 96 N (%)	72 (35.1%)	59 (28.0%)	131 (31.5%)
>96 N (%)	45 (22.0%)	11 (5.2%)	56 (13.5%)
Missing N (%)	75 (36.6%)	71 (33.6%)	146 (35.0%)
Body mass index (kg/m²)			
Mean ± SD	29.00 ± 4.00	28.60 ± 5.40	28.80 ± 4.80
Median (range)	28.20 (22.31, 40.86)	28.00 (18.89, 46.87)	28.20 (18.89, 46.87)
<26 N (%)	22 (10.7%)	41 (19.4%)	63 (15.1%)
26 to 32 N (%)	51 (24.9%)	49 (23.2%)	100 (24.0%)
>32 N (%)	19 (9.3%)	24 (11.4%)	43 (10.3%)
Not requested N (%)	38 (18.5%)	25 (11.8%)	63 (15.1%)
Missing N (%)	75 (36.6%)	72 (34.1%)	147 (35.3%)
Acromegaly severity, baseline GH (ng/ml)			
<10 N (%)	86 (42.0%)	97 (46.0%)	183 (44.0%)
≥10 N (%)	41 (20.0%)	41 (19.4%)	82 (19.7%)
Missing N (%)	78 (38.0%)	73 (34.6%)	151 (36.3%)

Source: Sponsor's Appendix 4 - Statistical Table BL.1.1

¹ Height was not recorded in Study 081

² N=416: 23 patients received lanreotide in more than one study.

The demographics of the male and female participants in these studies were well matched, with the exception of the mean patient height and weight which was greater for males than for females, as expected. The mean±SD body mass index (BMI) was similar for patients of both sexes (29.00±4.00 kg/m² for males and 28.60±5.40 kg/m² for females). Enrollment of patients from US centers was 12% (49/416). Race was recorded as Caucasian for 79% of patients (329/416). No race data were recorded for 15% of patients (63/416). Patient age at entry was 40 to 65 years for 66% (275/416) patients and the average age at entry was 52.7±12.9 years. The total age range spanned 65 years (19 to 84 years of age). Severity of acromegaly at baseline was not reported for 36% (151/416) patients. Of the remaining 265 patients, baseline serum GH levels were < 10 ng/mL for 69% (183/265) patients and ≥ 10 ng/mL for 31% (82/265) patients.

The demographic characteristics of acromegalic patients in the four lanreotide Autogel studies in acromegaly that were not part of the pooled analysis are shown below in Table 7.2.1.2.2.

Table 7.2.1.2.2: Patient Demographics: Acromegalic Patients In Nonpooled Lanreotide Acetate Studies (150, 095, 077 and 046)

Demographic characteristics	Study 150 N=30		Study 095 N=12		Study 077 N=63		Study 046 ^d N=93	
Race								
Caucasian	n (%)	30 100%	12 100%	60 95.2%	93 100%			
Black	n (%)	0 0%	0 0%	0 0%	0 0%			
Asian	n (%)	0 0%	0 0%	0 0%	0 0%			
American Hispanic	n (%)	0 0%	0 0%	0 0%	0 0%			
Other	n (%)	0 0%	0 0%	3 4.8%	0 0%			
Not requested	n (%)	0 0%	0 0%	0 0%	0 0%			
Gender								
Male	n (%)	17 56.7%	8 67%	28 44%	42 45.2%			
Female	n (%)	13 43.3%	4 33%	35 56%	51 54.8%			
Age (years) at entry								
Mean±SD		49.7±13.99 ¹ 69.2±8.08 ²	57.5±9.2	48.0±14.6	50.8±13.4			
Median		51.0 ¹ 71.0 ²	56.5	48.0	53.0			
Range		29, 77 ¹ 50, 86 ²	41, 72		23, 75			

Source: Sponsor's Individual CSRs

¹ Test group (self-injection or injection by a partner)

² Control group (injection by healthcare professional)

³ ITT population

In the four nonpooled studies with study reports, all patients were enrolled in centers outside the US. All patients were Caucasian, with exception of 3 (4.8%) patients in Study 077 (race not specified). Apart from Study 095, which had only 12 patients, there were similar numbers of male and female patients in each study. Mean patient age at entry was between 48 and 57.5 years for all studies except the control group in Study 150, where the patients were older (mean age 69 years). The total age range spanned 63 years (23³ to 86 years of age).

Table 7.2.1.2.3 presents the acromegaly history for patients in the pooled lanreotide acetate studies.

Table 7.2.1.2.3 Acromegaly History: Acromegalic Patients in Pooled Lanreotide Acetate Studies (717, 721, 076, 081, 709, 710 and 087)

Baseline characteristic	Total (N=416 ³)	
Time since acromegaly diagnosis (years)	281	
n	6.60 ± 7.20	
Mean ± SD	4.40 (0.0, 42.4)	
Median (range)		
Previous SSA treatment		
Naive N (%)	42	(10.1%)
Not treated within last 3 months N (%)	69	(16.6%)
Previously treated N (%)	246	(59.1%)
Unknown ¹ N (%)	59	(14.2%)
Dopamine agonist at baseline		
Yes N (%)	96	(23.1%)
No N (%)	261	(62.7%)
Unknown ² N (%)	59	(14.2%)
Previous surgery		
Yes N (%)	164	(39.4%)
No N (%)	252	(60.6%)
Time since last previous surgery (years)	164	
n	7.00 ± 6.60	
Mean ± SD	5.00 (0.2, 33.3)	
Median (range)		
Previous radiotherapy		
Yes N (%)	112	(26.9%)
No N (%)	304	(73.1%)
Time since last radiotherapy (years)	112	
n	7.60 ± 7.40	
Mean ± SD	5.20 (0.2, 39.4)	
Median (range)		

Source: Sponsor's Appendix 4 - Statistical Table BL.1.2

¹ SSA history was not assessed in the CRF for 2 subjects in Study 717 and 8 subjects in Study 710. Due to the CRF design of Study 081, it is not possible to distinguish if the previously treated subjects were treated with dopamine agonist or SSA treatment.

² Dopamine agonist at baseline was not assessed in the CRF for 10 subjects in Study 721.

³ N=416: 23 patients received lanreotide in more than one study. See section 5.1.2 for details.

Information about the time of acromegaly diagnosis was recorded for 67.5% (281/416) patients, and was unknown for 32.5% (135/416) patients. The mean time since diagnosis was 6.60±7.20 years. The median time since acromegaly diagnosis is lower than the mean, at 4.40 years. Where SSA and dopamine agonist treatment history was adequately assessed, 69% (246/357) patients received SSA treatment in the 3 months prior to enrollment; 27% (42/357) received dopamine agonist treatment at baseline; and 12% (42/357) patients were naive to previous SSA treatment. Previous surgery had been performed in 39% (164/416) patients and previous radiotherapy in 27% (112/416) patients.

Approximately 91% of the acromegalic patients in pooled lanreotide acetate studies (717, 721, 076, 081, 709, 710 and 087) reported use of concomitant medications. The most common therapeutic classes of medication were thyroid therapy, analgesics and agents acting on the renin-angiotensin system used by 29% patients each. Medications (preferred terms) used by ≥10%

were: thyroid hormones (28%), ACE inhibitors (plain) (20%), glucocorticoids (19%), anilides (15%), dihydropyridine derivatives (15%), 3-oxoandrost-4-en derivatives (15%), beta blocking agents (selective) (14%), benzodiazepine derivatives (13%), propionic acid derivatives (11%), and platelet aggregation inhibitors excluding heparin (10%).

Antihypertensives used fell into two therapeutic classes. Beta blocking agents were used by 19% patients. Of these, beta blocking agents (selective) were the most common, used by 14% of patients. Anti-inflammatory products were used by 23% patients. Antidiabetic medication was used by 17% patients. Biguanides (8%) and sulfonamides/urea derivatives (8%) were the most common drugs used in diabetes.

A total of 98% acromegalic patients in the pooled lanreotide acetate studies reported any medical or surgical history. The most common System Organ Class (SOC) was surgical and medical procedures, reported by 68% subjects. Within this SOC, angioplasty was most commonly reported, by 26% of subjects. Vascular disorders were reported by 59% of patients, with hypertension being the most common term reported within this SOC (55.5%). Other commonly reported SOC include endocrine disorders (48%), nervous system disorders (48%), cardiac disorders (41%), metabolism and nutrition disorders (39%), respiratory, thoracic and nervous system disorders (34%), hepatobiliary disorders (32%), musculoskeletal and connective tissue disorders (32%) and general disorders and administration site conditions (30%).

The following SOC were also reported by $\geq 5\%$ of subjects, gastrointestinal disorders (29%), neoplasms benign, malignant and unspecified (including cysts and polyps) (23%), investigations (18%), infections and infestations (17%), renal and urinary disorders (14%), reproductive system and breast disorders (13%), eye disorders (11%), injury, poisoning and procedural complications (10%), blood and lymphatic system disorders (9%), immune system disorders (7%), skin and subcutaneous tissue disorders (6.5%) and ear and labyrinth disorders (5.5%).

The most common specific concomitant illness reported by subjects in pooled lanreotide acetate studies in acromegaly was cardiovascular disease, reported by 64% patients. This was followed by hypertension in 56% patients, and diabetes in 31.5% patients. Impaired hepatic function and impaired renal function were reported by 5.5% and <1% of subjects respectively.

7.2.1.3 Extent of exposure (dose/duration)

Lanreotide Acetate Studies in Healthy Subjects

A total of 107 healthy subjects received at least one dose of lanreotide acetate in Studies 149, 038 and 047. All 107 subjects received single dose injections of lanreotide acetate 60 mg (52 subjects), 90 mg (28 subjects), and 120 mg (27 subjects). Eighty of these subjects, enrolled in Studies 149 and 038, had received a single dose of lanreotide IRF prior to the single dose of lanreotide acetate.

Pooled Lanreotide Acetate Studies in Acromegalic Patients

A total of 416 unique patients received 439 lanreotide acetate long term treatment courses (at least 48 weeks) in the pooled lanreotide acetate studies in patients with acromegaly. Patient

assessments were conducted at 3-monthly intervals and investigators recorded the continuing lanreotide treatment at the date of the visit. In some studies, where the injection record is required for the data summary, only patients with complete dosing data were included (N=332). However, for certain data summaries, the sponsor imputed dosing records. Exposure to lanreotide acetate is provided in Table 7.2.1.3.1.

Table 7.2.1.3.1. Study Drug Exposure: Acromegalic Patients in Pooled Lanreotide Acetate Studies (717, 721, 076, 081, 709, 710 and 087)

Exposure Variable	Lanreotide Autogel Studies N=332	Lanreotide Autogel Studies N=416
Lanreotide Autogel cumulative dose (mg)¹		
Mean ± SD	1249.6 ± 543.9	1239.4 ± 526.2
Median	1320.0	1290
Range	[60, 3480]	[42, 3480]
Lanreotide Autogel exposure (days)²		
Mean ± SD	376.0 ± 135.2	376.8 ± 123.6
Median	365.0	385
Range	[28, 818]	[28, 818]
Average monthly lanreotide Autogel dose (mg)³		
Mean ± SD	93.0 ± 21.4	92.0 ± 23.6
Median	95.8	91.2
Range	[51.9, 126.5]	[30.9, 202.1]

Source: Sponsor's Appendix 4 - Statistical Table E.1.1 (N=332, all available dosing data), E.1.1a (N=416, all available dosing data including imputed data).

1 Study lanreotide cumulative dose (mg) = Total amount of lanreotide given cumulative across studies in this set

2 Study lanreotide exposure (days) = (Date of the last dose - date of the first dose) + 28 + 1

3 Average monthly lanreotide dose (mg) = $28 \times (\text{study drug cumulative study lanreotide dose}) / (\text{number of injections})$

Median cumulative dose of lanreotide acetate was 1250 mg over a median duration of exposure of more than one year (376 days). The median average monthly lanreotide acetate dose was 93.0 mg. When missing study medication dates are imputed for patients in Studies 721 and 065, the overall exposure data is similar, with mean cumulative dose of acetate 1240 mg over 377 days and median monthly lanreotide acetate dose of 92.0 mg. One difference was the range of average monthly dose, with 51.9 to 126.5 (N=325) compared to 30.9 to 202.1 (N=416). The maximum duration of exposure to lanreotide allows for multiple enrollments and so represents treatment in more than one pooled lanreotide acetate study.

Other Studies with Lanreotide Acetate Not Included in the Pooled Analysis

Available exposure data from the four individual adequate lanreotide acetate studies in patients with acromegaly (Studies 150, 095, 077 and 046) that were not pooled are summarized below:

- Study 150: A total of 30 patients received 60 mg (15 patients), 90 mg (8 patients) and 120 mg (7 patients) lanreotide acetate every four weeks. Exposure data were tabulated separately for the test group (patients who self-administered lanreotide acetate) and the control group (patients who received injections in the clinic). Mean duration of exposure was 259.1 ± 19.81 days for the 15 patients in the test group and 314.5 ± 11.39 days for the 15 patients in the control group with a range across all 30 patients of 248 to 347 days.
- Study 095: All 12 patients received fixed dose strengths of lanreotide acetate 90 mg every four weeks in the first phase of the study. Two patients withdrew during this period and 10 patients entered the second phase of study, during which 5 (50%) patients remained on 90 mg, 3 (30%) patients titrated to 120 mg and 2 (20%) patients titrated to 60 mg.

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- Study 077: All 63 patients received lanreotide acetate 120 mg every 8 weeks during Period 1 of the study; four patients withdrew prior to Period 2 in which patients received dosing every 8 (18 patients), 6 (16 patients) or 4 (25 patients) weeks dependent on GH level. Mean (median) duration of exposure across the 63 treated patients was 266.5 ± 75.53 (282) days with a range of 1 to 328 days.
- Study 046: A total of 97 patients received 120 mg lanreotide acetate on three dosing schedules: every 28 (13 patients), 42 (31 patients) or 56 (53 patients) days. A total of 95/97 (97.9%) patients received 8 or more weeks of therapy, 89 (91.8%) received 12 or more weeks, 78 (80.4%) received 16 or more weeks and 17 (17.5%) received 20 or more weeks of treatment.

Postmarketing Exposure to Lanreotide

Lanreotide has been marketed since 1995 and the total postmarketing exposure estimated from product sales from 1995 to 2005 is 35,000 patient-years for all formulations and dose strengths combined. Postmarketing spontaneous reports are summarized in Section 7.1.17.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Because of the world-wide marketing status, the nature of lanreotide development and the extensive number of clinical studies conducted, Ipsen presented and FDA agreed at the Pre-NDA Meeting that, given the legacy nature and expanse of clinical studies conducted in numerous indications, the clinical studies would be classified into three categories, each reporting a different level of safety and efficacy information. This categorization is described in Table 7.2.2.1.1.

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Table 7.2.2.1.1. Summary of Reporting Category and Corresponding Safety Information

Category Purpose • Description	Safety Data to be Submitted as Agreed with FDA
Category 1 <u>Full Efficacy and/or Safety</u> • All pivotal and other Autogel studies in acromegalic subjects (using the specific 24.6% formulation in the 60, 90 and 120 mg strengths intended for US market) • All pivotal efficacy studies included in the _____ (prolonged release microparticle formulation of lanreotide acetate) _____ • Pivotal clinical pharmacology studies and Autogel studies conducted in healthy volunteers (using the specific 24.6% formulation in the 60, 90 and 120 mg strengths intended for US market)	Full safety data (i.e. Adverse events, (AEs) deaths, Serious Adverse Events (SAEs), AEs leading to withdrawal and other safety evaluations).
Category 2 <u>Limited Safety</u> • Studies conducted in acromegalic subjects and healthy volunteers with other formulations of lanreotide or strengths of Autogel not intended to be registered. • Studies with non-systematic data collection	Deaths, SAEs and AEs leading to withdrawal.
Category 3 <u>Limited Safety</u> • Studies in all other indications (regardless of formulation of lanreotide or strength of Autogel)	Serious Adverse Reactions (SARs - drug related SAEs). (Presented as a textual summary)
Post Marketing Spontaneous Reports (PMS)	All adverse reactions (all indications) first reported to Ipsen prior to a selected cut-off date. (Presented as a textual summary)

Sponsor's Table 4

The basis of this review is primarily the Category 1 data but Category 2 and 3 data is briefly reviewed throughout this application.

7.2.2.2 Postmarketing experience

See Section 7.1.17.

7.2.2.3 Literature

The applicant has provided relevant references to the review of lanreotide. The clinical reviewer has also searched the medical literature for additional references to address specific issues of review, and these references are provided below, within the text of the document and in the References section at the end of this document.

1 Page(s) Withheld

 ✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

7.2.3 Adequacy of Overall Clinical Experience

A total of 416 unique patients received 439 lanreotide acetate long term treatment courses (at least 48 weeks) in the pooled lanreotide acetate studies in patients with acromegaly. While the ICH E1 guidance mentions a minimum total exposure of about 1500 subjects, with 300-600 for 6 months and 100 for one year for products intended to treat chronic conditions, lanreotide for the treatment of acromegaly is an orphan indication. In this reviewer's opinion, the lanreotide clinical experience regarding extent and duration of exposure needed to assess safety is adequate.

The design of studies intended to demonstrate the safety and efficacy of lanreotide for the indications proposed is adequate. The majority of the studies were open-label; blinding techniques were used in Studies 717 and 076.

The applicant evaluated effects of lanreotide in older subjects and in subjects with hepatic insufficiency but provides very limited clinical exposure data on patients with renal impairment or non-Caucasians. Potential class effects on cholelithiasis and cardiac valvulopathy were adequately assessed in this application.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see Dr. Yao's toxicology review for details of the adequacy of preclinical testing of lanreotide. In general, preclinical testing for lanreotide was adequate.

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing performed routinely in the studies was adequate to elicit adverse events and other clinical, electrocardiographic and laboratory parameters that could represent a safety concern.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Dr. Jayabharathi Vaidyanathan's Biopharmacology review and Section 5 for details on the adequacy of the lanreotide PK evaluation program. The overall program is adequate to learn about the PK of lanreotide and interactions with relevant classes of drugs. There were limited (only 2) patients with severe hepatic impairment evaluated in the PK studies. Labeling will reflect a recommendation to decrease the starting dose to 60 mg in patients with moderate to severe renal impairment and moderate to severe hepatic impairment.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has adequately collected data on potential adverse events that could be resulting from exposure to Lanreotide Acetate. For this purpose the applicant has conducted a QT interval study, a study evaluating the risk of new or worsening cardiac valvulopathy and/or bradycardia, and a study evaluating the onset of cholelithiasis with the use of lanreotide. 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. The assessments of the gallbladder in clinical studies of lanreotide acetate and other formulations showed evidence consistent with the known propensity of SSAs to reduce gallbladder motility.

7.2.8 Assessment of Quality and Completeness of Data

The overall assessment of the application and study reports regarding the safety of lanreotide is that sufficient data to assess risk to benefit profile of lanreotide has been provided. Data that is complete and of good quality is available for review, and the applicant provided in the study report important analyses of the safety data.

7.2.9 Additional Submissions, Including Safety Update

This 120-day safety update provides additional information from newly reported studies not available at the time of the original submission (see Table 7.2.9.1), and for spontaneous reports received between 01 October 2005 (the NDA data cut off date) and 31 October 2006 (the 120-day data cut off date).

Table 7.2.9.1 Clinical Studies Included in the 120-Day Safety Update

Study Number	Formulation and dosing	Hereafter referred to as
Category 1 adequate studies with the dose strength and dosing interval intended for the US market		
E-54-52030-073/E-54-52030-094	Lanreotide Autogel - 60, 90 or 120 mg / 28 days	073/094
Other Category 1 studies		
A-92-52030-168	Lanreotide Autogel - 120 mg / 28, 42 or 56 days	168
A-92-52030-169	Lanreotide Autogel - 120 mg / 28, 42 or 56 days	169
A-93-52030-080	Lanreotide Autogel - 120 mg / 28, 42 or 56 days	080
A-96-52030-155	Lanreotide Autogel - 60, 90, 120 mg / 28 days	155
A-94-52030-072	Lanreotide Autogel - 60, 90 or 120 mg / 28 days	072
Category 2		
2-55-52030-724	Lanreotide immediate release formulation (IRF) then a single 240 mg dose of the — lanreotide formulation	724
Category 3		
	No Studies Reported	

Clinical Studies

Category 1 studies were defined as lanreotide acetate studies in acromegaly or healthy subjects. This update contains safety information, including all reported adverse events (AEs), relating to

48 new unique acromegalic patients treated with lanreotide acetate in Study 080 and Study 155. Safety data is also presented for 140 acromegalic patients in Studies 073/094, 168, 169 and 072. These are follow-up studies and these patients were included in the original NDA 22-074.

Category 2 was defined as studies with other formulations of lanreotide in acromegaly or in healthy subjects. Study 724 is the only newly reported study from this category. This study was conducted in 24 healthy subjects, 16 of whom received lanreotide immediate release formulation (IRF) followed by a single 240 mg dose of the — lanreotide formulation, compared to eight who received placebo. Information presented for studies in this category focuses on serious adverse events (SAEs), with other relevant findings summarized where applicable.

Category 3 was defined as studies with any formulation of lanreotide in other indications. There are no newly reported studies in Category 3.

Study 073 was a phase III study conducted in acromegalic patients who had completed the previous phase III Study E-28-52030-710 in France. The primary objective of the study was to document the long term efficacy of lanreotide acetate, administered at titrated dose strengths (60, 90 or 120 mg) every 28 days, in terms of mean growth hormone (GH) levels. Twelve subcutaneous (s.c.) injections of lanreotide acetate were administered to each patient every 28 days. Dose strengths of lanreotide acetate (60, 90 or 120 mg) were determined according to the optimal hormonal control of the patients.

Study 094 was a phase III study conducted in acromegalic patients who had completed the previous phase III Study 073 in France. The dose of the first lanreotide acetate injection was the same as the last dose received in the previous Study 073.

Study 168 was a phase III study conducted in acromegalic patients who had completed Study E-28-52030-710 in Spain. Formal objectives were not defined for this extension.

Study 169 was a phase III study conducted in acromegalic patients who had completed the previous phase III Study A-92-52030-046. The primary objective of the study was to evaluate the comparative therapeutic efficacy of lanreotide acetate, the prolonged release form of the somatostatin analog (SSA) lanreotide, in acromegalic patients who were responders to lanreotide MPF. Patients were treated with the same dose strength and dosage interval they received in Study A-92-52030-046: lanreotide acetate 120 mg every 28, 42 or 56 days dependent on the treatment rule followed with lanreotide MPF prior to inclusion into Study A-92-52030-046.

Study 080 was an open phase III, multicenter study conducted in acromegalic patients previously treated with octreotide LAR. The primary objective of the study was to evaluate the efficacy of lanreotide acetate 120 mg on the control of GH secretion in acromegalic patients previously treated with octreotide LAR.

Study 155 was an open phase III multicenter study conducted in acromegalic patients, who had previously received or not received treatment with SSAs. The main objective of the study was to evaluate efficacy of injections of lanreotide acetate, administered every 28 days, expressed as

percentage of patients with normal (age adjusted) levels of insulin-like growth factor-1 (IGF-1) at the end of the study.

Study 072 was a phase III study conducted in 22 acromegalic patients who had completed the previous phase III Study E-28-52030-710 in Germany. The primary objective of the study was to demonstrate that after repeated deep s.c. administrations of lanreotide acetate at dose strengths 60, 90 or 120 mg every 28 days, individually titrated in the previous Study E-28-52030-710, local and systemic tolerance, standard hematology and biochemistry analysis and ultrasound examination of gallbladder, doses of insulin or other antidiabetic treatment in diabetic patients were maintained. Due to difficulties with the conduct of the study this is considered a nonGCP study.

Study 724 was a phase I study conducted in healthy male and female subjects. The primary objective of the study was to evaluate the pharmacokinetic (PK) profile of lanreotide after a single 240 mg deep s.c. injection of lanreotide formulation. This formulation was developed and the intent of the study was to determine if the PK characteristics of this development formulation were suitable of this development formulation were

Treatment Emergent Adverse Events (TEAE)

In pooled study 073/094, the SOCs general disorders and administration site conditions and hepatobiliary disorders were the two most common type of TEAE, both reported by 6/14 patients. The most commonly reported individual TEAE was cholelithiasis, which was experienced by 5/14 patients. Diarrhea, white blood cell count increased and metrorrhagia were all experienced by 2/14 patients. The most commonly reported individual TEAEs observed were generally consistent with the most common TEAEs reported within the original submission.

Data from the four nonpooled Category 1 lanreotide acetate Studies 168, 169, 080 and 155 supported that of both the data presented in the original submission and the pooled analysis Studies 073/094, in that the gastrointestinal (GI) disorders, mainly diarrhea, abdominal pain and flatulence were among the most commonly reported TEAEs.

TEAEs that led to withdrawal

A TEAE that led to withdrawal was reported by one acromegalic patient in the pooled Category 1 lanreotide acetate Studies 073/094. This patient (000845) presented with a series of TEAEs, all of which were not considered related to study drug. This was a fatal SAE and is described in more detail in the section below.

In the five nonpooled Category 1 lanreotide acetate studies in acromegalic patients (Studies 168, 169, 080, 155 and 072), 1.7% (3/174) patients reported an AE leading to withdrawal (all three occurred in Study 169). One of these was considered serious and is considered in more detail in the SAE section below.

- Patient 000411, a 47 year old male who received lanreotide acetate 120 mg every 56 days, presented with severe headaches. Causality was specified as related to the study drug.

- Patient 001165, a 44 year old female who received lanreotide acetate 120 mg every 42 days presented with “neoplasm benign cysts”, of mild intensity. Causality was specified as not related to the study drug.

Deaths

There were two deaths in the Category 1 studies:

- Studies 073/094, Patient 000845 (fatal pulmonary embolism)
This 67 year old female, with a medical history of pulmonary and cardiovascular disorders, joined Study 094 after completing Study 073 and received one injection of lanreotide acetate 120 mg on 18 December 2000. The patient died on _____, due to a severe pulmonary embolism. Causality was specified as not related to the study drug, and the event was recorded as a withdrawal from the study as result of death.
- Study 072, Patient 000776 (fatal breast cancer)

Serious Adverse Events (SAE)

At least one SAE was reported by 29 of the 188 patients in the Category 1 studies (15.4%). SAEs were considered related to lanreotide in 5/188 patients (2.7%). The SAEs that may have been related to lanreotide include

1. Patient 000634, a 57 year old woman previously included in Studies E-28-52030-709/710, joined Study 073 on 30 November 1999 and subsequently received lanreotide acetate 120 mg. Presenting with biliary colic on 30 June 2000, the patient was admitted to hospital on _____. The following day the patient underwent cholecystectomy by celioscopy and was subsequently discharged from hospital on _____.
2. Patient 000413, a 68 year old female, received injections of lanreotide acetate 120 mg every 56 days. This patient presented with cholecystitis, of severe intensity and also underwent a cholestectomy.
3. Patient 001144, a 71 year old female, who received lanreotide acetate 120 mg every 42 days presented with acute pancreatitis of severe intensity and diabetes mellitus inadequate control of moderate intensity.
4. Patient 000931 who received an unknown dose strength of lanreotide acetate experienced two SAEs (gallbladder perforation and peritonitis perforative) both of severe intensity.
5. Patient 000411, a 47 year old male, who received lanreotide acetate 120 mg every 56 days presented with a pituitary tumor benign of severe intensity. Causality was specified as not assessable so was therefore considered as related to the study drug, and the patient was subsequently removed from the study following receipt of radiotherapy.

Postmarketing Exposure

The total postmarketing exposure estimated from product sales between 01 October 2005 to 31 October 2006 is over 8000 patient years for all formulations and dose strengths combined, including more than 6500 patient years of exposure to lanreotide acetate. During the 120-day safety update period, there were 48 new PMS reports (105 reactions). Of these, 21 reports (53 reactions) were in acromegalic patients, nine reports (13 reactions) were for unspecified indications, and 18 reports (39 reactions) were in other indications: 56 reactions were serious and 49 reactions were not serious. There were four updated PMS reports (seven reactions).

In acromegalic patients, the most frequent reactions were of the SOC, GI disorders (17 reactions). There were four reactions involving GI and abdominal pain, four involving diarrhea, and four involving nausea and vomiting symptoms. Other SOC with four or more reactions in acromegalic patients were general disorders and administration site conditions (10 reactions, including five injection and infusion site reactions), nervous system disorders (seven reactions, including three disturbances in consciousness), skin and subcutaneous tissue disorders (three reactions), investigations (four reactions), metabolism and nutrition disorders (three reactions), vascular disorders (one reaction) and hepatobiliary disorders (three reactions). In every other SOC, HLT or PT there were fewer than four reactions in total.

In the total PMS reports across all indications, the most frequent reactions were also of the SOC GI disorders (27 reactions, including eight GI and abdominal pains, seven diarrhea). The SOC general disorders and administration site conditions (26 reactions, including 18 injection site reactions) and nervous system disorders (14 reactions including seven disturbances in consciousness) were next most frequently reported. The SOC hepatobiliary disorders were reported less frequently (four reactions), however the proportion of reactions was greater in acromegalic patients, 3/53 reactions (5.7%), than in those treated for not specified or other indications, 1/52 reactions (1.9%).

The profile of adverse reactions was consistent with that observed for treatment-related TEAEs in the clinical studies in NDA 22-074, those reported most frequently being GI disorders, and general disorders and administration site conditions.

Safety Aspects of Particular Interest

Cardiac safety

The findings from clinical studies during the 120-day safety update reporting period were consistent with those reported in NDA 22-074. Overall, cardiac AEs were uncommon in Category 1 lanreotide acetate studies, affecting only two patients in Studies 073/094 and 12 patients in Studies 168, 169, 080, 155 and 072. The most frequent were hypertension in five patients, followed by atrial fibrillation, edema peripheral and flushing, all of which were reported by two patients.

Local tolerability

In Studies 073/094 there were four AEs that could represent local reactions to lanreotide injection. The events were injection site induration, injection site nodule, injection site pain and induration. In the nonpooled studies, there were 13 AEs that could represent local reactions to lanreotide injection, all from Study 080 (11 injection site pain, one injection site swelling, one injection site pruritus). PMS reports made during the 120-day safety update period showed 18 injection and infusion site reactions and two injection site abscesses.

Hypersensitivity

The PMS reports were identified that may have been hypersensitivity reactions, one in a patient treated for acromegaly and one in a patient treated for other indications. Both reactions were serious. An acromegalic patient (20120060398) previously treated with sandostatin suffered pain

and inflammation in the right wrist and forearm after a single injection of lanreotide acetate that spontaneously resolved. A patient treated for endocrine tumor of the pancreas (10E20060284) suffered urticarial rash at the injection site on the third injection of lanreotide acetate; he recovered completely with antihistamines.

Gastrointestinal Effects

Data from the Category 1 lanreotide acetate Studies supported the data presented in the original submission, in that the gastrointestinal (GI) disorders, mainly diarrhea, abdominal pain and flatulence were among the most commonly reported TEAEs.

Gallbladder and Pancreas

Cholecystitis and cholelithiasis AEs were reported by 11.7% (22/188) acromegalic patients treated with lanreotide acetate. SAEs involving the gallbladder or pancreas were reported by five patients: biliary colic (001235), cholecystectomy (000634, 000413), gallbladder perforation with perforative peritonitis (000931), and severe acute pancreatitis (001144). In ongoing Study A-94-52030-163, patient 01-01 developed a worsening of cholelithiasis that required cholecystectomy. Three cases of cholelithiasis occurred during Study 724, where healthy subjects received a single 240 mg dose of the — lanreotide formulation. One required a cholecystectomy, and two were followed to their eventual resolution after study completion.

Among the PMS reports related to the gallbladder during the 120-day safety update period, four reactions were coded to the SOC hepatobiliary disorders, of which two were serious.

There was one serious reaction in an acromegalic patient (10E20060999, bile duct stone, a co-manifestation with pancreatitis) and one serious reaction in a patient treated for a not specified indication (23320051199, cholelithiasis). There were two not serious reactions in acromegalic patients (one cholelithiasis and one gallbladder disorder). There were four PMS cases relevant to the pancreas reported during the 120-day safety update period. Two reactions were in acromegalic patients (10E20060999, pancreatitis and 10E20060466, pancreatitis acute), one in a patient treated for a not specified indication (23320051199, pancreatitis acute) and one in a patient treated for another indication (10I20061604, pancreatitis).

Glycoregulation

In the lanreotide acetate studies there were seven TEAEs relating to glycoregulation. In Studies 073/094 there were two AEs: one case of diabetes mellitus and one case of hyperglycemia. In Study 168 there was one case of diabetic retinopathy. In Study 169 there were three cases relating to glycoregulation: one case of diabetes mellitus, one SAE of diabetes mellitus inadequate control (patient 001144), and one case of hypoglycemia. In Study 072 there was one AE of HbA1c increased. There were no TEAEs relating to glycoregulation in Studies 080 and 155. There were two PMS reports relevant to glycoregulation during the 120-day safety update period.

Thyroid and Pituitary

There were no TEAEs relevant to thyroid and pituitary function in Studies 073/094 155, 168 and 080. In Study 072 there was one event of hypopituitarism which was considered not related to the study drug (patient 001021, SAE of Addison crisis). In Study 169 there was one event of secondary hypothyroidism and one SAE of benign pituitary tumor.