

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-074

MEDICAL REVIEW(S)

8/30/07

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



OFFICE DIRECTOR'S SIGNATORY MEMORANDUM

Date: Thursday, August 30, 2007
NDA: 22-074
Sponsor: Beaufour Ipsen Pharma
Proprietary Name: Somatuline (lanreotide) Depot injection; 60, 90 and 120 mg
Author: Robert J. Meyer, MD, Director, ODE II

Introduction: Given my concurrence with the comprehensive and well reasoned Director's memo from the division (Dr. Mary Parks, Director of the Division of Metabolic and Endocrine Products), this signatory memorandum will be brief. The reader is referred to Dr. Parks' memorandum and the various discipline reviews for more comprehensive information.

Lanreotide is a synthetic polypeptide that is an analogue of somatostatin. It is proposed to treat acromegaly, a condition of excessive growth hormone (GH) release from the pituitary gland. Acromegaly usually results from a benign adenoma most frequently occurring in adult patients in their midyears of life (30's to 50's). While surgery and/or radiation are the primary first line treatments for this condition, there is a need for medical measures beyond these therapies. This medical need is a result of the fact that some patients are not candidates for surgery or radiation and, even if they are, not all patients reach full control of their disease with these measures. Hence, medications, including somatostatin-analogues, are used based on biochemical parameters (e.g., excessive GH levels).

Somatostatin is a naturally occurring peptide with pleiotropic actions. Two particular somatostatin receptors – SST2 and SST5 – are present on GH-producing pituitary tumors. Somatostatin can downward modulate the release of GH by these tumors through stimulating these receptors. Lanreotide has reasonable avidity for these receptors and hence is expected to lower GH in acromegaly. Lanreotide is widely available outside the US,

This current application is for a long-acting formulation of lanreotide accomplished by creating a supersaturated solution of lanreotide that interacts with physiologic fluid to slowly release the drug over time. The drug product is intended to be given as a deep subcutaneous injection at 90 mg every 4 weeks via single use prefilled syringes. Lanreotide dosing can be titrated after 3 months (i.e., 3 doses), based on GH and insulin-like growth factor-1 (IGF-1) response and tolerability (IGF-1 is a secondary effector of GH's effects on somatic tissues).

Acromegaly is an orphan indication and, indeed, this drug has been designated as an orphan drug. Amongst other things, this means PREA does not apply and hence there will be no deferrals or phase 4 commitments for pediatric studies.

Chemistry/Manufacturing and Controls:

No outstanding issues have been identified. The review included a microbiology assessment and a review of the related-DMFs. The drug substance and the drug product have been deemed by ONDQA to be acceptable. The drug was given a 24-month expiry if kept refrigerated (2 to 8 degrees C)

Preclinical: Two chronic toxicity studies formed the basis of this application, one in dogs and one in rats. These studies supplemented studies previously done —
— The major findings, outside of predictable physiologic responses, were local tissue site reactions, including fibrosis and granulomas, but these were occurred at higher exposures than proposed clinically (though only about 2x for the dogs).

There was no genotoxic potential demonstrated for lanreotide, but the carcinogenicity studies were positive with cutaneous fibrosarcomas and fibrous histiocytomas seen in mice. However, this study was done with daily dosing (unlike the clinical dosing of monthly) and these lesions occurred at doses that resulted in higher systemic levels (3x) compared to those clinically. For these reasons, it appears doubtful that these findings are of significant clinical concern.

There was a debate over the pregnancy classification in the PT team, since the drug showed embryocidal effects in reproductive toxicity testing. However, with further review by the team (including tertiary input), the final recommendation is for a category C, based on the fact that the effects in the pups is presumably caused by a GH/IGF-1 deficiency in the mothers resulting from pharmacology of the drug, whereas in acromegaly, the intent of treatment is to lower GH/IGF-1 back towards normal levels. Given the data and the recommendations of the team, I concur with the category C designation.

Biopharmaceutics: The formulation appears to result in a satisfactory long-term, slow release characteristic, with the $T_{1/2}$ terminal = 23 – 30 days. While there is some early peak, the release does not result in an undue early bolus. This drug, like other polypeptides molecules, does not undergo usual hepatic metabolic degradation. It therefore has a low potential for direct drug-drug metabolic interactions. However, due

to previous findings with other somatostatin-like drugs, an interaction study was done with coumadin and with cyclosporine A. The latter study showed a small, but potentially relevant effect on cyclosporine levels (19% decrement in AUC), perhaps due to altered absorption. This is reflected in the labeling. No other significant issues were found in the clinical pharmacology review.

Efficacy: As per Dr. Craig's review (and Dr. Parks' summary memo), the sponsor has provided reasonable, substantial data to support efficacy and to define dosing recommendations for the labeling. The initial phase of study of 717 was a dose-ranging, placebo-controlled 4 week period (i.e., assessment was just before a second dose). The primary endpoint assessed at the end of this period was the proportion of patients achieving a reduction in mean GH level by 50%. By this assessment, lanreotide led to a 63% overall response at 4 weeks, compared to 0% in placebo. There was not strict dose ordering seen in the doses studied (60, 90 and 120 mg), but patients assigned to the highest, 120 mg dose showed a 90% response versus 52 and 44% respectively for the 60 and 90 mg group. This study continued on without a control group (so that all patients would be treated) into a titration phase that also examined durability of response. This study supports that patients with acromegaly can obtain substantial reductions in GH and IGF-1 levels with lanreotide dosed every 4 weeks and that the response is durable. The study was not designed to rigorously assess long-term outcomes, but did attempt to assess the attenuation of symptoms and signs of GH excess (headache, fatigue, sweating, swelling of limbs, etc) in relation to therapy. While many symptoms indeed substantially abated over time compared to baseline, the effect on symptoms was not so clear at 4-weeks in the placebo-controlled portion of the study. Therefore, without controlled data against which to judge these subjective results in the open-label period of the study, one cannot fully conclude the findings represent a result of drug treatment.

The findings of study 717 were further supported by an uncontrolled, open label study allowing for titration based on biochemical response. This study enrolled patients with more deviations in IGF-1 and with a higher proportion of prior therapy, compared to study 717. At the end of study, 43% of the patients had obtained normal IGF-1 levels and mean GH levels fell from 6.2 ng/mL at baseline to an average of 1.5 ng/mL at the end of the study. This study adds additional dosing information, in addition to further supporting the efficacy of lanreotide in patients who have inadequately biochemical control despite previous therapies.

Safety: This product appears to have the profile expected for a somatostatin-analogue, with the most common adverse events being diarrhea, abdominal pain, flatulence, bradycardia and anemia. In addition to those patients with reports of frank bradycardia, many more patients had decreases in heart rate not meeting criteria for bradycardia and which were not symptomatic. This consequence of therapy bears mention in labeling, particularly for susceptible patients (e.g., patients on beta blockers). Due to somatostatin's known effects on the gall bladder, lanreotide is associated with cholelithiasis and related events, with an overall rate of approximately 20% for cholelithiasis in the safety database. This is not, however, out of bounds with what is seen with other approved analogues. This class of drugs is also known to lead

mechanistically to dysglycemic events (either hyper and/or hypoglycemia), as somatostatin alters both insulin and glucagon secretion. Such events were indeed observed in the clinical trials.

One notable safety issue, discussed in the introduction,

_____ was the question of differential cardiac valvular effects for this treatment compared to other approved analogues. In answer to FDA's concern, the sponsor conducted a head-to-head echocardiography study of lanreotide against octreotide, since a long-term placebo-controlled study would not be ethically acceptable. The rate of new or worsening valvular regurgitation at any valve was 34% (28 out of 82) with lanreotide and 33% (27 out of 82) with octreotide as documented by echo doppler. While one cannot conclude there is no drug role in changes seen in valvular regurgitation, one can reasonably conclude that there is no differential effect for lanreotide vs. octreotide (95% CI for the risk ratio were 0.71 – 1.39 with a point estimate of 0.99) based on these results and GH excess does otherwise effect cardiac function. Given the findings of this safety study, it appears the issue of a differential untoward effect of lanreotide has been reasonably addressed.

Conclusions:

Consistent with the recommendations of the various review teams, including the clinical team, I find that Beaufour Ipsen has presented sufficient information to allow FDA to conclude that there is a reasonable benefit - risk profile for this drug in the treatment of acromegaly, based on its demonstrated effects in rectifying the important biochemical mediators of the disease and the less definitively demonstrated effects on signs and symptoms.

_____ We do not know that medical treatment of acromegaly with lanreotide or any other medical treatment changes long-term outcomes, such as premature mortality, but given the size of the patient population and the ethics of leaving individuals uncontrolled, a study to define such effects would be infeasible. The indication for patients with acromegaly will be limited to patients who either cannot undergo surgery and/or radiation, or who have undergone these measures and failed, since surgery and radiation are first line therapies and provide potentially definitive results.

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/s/

Robert Meyer
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MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002DIVISION DIRECTOR'S MEMO

NDA	22-074
Drug Product	Somatuline (lanreotide acetate)
Applicant	Beaufour Ipsen Pharma
Indication	Acromegaly
Date of Submission	October 27, 2006

1. INTRODUCTION

Acromegaly is a disorder in adults resulting from the abnormal secretion of growth hormone (GH). The majority of cases are due to a benign, monoclonal pituitary adenoma that secretes only GH; however, approximately 25% may co-secrete prolactin (PRL). Rarer causes of acromegaly include excess stimulation of GH secretion by GH-releasing hormone (GHRH), extrapituitary ectopic secretion of GH, or familial syndromes with associated pituitary adenomas (e.g., MEN-I, McCune Albright, Carney's complex).

GH binds to the GH receptor expressed primarily in the liver and in cartilage. It induces the synthesis of insulin-like growth factor I (IGF-1) which through endocrine and autocrine activity, mediates most of the effects of GH. GH and IGF-1 receptors are also located on cardiac myocytes. Much of the clinical signs and symptoms associated with acromegaly can be attributed to the excessive stimulation of tissue growth or function by GH/IGF-1 including enlargement of acral bones, soft-tissue swelling, arthralgias, prognathism, organomegaly, sleep apnea, glucose intolerance or diabetes, hypertension and cardiac failure. In addition, pituitary tumor enlargement may encroach on the optic nerve causing visual impairment and mass effect on other pituitary cells may result in multiple endocrine defects including hypothyroidism, hypogonadism, and diabetes insipidus. Retrospective cohort studies have observed a higher rate of death due to colon cancer in acromegalic patients. Premature death has also been linked to increased GH levels, and more recently IGF-1 levels, and control of GH and IGF-1 secretion is significantly correlated with normalized mortality rates in acromegaly. However, much of these data are derived from cohort studies employing older immunoassays for both biomarkers. Additional studies with more recent assay methodologies are needed to better determine the degree of risk of mortality and other co-morbidities and the level of GH/IGF-1 elevation.

The disease is insidious and often goes undiagnosed for years. Macroadenomas are present in > 70% of patients at time of diagnosis and are more common in men than women which may relate to the reporting of hypogonadism (as amenorrhea or menstrual irregularities) sooner in the latter population. The diagnosis requires biochemical testing but shortcomings of tests are present which include the pulsatile nature of GH release, inconsistent correlation of GH and IGF-1 levels, assay sensitivities and lack of standardization of tests. Typically, an oral glucose tolerance test (OGTT) with subsequent measurement of GH and IGF-1 levels is performed for diagnosis and assessment of therapeutic intervention. OGTT

ng/mL and normal IGF-1 levels standardized for age. 27% of patients reached this goal after 2 injections every 14 days. Increasing the frequency of injection to every 7 to 10 days further increased the percentage achieving goal resulting in an overall 35% of patients achieving a GH \leq 2.5 ng/mL and normal IGF-1 level. A clinical safety concern was raised in an echocardiographic substudy of 18-months' duration. Twenty-two patients were enrolled in this substudy. Of these, 18 (82%) developed new or worsening retrograde transvalvular flow on echo. Consequently, the applicant was informed that an echo study comparing lanreotide to octreotide was required to address this safety concern.



Lanreotide MPF is approved and marketed in approximately 50 countries.

This application proposes the marketing of a new formulation for lanreotide acetate which can be administered every 4 weeks. As per Dr. Craig's review, this formulation is registered in approximately 40 countries for the treatment of acromegaly and carcinoid. The clinical development program for this NDA included two pivotal studies using the proposed formulation in 171 acromegalic patients. Additional data from the studies previously reviewed under _____ were also included in this application. In addition, an active-control study of 12-months' duration evaluating valvular changes in acromegalic patients treated with either lanreotide or octreotide was submitted to address the clinical safety deficiency. In total, there were 416 unique patients who received lanreotide acetate and whose data contributed to the findings of safety and efficacy in this application.

3. CHEMISTRY, MANUFACTURING, AND CONTROL/MICROBIOLOGY

_____ For this application, a different drug formulation has been manufactured that contains only the drug substance and water as a supersaturated solution contained in syringes. After subcutaneous injection, a reaction under physiologic conditions results in the formation of a depot with sustained release properties. _____

Lanreotide is available in 3 strengths (30, 60, and 90 mg - free base) in sterile, ready-to-use, pre-filled syringes for one time use. Dr. Niu's review thoroughly discusses the CMC issues and has found this application acceptable.

_____ sterilization is achieved _____ which has minimal effect on product purity or potency. Microbiology review has found the drug substance, drug product and manufacturing process acceptable for approval.

Stability testing was performed under recommended storage conditions (2 to 8°C) and accelerated conditions for up to 24 months. Based on these tests an expiry date and shelf life of 24 months is supported.

CGMP inspection of manufacturing sites for drug substance, drug product, and testing sites were found to be acceptable by the Office of Compliance.

4. PHARMACOLOGY/TOXICOLOGY

Many of the toxicology studies were performed with the IPF or MPF lanreotide and reviewed under — . For this NDA, the applicant submitted two chronic toxicity studies using the proposed formulation. Somatuline was administered every 14 days sc in rats and dogs for 26 weeks and achieved higher exposures than studies performed with the previous formulations. In both animals, the predominant clinical signs involved injection site reactions. Overall, no new toxicity was identified with these two additional studies.

There was no evidence of significant HERG channel inhibition in human embryonic kidney cells. No adverse effects on cardiac action potential were noted in isolated canine Purkinje fibers. Several *in vivo* studies were conducted with extensively evaluated changes in vital signs and telemetry monitoring was included two studies. Lanreotide was not associated with QTc prolongation or increased arrhythmia. Bradycardia was observed in a dog study involving 20 or 80 ug/kg iv doses of lanreotide.

—, carcinogenicity evaluations were requested — in addition, the applicant was informed that genetic and repro toxicity test batteries may be necessary — These studies were performed — In the two 2-year carcinogenicity studies, subcutaneous tumors (fibrosarcomas and histiocytomas) were observed at the injection site. Both species tested were treated with daily injections of lanreotide acetate which were thought to contribute to the tumor findings. As the clinical dosing is once-monthly, the animal findings were considered not clinically relevant.

A notable recommendation from Pharmacology/Toxicology is the change for Pregnancy Category Labeling from — in Dr. Yao's review dated August 21, 2007. This recommendation is based on repro tox studies in rats and rabbits at doses below human clinical exposure which showed decreased fetal survival and increased skeletal malformations. This initial recommendation has been reviewed by Dr. Abigail Jacobs. In her memo also dated August 21, 2007, she recommends that lanreotide receive a pregnancy category C label based on the following:

- impaired fertility in animal studies may reflect GH and IGF-1 deficiency secondary to drug effect. Since clinical use in acromegalic patients may not result in a GH/IGF-1 deficiency state, it is not certain that these animal findings can be extrapolated to the patient population intended for use.
- lanreotide caused decreased maternal weight in the animal studies which may account for skeletal findings and growth retardation in the offspring

Dr. Jacobs has discussed her findings with Drs. Yao and Davis-Bruno who also concur that the pregnancy category can be "C".

5. CLINICAL PHARMACOLOGY

The Office of Clinical Pharmacology has recommended approval without any additional Phase 4 studies.

The current formulation proposed for marketing forms a depot at the site of injection with a minimal initial burst release followed by a more sustained release of drug with a terminal half-life of approximately 23-30 days. AUC in the initial 2 days after administration was only ~11% of total AUC arguing against any dose dumping. This is an important finding as another somatostatin analogue — with markedly increased C_{max} was associated with preclinical safety findings that were suggestive of cardiac toxicity (sudden death in one monkey without histopathological finding and myocardial fibrosis in animals sacrificed after chronic dosing).

PK and PD evaluations were conducted in healthy and acromegalic study populations. After repeat dosing, lanreotide exhibited linear pK without differences in either study populations. There were no significant differences in pK by age. Higher C_{max} levels were achieved in males versus females which may reflect differences in adiposity; however, repeat dosing did not show any differences in exposures by gender. No dose adjustments are recommended by age, gender, or body weight.

The applicant only evaluated the pK profile in patients with end-stage renal disease. In ESRD, exposure is increased by approximately 2 to 4-fold. Only 3 patients with mild to moderate renal impairment were studied in the clinical trials. OCP believes there are sufficient data from other studies to extrapolate exposure in the mild-to-moderate renal impairment population and has recommended that dosing be initiated at 60 mg in this population. Should the applicant request a higher starting dose, a specific pK study should be performed in the mild-to-moderately impaired renal patient population.

Similarly, single dose pK studies were performed in patients with different degrees of hepatic impairment. There was marked variability and overlap in C_{max} and AUC across the different patient groups and the small sample sizes preclude a definitive conclusion on these findings; however, there was a trend towards increased exposure in patients with moderate and severe hepatic impairment compared to healthy subjects. A lower starting dose is also recommended in this patient population.

Specific recommendations are proposed for concomitant use of cyclosporine, anti-diabetic therapies, and bradycardia-inducing drugs. These recommendations are based on studies providing evidence of an interaction (cyclosporine) or are based on the pharmacologic effect of somatostatin that might potentiate the drug's risk profile (bradycardia and dysglycemia).

As noted earlier, this application includes studies employing previous formulations of lanreotide. No comparative pK studies were conducted across the different formulations; however, Section 10.1.6 of Dr. Craig's review summarizes Study 709 which evaluated efficacy in patients treated with lanreotide 30 mg MPF who were then treated with this proposed formulation administered at fixed doses of 60, 90, or 120 mg for 3 sc injections. Mean GH levels achieved were similar with both formulations which would suggest that any difference in pK profiles among the different formulations (which would be expected) does not appear to alter efficacy (and likely safety).

6. CLINICAL MICROBIOLOGY

Not applicable.

7. CLINICAL/STATISTICAL

My memo will focus primarily on the two pivotal studies and the echocardiographic sandostatin-controlled study. Please see Dr. Craig's review for details of all trials submitted in support of this application. In particular Appendix 10 provides the individual study reports for each trial.

Tables 4.2.1 and 4.2.2 from Section 4.1 of Dr. Craig's review summarize the two pivotal studies and the seven studies considered in the safety review. The two pivotal studies supporting efficacy results were Study 717 and Study 081. Both studies used the to-be-marketed formulation at all three proposed doses and were approximately one-year studies; however, the study designs were distinct enough to preclude pooling data for efficacy analysis. Of note, unlike Sandostatin LAR programs, patients in the lanreotide program who were naïve to drug therapy did not receive a test dose of octreotide sc prior to study enrollment.

EFFICACY

Study 717

Study 717 was a 52-week study in patients with active acromegaly, as defined by GH levels dependent upon current treatment status (GH > 5 ng/mL if no prior medical therapy or discontinued at least 3 mos before study; GH > 3 ng/mL if current use of SSA/DA or at least a 100% increase in mean GH levels between Visits 1 and 2). Prior medical therapy was allowed but these patients were then enrolled in a 12-week washout period. Patients treated with radiotherapy within the past 3 years or who had pituitary surgery within the past 3 months were excluded. There were three different treatment periods (after the washout period):

- A 4-week, double-blind, placebo-controlled period in which patients were randomized to a lanreotide 60-mg, 90-mg, or 120-mg treatment group. Each treatment group was comprised of 24 drug-treated patients and 8 placebo-treated patients. The primary efficacy endpoint was determined at the end of this period.
- A 16-week, single-blind, fixed-dose period in which patients received 4 injections of the assigned lanreotide doses (either 60-mg, 90-mg, or 120-mg). Patients previously treated with placebo received lanreotide at the dose of the assigned treatment group (see Figure 6.1.3.1 from Dr. Craig's review)
- A 32-week, open-label, dose-titration period in which patients received a total of 8 injections. During this period, titration was allowed at two specified visits based on the GH and IGF-1 levels measured at the previous study visit

The primary endpoint was the proportion of patients with a >50% reduction in mean GH from baseline to Week 4 after a single injection of drug or placebo. The primary efficacy analysis was performed on the ITT population, defined as all randomized patients who received at least one dose of study drug. Mean GH levels were calculated from serial samples obtained after an 8-hr fast. Comparisons between lanreotide dose and placebo were performed within each treatment group and also for the overall study cohort.

Section 10.1.1 of Dr. Craig's review summarizes other secondary efficacy measures including evaluation of clinical symptomatology at Baseline, Weeks 4, 16, 32, 52, and at any time point for early withdrawal, proportion of patients achieving some absolute GH level and proportion with normalization of IGF-1 levels.

A total of 108 patients were enrolled in the double-blind treatment period: 27 received lanreotide 60 mg; 27 received lanreotide 90 mg; 29 received lanreotide 120 mg; and 25 received placebo. The mean age was 53.5 years, 84% of the cohort was Caucasian; 47% male; and the median/mean duration since diagnosis of acromegaly was 3.4 and 6.5 year, respectively, with a range of 0 to 42 years. Co-morbid conditions of acromegaly were present in many of these patients: 41% had HTN; 25% diabetes; 13% hypothyroidism; 10% sleep apnea.

Previous surgical and radiation therapy was performed in 55% and 11% of the study population, respectively. Half of the population had either never received medical therapy or had discontinued treatment 3 or more months prior to study entry.

A substantial number of the originally-dosed patients entered and completed both the single-blind, fixed-dose phase and the open-label, dose-titration phase. The following table from the applicant and Dr. Craig's review summarizes the patient disposition throughout all three treatment periods.

Table 1. Patient Disposition in Study 717

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

Lanreotide, at all three doses tested, resulted in statistically significantly more patients with a > 50% reduction in mean GH levels than placebo. The following table summarizes the proportion of patients with a > 50% reduction after a single administration of assigned treatment.

Table 2. Response to Treatment at Week 4

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

Similarly, more patients in the lanreotide treatment groups than placebo achieved a mean GH < 2.5 ng/mL, normalized IGF-1 levels, and the combination of both these measures.

symptoms associated with acromegaly. This was reported as absent, mild, moderate or severe by the investigator at screening, Baseline, and several pre-specified time points during the study. Given the subjective nature of these measures and possible bias in data ascertainment, the placebo-controlled, double-blind period is the most relevant period of assessment. From Dr. Craig's review, I have summarized these findings in tabular format:

Table 3. Percent with Improvements from Baseline to Week 4 in Clinical Symptoms Assessed

Symptoms	All Lanreotide	Placebo
Headache	22%	13%
Fatigue	30%	13%
Perspiration	30%	38%
Swelling of extremities	30%	33%
Joint pain	33%	33%
Gender-specific*		
Oligomenorrhea	10%	33%
Impotence	3%	8%

*very few reports overall for these clinical symptoms.

The placebo-controlled evaluation shows no consistent improvement in clinical symptoms. While reports of improvements in headache and fatigue were higher for drug group, reports for other symptoms (perspiration, joint and extremity symptoms) favored placebo. The applicant reported stable or improvements in clinical symptomatology during the uncontrolled treatment periods.

The clinical symptoms are variable, highly subjective, and diverse. The majority of the treatment duration for Study 717 involves a study design (i.e., uncontrolled) that will not allow for a conclusion that improvements are a direct effect of drug treatment as opposed to waxing/waning of symptoms, spontaneous improvements, or improvement as a result of other interventions (e.g., analgesic use for pain and headache). While I would not doubt that control of GH and IGF-1 levels will alleviate many clinical symptoms, not all are reversible and may reflect prolonged exposure to the growth factors. On this note, the long-term morbidity and mortality of acromegaly are related to the chronic effects of GH/IGF-1, particularly on the cardiovascular system. Improvements in clinical symptoms are important but should not guide therapy as it may result in suboptimal control of elevated GH levels which can contribute to the more insidious complications.

A total of 107 patients entered the 16-week, fixed-dose treatment period and 105 entered the 32-week, open-label, dose-titration period. During the fixed-dose period, efficacy achieved during the initial 4-week phase was maintained. Further treatment with dose adjustments demonstrated maintenance of efficacy throughout the total 52-week treatment duration. Table 10.1.1.21 from Dr. Craig's review provides a nice overview of the different efficacy measures and the durability of effect. The open-label dose-titration period suggests that maintenance of efficacy required higher doses of lanreotide in the majority of patients.

Table 4. Change in dosages from fixed-dose to open-label, dose-titrated period

Treatment group at beginning of Fixed-dosed period	N	Dose at end of open-label period
60 mg	34	60 mg (n=12) 90 mg (n=5) 120 mg (n=17)
90 mg	34	60 mg (n=7) 90 mg (n=7) 120 mg (n=20)
120 mg	37	60 mg (n=2) 90 mg (n=3) 120 mg (n=32)

As response to lanreotide may be affected by previous medical therapy, the applicant was requested to provide efficacy data by this baseline medical history. Three subgroups were identified:

- Naïve – no medical therapy, surgery or radiation possible
- Not treated w/in 3 months prior to study entry
- Treatment at Baseline (entered washout period)

From Table 10.1.1.22 of Dr. Craig's review the percent achieving a > 50% reduction from baseline to last available data was 86.7%, 64.1%, and 82.4%, respectively, for the aforementioned subgroups. Normalization of IGF-1 or the combined endpoint of GH ≤ 2.5 ng/mL and normal IGF-1 was achieved in

a higher proportion of patients who had been receiving a SSA or dopamine agonist at Baseline. This finding may be the result of a selection bias for SSA responders or it may represent a population whose biochemical values were already near normalization (recall that the inclusion criteria had a lower GH elevation requirement for those patients currently receiving medical therapy). Table 10.1.1.23 of Dr. Craig's review reveals that nearly 50% of the previously treated subgroup had Baseline GH levels ≤ 5 ng/mL whereas no patients in the other two subgroup had values below 5 ng/mL. Overall, this analysis does not suggest that response to lanreotide is limited to naïve or previously-treated patients.

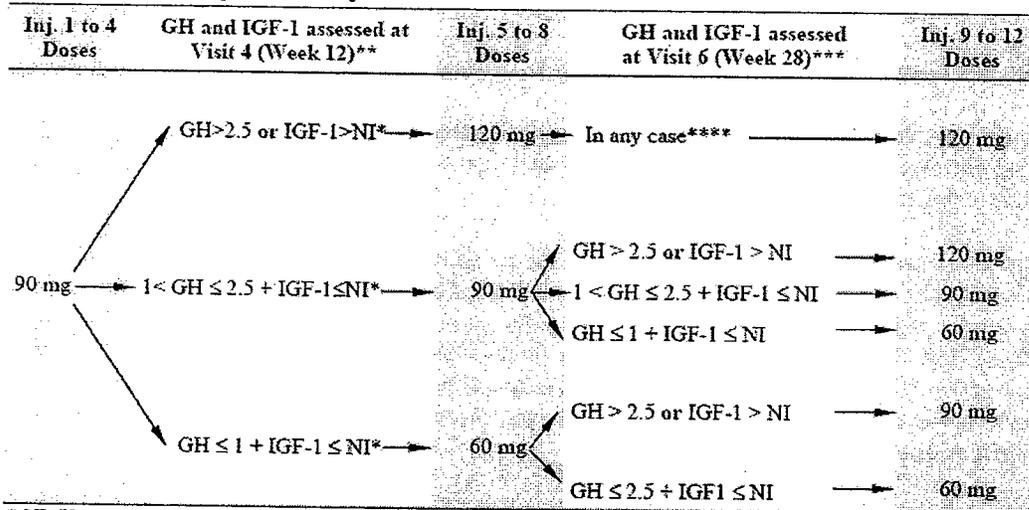
Study 081

Study 081 was a one-year, uncontrolled, open-label study in 63 acromegalic patients who received repeated subcutaneous administrations of lanreotide, initially all at 90 mg weekly x 4 weeks then at titrated doses (60, 90, or 120 mg) based on biochemical response. Unlike Study 717, patient selection was based on IGF-1 levels (had to be $> 1.3 \times$ ULN). Exclusion criteria were similar to those in Study 717. Previously treated patients with a SSA or DA were entered into a 12-week washout period. The trial was divided into the following treatment phases:

- fixed 90 mg weekly dosing for 4 weeks
- two titrated phases based on biochemical response then adjustment of dose

The following figure from Dr. Craig's review illustrates this study design.

Figure 1. Study Design for Study 081



* NI: Upper limit of normal range (age-adjusted); GH values are in ng/mL.
 ** Before the fourth injection.
 *** Before the eighth injection.
 **** In case of dose increase at Visit 5, no re-adjustment was allowed at Visit 7.

The primary efficacy endpoint was the proportion of patients with a normal IGF-1 level (adjusted for age) at the end of study. Several secondary endpoints were similar to efficacy measures obtained in Study 717 including response according to GH levels and clinical symptoms. Only descriptive statistics were reported in this trial with comparisons made to Baseline values.

A total of 63 patients received at least one injection of lanreotide at Study Visit 1; 57 completed the full 48-week treatment course. In this table, Dr. Craig summarizes the exposure by dose. It is notable that after the fixed-dose period of 90 mg, the majority of patients required the highest dose to achieve a biochemical response.

Table 5. Changes in Doses Required Throughout Study 081

Visit	Dose	Number of Patients (N=63)
Visit 1	60 mg	0 (0%)
	90 mg	63 (100%)
	120 mg	0 (0%)
Visit 5	60 mg	11 (17%)
	90 mg	4 (6%)
	120 mg	44 (70%)
Visit 7	60 mg	9 (14%)
	90 mg	4 (6%)
	120 mg	46 (73%)

Table 10.1.2.2 from Dr. Craig's review summarizes the Baseline characteristics of the study population. This was a similar population to Study 717; however, a higher proportion had received previous medical therapy (78%) in Study 081.

At Baseline, mean IGF-1 level was 743.7 ± 291.2 ng/mL; the range of values was 1.3 to 5.8 times the ULN (mean 2.5 x ULN). At the end of study, 27 patients (43%) had normalized IGF-1 levels and the mean IGF-1 level at end of study was 376.9 ± 211.4 ng/mL. Mean GH levels also decreased over the 48-week treatment course from Baseline 6.2 ng/mL to 1.5 ng/mL at end of study. Similarly, proportion of patients with GH levels < 2.5 ng/mL, < 1.0 ng/mL, and a > 50% reduction increased throughout the study.

There were reported improvements in clinical symptoms of asthenia, excessive perspiration, joint pain, joint swelling and headache. No correlation of these findings to lanreotide therapy can be made given the uncontrolled study design.

Overall, Study 081 provides additional supportive evidence of the effectiveness of lanreotide. The absence of a controlled treatment period does add some limitation to the data interpretation; however, the progressive nature of this disease with low probability for spontaneous remission/cure of the pituitary adenoma does allow for use of each patient as his/her own control for Baseline comparison. Similar to Study 717, it appears that the majority of patients will require the highest proposed dosing regimen (120 mg weekly) to achieve an adequate biochemical response. Both studies demonstrate durability of effect over the course of one-year evaluation.

SAFETY

Dr. Craig presented safety data within the following categories: 7 pooled studies, 4 non-pooled studies, and the healthy patient population. Safety for individual studies was also summarized in Appendix 10. In addition to a general review of safety in this application, a targeted review of known adverse events associated with somatostatin analogs was undertaken by Dr. Craig and the applicant. In particular, adverse events involving the biliary system, glucose regulation, cardiovascular (rhythm disturbances and valvulopathy), and other endocrinopathies were discussed at length by Dr. Craig.

There were a total of 6 deaths reported in the clinical trials and 18 deaths reported in the European post-marketing experience (from 1995-2005) summarized under Section 7.1.1 of Dr. Craig's review. Several of these cases were cardiovascular-related in patients with extensive history of CVD or risk factors separate from acromegaly for CVD. The absence of a control group makes it difficult to formulate any conclusion on the relationship between the fatal event and lanreotide.

GI side effects were among the most commonly reported AEs in this clinical database and included complaints of diarrhea, abdominal pain, flatulence, nausea and vomiting, and watery stools. In the pooled database of acromegalic patients the incidence of GI AEs was 56.5% but was as high as 71% in the healthy patient population database. In the first 4 weeks of Study 717, the incidence of diarrhea was dose-related (11%, 37%, and 45%) and no cases were reported in placebo. In the following table, Dr. Craig also summarizes other AEs occurring at $\geq 5\%$ during the placebo-controlled period and in all categories the events are occurring in lanreotide except for abdominal pain. I have added the last column of Pooled Studies to provide rates in long-term exposure data in a larger database (although mostly non-comparison data).

Table 6. AEs Occurring at $\geq 5\%$ in 4-week, Placebo-controlled Treatment (w/ last column summarizing rates in those AEs from longer duration of exposure)

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)	Pooled Studies* (N=416)
Diarrhea	3 (11%)	10 (37%)	13 (45%)	26 (31%)	0	26 (24%)	155 (57%)
Abdominal Pain	2 (7%)	2 (7%)	2 (7%)	6 (7%)	1 (4%)	7 (6%)	79 (19%)
Bradycardia	3 (11%)	2 (7%)	2 (7%)	7 (8%)	0	7 (6%)	13 (3%)
Weight Decrease	2 (7%)	4 (15%)	1 (3%)	7 (8%)	0	7 (6%)	16 (4%)
Anemia	1 (4%)	4 (15%)	1 (3%)	6 (7%)	0	6 (6%)	14 (3.4%)
Flatulence	0	2 (7%)	3 (10%)	5 (6%)	0	5 (5%)	30 (7%)

*separate database from the data summarized for the 4-week, placebo-controlled study. Pooled studies included here for comparison of rates with longer duration of exposure

Somatostatin analogs inhibit gallbladder contractility and are associated with the development of biliary sludge and gallstone formation. In the pooled database which included studies with routine gallbladder ultrasound evaluation, the incidence of cholelithiasis was 20.2% with an apparently higher rate in the 120 mg dose group. Three serious AEs resulted from the development of cholelithiasis (biliary colic, cholecystectomy, and pancreatitis requiring cholecystectomy).

Somatostatin also has inhibitory effects on insulin and glucagon secretion with expected findings of hypo- and hyperglycemia. The rates of dysglycemia were variable, as described in on page 84 of Dr. Craig's. Much of this may be due to differences in criteria of evaluation or reporting a particular event. There was no systematic approach regarding use of OGTT or measurement of insulin levels hence reports relied primarily on blood glucose levels or HbA1c. Across the different studies, hyperglycemia was reported up to 16% of patients without evidence of a dose-relationship. Hypoglycemia was also reported but less frequently. Some cases of hypoglycemia and hyperglycemia were reported as serious (requiring hospitalization) but all recovered with appropriate management and without serious sequelae.

Other endocrinopathies are associated with acromegaly including pituitary dysfunction. Much of this may be the result of mass impingement on surrounding structures and normal pituitary tissue although somatostatin has a known inhibitory effect on TSH and prolactin secretion. MRIs of the pituitary were only performed in a subset of studies with one study assessing tumor size in 44 patients who have had no previous surgical resection (Study 077). The data in this small subset of patients suggest some reduction in size of the adenoma;

A safety concern of lanreotide and development of valvulopathy was raised in the initial review of the application. As a result, the applicant was required to conduct a clinical study to further investigate

the effects of lanreotide on the risk of valvulopathy. The applicant proposed and the agency agreed that an active control study (Study 721) in which lanreotide was compared to the approved product, octreotide, to assess the rate of new or worsening regurgitation at any of the four valves would be sufficient to address this safety concern. A placebo group was not feasible given the ethics of not treating acromegalic patients for the duration necessary to evaluate valvular changes. While this study would not allow us to establish that lanreotide carried no risk of valvulopathy, it would inform us of the risk of lanreotide relative to another somatostatin analogue that has been marketed for many years. The study was designed to have > 90% power at detecting a 2-fold relative risk of new or worsening valvular regurgitation at a 5% alpha level using an estimated 25% incidence rate in the octreotide group.

Not only was lanreotide compared to octreotide in this trial but enrollment was matched for previously-treated and *de novo* patients. Dr. Craig's review of this protocol details the patient and matching criteria. Below is a table summarizing the two treatment groups by baseline treatment status and analysis population.

Table 7. Study Population in Cardiac Echo Safety Study

Population	Lanreotide			Octreotide		
	De Novo N=13	Pre-treated N=94	Total N=107	De Novo N=17	Pre-treated N=101	Total N=118
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Safety	13 (100%)	94 (100%)	107 (100%)	17 (100%)	101 (100%)	118 (100%)
ITT	12 (92%)	84 (89%)	96 (90%)	13 (76%)	87 (86%)	100 (85%)
ITT matched	10 (77%)	72 (77%)	82 (77%)	10 (59%)	72 (71%)	82 (69%)
PP	8 (62%)	72 (77%)	80 (75%)	11 (65%)	71 (70%)	82 (69%)
PP matched	7 (54%)	54 (57%)	61 (57%)	7 (41%)	54 (53%)	61 (52%)
PP complete cases	5 (38%)	40 (43%)	45 (42%)	8 (47%)	34 (34%)	42 (36%)

The primary endpoint was the odds ratio approximation for the relative risk of new or worsening valvular regurgitation in any valve (mitral, aortic, tricuspid, and pulmonic) of lanreotide in comparison to octreotide at 12 months as assessed by echocardiograms. Two independent cardiologists blinded to treatment and sequence of evaluation reviewed the echocardiograms. The primary efficacy analysis was performed in the ITT population for the combined treatment groups (pre-treated and *de novo*). Additional analyses were done by baseline treatment status. The following table summarizes the primary analysis on the overall ITT population:

Table 8. Primary Efficacy Results from Study 721

Any valve:	Lanreotide N=82	Octreotide N=82	Statistical Analyses ²
	N (%)	N (%)	
Number of evaluable patients	82	82	
New valvular regurgitation	17 (21%)	16 (20%)	
Worsening valvular regurgitation	14 (17%)	13 (16%)	
New or worsening valvular regurgitation	28 (34%)	27 (33%)	
Risk difference (95% CI)			0.01 (-0.13, 0.16)
Relative risk (95% CI)			1.04 (0.67, 1.60)
Odds ratio (95% CI)			0.86 (0.41, 1.82)
p-value for odds ratio			0.694

Echocardiograms were non-evaluable in 7%, 6%, 16%, and 52% of study population at baseline for the mitral, aortic, tricuspid, and pulmonic valves, respectively. These patients were excluded from the ITT analysis; however, a sensitivity analysis employing the worse case scenario wherein these patients were included and considered to have new or worsening valvular regurgitation was also performed. The RR in

this analysis was 0.99 (95% CI: 0.71-1.39) upholding the finding of non-significant difference between the two treatment regimens for development of new or worsening valvular regurgitation. While there were only 10 evaluable *de novo* patients in each treatment group, it was reassuring to note that there was no clinically relevant worsening of valve findings over the 12-month treatment course.

There was no discernible difference in efficacy or other safety profiles between lanreotide and octreotide in this study; however, GI-related AEs were more frequently reported in the lanreotide group.

Other notable safety findings to be discussed in labeling include bradycardia, anemia, and injection site reactions. None of these reports were serious; however, patients with underlying conduction abnormalities or on medications which may result in decreased heart rate should be monitored.

Immunogenicity evaluation was performed in seven clinical studies as described under Section 7.1.10 of Dr. Craig's review. Antibody formation was low (< 1-4%) regardless of previous SSA use or non-use. There was no evidence of alteration in efficacy or safety profile as a result of antibody presence.

8. ADVISORY COMMITTEE MEETING

Not applicable.

9. OTHER RELEVANT REGULATORY ISSUES

No pediatric studies are required under PREA, as this is an Orphan indication. Regardless, acromegaly is an adult condition and this requirement would have been waived for reason of non-applicability to the pediatric population.

10. FINANCIAL DISCLOSURE

Reviewed by Dr. Craig and found to be acceptable.

11. LABELING

The label submitted incorporates changes under PLR and is currently under negotiations with the applicant. The applicant has proposed the following _____:

1. the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option _____

Tradename

The applicant proposed the tradename, Somatuline Autogel which was rejected by DMETS. Subsequently, Somatuline _____ was proposed by the applicant but this was again rejected by DMETS due to concerns of unfamiliarity of the modifier. DMETS proposed the applicant select _____ or depot. In its rebuttal submitted on August 3, 2007, the applicant maintained that the _____

_____ In order of preference, the applicant proposed _____, Somatuline (lanreotide) injection, then Somatuline (lanreotide) depot.

I recommend the applicant be approved with the proprietary name, Somatuline (lanreotide) depot as it accurately conveys the formulation and extended pharmacokinetics of the product.

12. DSI AUDITS

See DFS memo by Dr. Andrea Slavin. Clinical sites selected for DSI inspection did not reveal significant violations.

13. CONCLUSIONS AND RECOMMENDATIONS

the applicant has submitted an application for a new formulation for lanreotide acetate.

Other review discipline deficiencies have been adequately addressed in this application. In particular, the applicant has conducted an active comparator study to evaluate the risk of new or worsening valvular regurgitation and demonstrated no increased risk to another somatostatin analogue that has been marketed worldwide for the treatment of acromegaly since 1992.

Pending acceptable labeling negotiations, NDA 22-074 should be approved for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.

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

/s/

Mary Parks
8/28/2007 07:40:31 AM
MEDICAL OFFICER

Robert Meyer
8/28/2007 12:02:40 PM
MEDICAL OFFICER

I am in substantial agreement with this excellent summary memorandum. In particular, I agree with the finding of a favorable risk-benefit relationship of this drug.

8/2/07

CLINICAL REVIEW

Application Type NDA 22-074
Submission Number 000
Submission Code S

Letter Date 2006-10-27
Stamp Date 2006-10-30
PDUFA Goal Date 2007-8-30

Reviewer Name Eileen M. Craig, MD
Review Completion Date 2007-7-30

Established Name lanreotide acetate injection
(Proposed) Trade Name Somatuline® Autogel®
Therapeutic Class somatostatin analog
Applicant Beaufour Ipsen Pharma

Priority Designation S

Formulation prolonged release injection
Dosing Regimen 60, 90, or 120 mg every 4 weeks
Indication Treatment of Acromegaly
Intended Population Adult Patients with Acromegaly

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

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1 EXECUTIVE SUMMARY

This document is the Medical Officer's Clinical Review of lanreotide acetate injection, a new molecular entity. The indications sought are "for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option" and

Acromegaly is a chronic disease caused by excessive secretion of growth hormone (GH). Increased serum concentrations of GH cause the symptoms and pathology of the disease, directly through actions on target tissues and indirectly by stimulating excess secretion of insulin-like growth factor 1 (IGF-1). Acromegaly is a rare disease and is classified by the Food and Drug Administration (FDA) as an orphan indication.

Patients with acromegaly suffer from acute and chronic complications, with higher mortality rates than an age-matched control population. The overall standardized mortality ratio of patients with acromegaly is 1.48.^{1,2} Factors contributing to increased mortality among persons with acromegaly include the higher prevalence of hypertension, hyperglycemia or overt diabetes, cardiomyopathy, and sleep apnea in this population.³ The conventional first-line treatment for acromegaly is surgical excision of the pituitary tumor, sometimes accompanied by radiotherapy. Despite these treatments, acromegaly remains active in many patients, with increased concentrations of GH and IGF-1 and persistence of clinical symptoms. Further control of GH and IGF-1 concentrations can be achieved by medical treatment.

The New Drug Application reviewed in this document describes the development program for lanreotide acetate. Somatuline® Autogel® Injection, referred to as lanreotide acetate in this document, is a new pharmaceutical form of lanreotide. Lanreotide was first developed as an immediate-release formulation (IRF). The IRF was not developed for commercial use. Lanreotide (30 mg) was then developed for commercial use as a micro-particle formulation (MPF) administered every 7, 10 or 14 days.

Subsequently, the Somatuline Autogel formulation of lanreotide acetate was developed to further extend the duration of lanreotide release, allowing for administration once every 4 weeks. The proposed commercial formulation has been used in pivotal efficacy studies E28-52030-717 and E-54-52030-81. A total of 416 unique patients with acromegaly received 439 lanreotide acetate (Somatuline) long-term treatment courses (at least 48 weeks) in the seven pooled Somatuline studies in patients with acromegaly. There were 23 patients who received lanreotide in more than one of these seven 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).

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Somatuline® Autogel® Injection (lanreotide acetate) is a somatostatin analog indicated for the long-term treatment of acromegaly.

The evaluation of efficacy for lanreotide acetate is based on two pivotal controlled efficacy studies (E28-52030-717 and E-54-52030-081) conducted in 171 acromegalic patients. Study E28-52030-717 (referred to as Study 717) was a placebo-controlled, double-blind study evaluating the efficacy and safety of repeated subcutaneous administration of lanreotide acetate in 108 acromegalic patients for 52 weeks. The second study, E-54-52030-081 (referred to as Study 081) was a baseline controlled study evaluating the effect of lanreotide acetate on GH/IGF-1 levels compared to pre-treatment values, in 63 acromegalic patients for 48 weeks.

The evaluation for safety is based on seven studies:

1. Study 717
2. Study 081
3. Study E28-52030-709 (Study 709) with 144 patients for 12 weeks and the long-term follow up study 710
4. E28-52030-710: Study 709/710 with a primary objective to demonstrate that lanreotide acetate is not less effective than the MPF formulation in controlling GH and IGF-1 levels. Study 709 employed a "switch" design in which patients adequately controlled on the MPF formulation were switched to the Somatuline lanreotide acetate formulation to demonstrate maintenance or improvement of GH and IGF-1 levels. Study 710 (130 patients for 48 weeks) allowed dose titration to optimize GH and IGF-1 control.
5. Study 721: A multicenter, prospective controlled, observer blinded cohort study in 107 patients with acromegaly over 48 weeks to evaluate the risk of cardiac valvular regurgitation in patients treated with lanreotide relative to patients treated with octreotide
6. Study 076: A 16-week Phase II, randomized, parallel groups, double-blind pharmacokinetic study of lanreotide acetate (60, 90, or 120 mg) after 4 deep subcutaneous injections (administered every 28 days) in 18 acromegalic patients
7. Study 087: A Phase II multi-center, open-label study, evaluating the safety and efficacy of multiple deep subcutaneous administrations of lanreotide acetate (60, 90, 120 mg) in 11 acromegalic patients with abnormal IGF-1 level for 56 weeks

1.3.2 Efficacy

The primary parameters for the evaluation of lanreotide acetate efficacy were reductions in GH and IGF-1 concentrations in acromegalic patients. Reduced serum GH concentrations after treatment with somatostatin analogs have been associated with decreased mortality in acromegalic patients.⁴ Among 419 patients followed in the West Midlands Pituitary Database, increased mortality was ascribed primarily to elevated levels of growth hormone (above 2 µg per

liter) and to previous radiotherapy.⁵ Multivariate analysis of determinants of survival in long-term studies indicates that growth hormone levels of less than 2.5 µg per liter, a younger age, a shorter duration of disease, and the absence of hypertension independently predict longer survival.^{1,2} In some studies, increased IGF-1 levels are associated with higher mortality.^{6,7} However, growth hormone levels seem to be more consistently independent predictors of mortality than are IGF-1 levels.⁸ Clinical studies of acromegaly have generally not evaluated morbidity and mortality since such studies would require long durations (years) and a large number of patients, while the numbers of patients available to be recruited into such studies are relatively small. While none of the clinical studies in this submission evaluated mortality, there is data confirming the benefit of reduction of GH and IGF-1 levels to normal on morbidity and mortality.

Reduction of GH concentrations in acromegalic patients can lead to improvements in clinical symptoms of GH excess. The applicant examined the symptoms of acromegaly such as headache, perspiration, fatigue, swelling of extremities, joint pain, impotency and oligomenorrhea both before and after treatment with lanreotide acetate. While these measures may be clinically relevant, the symptoms are not specific to acromegaly and misclassification, reporting bias, and concerns regarding data ascertainment add to the uncertainty of their findings and association with disease management. The primary goal of therapy for acromegaly is reduction in GH and IGF-1 levels, with some expectation that clinical improvements will follow with successful biochemical control of the disease.

Study 717

Study 717 was a multicenter study conducted in 108 acromegalic patients in the US, Europe and Hong Kong. The study investigated the efficacy and safety of lanreotide acetate administered as a deep s.c. injection and consisted of four periods: (1) Washout period of up to 12 weeks, (2) 4-week double-blind, placebo-controlled period with four treatment groups, (3) 16-week single-blind, fixed-dose period (during the fixed-dose period both patients and investigators were blinded to dose strength, although the investigators were informed of the dose strength prior to the first visit of the dose-titration period in order to determine the appropriate dose-titration for each patient), (4) 32-week open-label, dose-titration period.

The primary objective of the study was to show whether a single injection of lanreotide acetate (60, 90, or 120 mg) had a greater effect on GH concentration than placebo. A secondary objective was to investigate the effect of lanreotide acetate at these doses on IGF-1 concentrations. In addition, the effect of repeated lanreotide acetate injections over time on GH and IGF-1 concentrations, as well as on acromegaly symptoms, was evaluated.

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 ≤ 2.5 ng/mL and normalized IGF-1 at Week 4 as compared to placebo (0 of 25)

($p = 0.033$). Fifty-two per cent of subjects on 60 mg, 44% of the 90 mg group, and 90% of the 120 mg group achieved a $>50\%$ decrease in GH compared to 0% in the placebo group ($p < 0.001$).

The values at the end of study reflect two possible dose titrations. The majority of subjects were taking the 120 mg dose by the end of the study; 21 (20%), 17 (16%), and 69 (64%) patients had received 60, 90, and 120 mg lanreotide acetate, respectively. By Week 52, 82% of subjects had a decrease in GH $>50\%$ and 43% achieved GH ≤ 2.5 ng/mL and IGF-1 normal for age.

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 to somatostatin or somatostatin analog therapy, not treated within 3 months of study and 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 naïve patient group. The difference in responses between patients previously treated and those patients in the naïve group may be due to a selection bias, as the naïve patient group may have been more likely to include responders as well as non-responders than the previously-treated group.

Study 081

Study 081 was an open label multicenter study, designed to assess efficacy and long term safety of lanreotide acetate administered as a deep s.c. injection in acromegalic patients over a treatment period of 48 weeks. The study was conducted in a total of 63 acromegalic patients in France and Switzerland. The study design included three distinct study periods: (1) Washout period of up to 12 weeks, (2) 16-week, open-label, fixed-dose period in which patients received four injections of 90 mg lanreotide acetate, (3) 32-week, open-label, dose-titration period in which patients received eight injections. During the latter period, two dose adjustments based on hormonal response (as measured by GH and IGF-1 concentrations) could be made.

The primary objective of this study was to evaluate the long term efficacy of repeated injections of lanreotide acetate administered at titrated doses in acromegalic patients. This objective was assessed by the response in terms of the primary efficacy parameter, the percentage of patients with a normal (age-adjusted) serum IGF-1 concentration at the end of treatment. Secondary objectives included assessment during the study of IGF -1 and GH concentrations and clinical signs of acromegaly.

After treatment with lanreotide acetate every 4 weeks, 43% (27/63) of the acromegalic patients in this study achieved normal age-adjusted IGF-1 concentrations. The proportion of patients with mean GH concentrations below 2.5 ng/mL increased during the fixed dose period from 35% (95% CI: 23.2, 46.7) to 77% (95% CI: 66.5, 87.6) after the first four injections and reached 85% (95% CI: 76.7, 94.3) at the end of the study. Similarly, the proportions of patients with mean GH concentrations <1 ng/mL increased throughout the treatment period from 11% (95% CI: 3.4, 18.9) at baseline to 31% (95% CI: 19.5, 42.8) at Week 12. During the dose titration period, the proportions of patients with mean GH concentrations <1 ng/mL had increased to 45% (95% CI: 32.8, 57.6) by the end of the study. At the end of treatment, 24/63 (38%) of patients had both

normal IGF-1 concentrations and a GH concentration of ≤ 2.5 ng/mL, and 17/63 patients (27%) had both normal IGF-1 concentrations and a GH concentration of < 1 ng/ml.

Subgroup Analyses:

Subgroup responder analyses were performed using pooled data from studies 717 and 081 with regard to the following criteria: gender, age, body mass index, body weight, acromegaly severity at baseline, surgery history, radiotherapy history, SSA history, race, and region (US and non-US). 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 with lanreotide acetate. However, lanreotide acetate was shown to be effective in treatment-naïve patients.

1.3.3 Safety

Safety data were pooled for all seven clinical studies of lanreotide acetate 60, 90, or 120 mg administered to acromegalic patients every 28 days by healthcare providers. A total of 416 unique patients treated with lanreotide acetate were included in this pooled safety analysis.

Deaths

There was one death in the pooled studies (in Study 710). One patient, a 48 year-old-female, died during the study due to sepsis followed by intravascular coagulation. This was not considered to be related to the study drug. There were no deaths in the 3 Phase I studies with lanreotide acetate in healthy subjects.

Serious Adverse Events (SAEs)

SAEs in pooled lanreotide acetate studies in acromegalic patients were reported by 15% (61/416) of patients. SAEs considered related to study drug were: cholecystectomy, diarrhea, pancreatitis, colitis, thrombophlebitis, aortic aneurysm, lethargy, malaise, biliary colic and cholelithiasis. Two (2%) of healthy subjects in Phase I studies with lanreotide acetate reported one SAE each, and both SAEs were considered related to study drug (biliary colic and gallbladder disorder).

Adverse Events Associated with Dropouts

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. AEs that were considered possibly related to study drug 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 possibly 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%).

Common Adverse Events that appear to be related to Lanreotide Acetate

GI Disorders

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 the pooled lanreotide acetate studies, GI disorders were the most common AE, reported by 56.5% (235/416) of acromegalic patients. The most commonly reported individual AE was diarrhea, which was experienced by more than a third (37%) of patients. This was followed by cholelithiasis (20%) and abdominal pain (19%). Other GI AEs reported by $\geq 5\%$ patients were nausea (11%), constipation (8%), flatulence (7%), vomiting (7%) and loose stools (5.5%).

Injection Site Reactions

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. 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 the pooled lanreotide acetate studies, injection site reactions occurred in 37/416 (8.9%) of subjects.

Gallbladder Effects

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. 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 the pooled studies where gallbladder ultrasound was performed (Studies 721, 717, 081 and 076), twelve percent (20/167) of patients who did not have gallstones at baseline had formation of gallstones at last value available (LVA); similarly 20/167 (12%) moved from an absence to presence of sludge from baseline to LVA.

In the pooled lanreotide acetate studies, cholecystitis and cholelithiasis AEs were reported by 20% (85/416) of patients. It appears that the occurrence of cholelithiasis is related to dose and time on treatment. Few patients developed acute symptoms requiring cholecystectomy.

Glycoregulation (hypoglycemia, hyperglycemia, diabetes)

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 AEs were reported by 14% (47/332) of patients. 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. Thus, glycoregulation in patients treated with lanreotide acetate is altered and adjustments in anti-diabetic medication may be necessary.

Cardiac Function (sinus bradycardia, hypertension)

The most common overall cardiac adverse events observed in three pooled lanreotide acetate 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 of sinus bradycardia was (13/416, 3%) and hypertension (20/416, 5%). During the double-blind placebo-controlled portion of Study 717 (weeks 0 to 4) bradycardia was reported in 8% of the lanreotide patients as compared to 0% of the placebo-treated patients.

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 3.4% (14/416). 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 7.6% (13/170).

Special Safety Study

Cardiac Valvular Regurgitation

In Study 721, twenty-eight (34%) of lanreotide-treated patients and 27 (33%) of octreotide-treated patients developed new or worsening valvular regurgitation of any severity. However, the occurrence of clinically significant mitral regurgitation (i.e. moderate or severe in intensity) or of clinically significant aortic regurgitation (i.e. at least mild in intensity) was low in both groups of patients throughout the study. Six percent of patients in the lanreotide group had clinically significant mitral regurgitation at baseline compared with 4% at Month 12. The corresponding prevalence in the octreotide group was 2% at both assessments. Clinically significant aortic regurgitation was present in 10% to 11% of patients in both treatment groups at the baseline and Month 12 assessments.

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. The size and duration of this study is adequate to detect a marked difference in the cardiovascular adverse event profile of the two drugs, lanreotide and octreotide.

1.3.4 Dosing Regimen and Administration

Patients should begin treatment with lanreotide acetate 90 mg given via the deep subcutaneous route in the superior external quadrant of the buttock, at 4 week intervals for 3 months.

After 3 months dosage may be adapted as follows:

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

Serum concentrations of lanreotide approached the median values sufficient to provide hormonal control of acromegaly after a single 90 or 120 mg injection of lanreotide acetate in Study 076. The 90 mg dose is a logical minimal effective starting dose strength based upon both 1) lower annual cumulative GH levels as compared to a 60 mg starting dose strength, and 2) serum levels of lanreotide sufficient to approach hormonal control of acromegaly after the first injection. The dose strength prescribed should be evaluated after 3 months and titrated to optimal clinical and hormonal control based upon individual response.

Subjects with moderate to severe renal insufficiency, severe hepatic impairment, or age >65 years showed decreases in total serum clearance of lanreotide and/or increase in half-life and AUC. Clinical studies with lanreotide acetate did not include sufficient numbers of subjects with moderate to severe renal insufficiency or moderate to severe hepatic impairment. Therefore, a starting dose of 60 mg is recommended in patients with moderate to severe renal or hepatic impairment. The dose strength should be re-evaluated after 3 months.

1.3.5 Drug-Drug Interactions

Cyclosporine

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

Antidiabetic Treatment

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

Bradycardia-inducing Drugs

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

Bromocriptine

One paper has shown that the bioavailability of the dopaminergic agonist bromocriptine was increased by approximately 40% when administered concurrently with octreotide. A similar interaction with bromocriptine may occur for lanreotide.

Cytochrome P450 metabolized drugs

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

1.3.6 Special Populations

Experience with lanreotide acetate in the pediatric population is limited and the sponsor has applied for a pediatric waiver, which in this reviewer's opinion is appropriate and should be granted.

In the 7 pooled safety studies, 51% (211/416) were female; 17% (72/416) were 65 years or older; only 6% (24/416) were Non-Caucasian; and 31% (131/416) were diabetic. The clinical studies are representative of the intended patient population by age, gender, BMI and acromegaly history. Special dosing considerations based on age, race, gender, weight or concomitant illness other than renal and hepatic impairment does not appear to be necessary for lanreotide acetate. The starting dose should be decreased in subjects with moderate to severe renal or hepatic impairment.

2 INTRODUCTION AND BACKGROUND

Acromegaly is a chronic disease caused by excessive secretion of growth hormone (GH). Increased serum concentrations of GH cause the symptoms and pathology of the disease, directly through actions on target tissues and indirectly by stimulating excess secretion of insulin-like growth factor 1 (IGF-1)⁸. Acromegaly is a rare disease, the average annual incidence is around 3 per million⁹. The prevalence of acromegaly in the population is estimated at 40 to 90 cases/million¹⁰ and this disease is classified by the Food and Drug Administration (FDA) as an orphan indication.

Patients with acromegaly suffer from acute and chronic complications, with higher mortality rates than an age-matched control population¹¹. The conventional first-line treatment for acromegaly is surgical excision of the pituitary tumor, sometimes accompanied by radiotherapy. Despite these treatments, acromegaly remains active in many patients, with increased concentrations of GH and IGF-1 and persistence of clinical symptoms. Further control of GH and IGF-1 concentrations can be achieved by medical treatment.

Somatostatin, a peptide that is produced in the hypothalamus and other tissues, was named for its inhibition of the synthesis and release of GH from the pituitary gland. It is an endogenous neuropeptide that inhibits the secretion of several hormones through five identified G protein-coupled somatostatin receptor subtypes. Somatostatin and its synthetic analogues are used clinically to treat acromegaly.

2.1 Product Information

Somatuline® Autogel® (lanreotide acetate) Injection is a new pharmaceutical form of lanreotide. Lanreotide was first developed as an immediate-release formulation (IRF). The IRF was not developed for commercial use. Lanreotide (30 mg) was then developed for commercial use as a micro-particle formulation (MPF) administered every 7, 10 or 14 days. Since 1994, it has been approved in approximately 50 countries.

Subsequently lanreotide acetate formulation was developed to further extend the duration of lanreotide release, allowing for administration once every 4 weeks. Lanreotide acetate is registered in approximately 40 countries for treatment of acromegaly and carcinoid syndrome since 2001. This NDA contains studies conducted with IRF, MRF as well as Somatuline Autogel (lanreotide acetate) formulations. The proposed commercial formulation has been used in pivotal efficacy studies (E28-52030-717) and E-54-52030-81). Lanreotide was designated as an orphan drug by the Agency for the treatment of acromegaly on September 11, 2000 (Orphan Drug Application 00-1363).

The drug substance Somatuline® Autogel® (lanreotide acetate) Injection 60, 90 and 120 mg is a prolonged-release formulation for deep subcutaneous injection containing the drug substance lanreotide acetate, a synthetic octapeptide with a biological activity similar to naturally occurring somatostatin, and water for injection. The drug product consists of a pre-filled syringe containing

a supersaturated solution obtained by mixing lanreotide and water for injection, to a final concentration of 0.246 mg/mg. The product is intended to deliver doses of 60, 90 or 120mg of lanreotide. The different doses are achieved by increasing the quantity of the supersaturated solution in the syringe. A deep subcutaneous injection in the buttock allows the prolonged release of lanreotide over a period of at least 4 weeks. The starting dose strength of lanreotide acetate proposed in this NDA is 90 mg every 4 weeks for 12 weeks. Thereafter the dose strength should be adjusted according to the response of the patient based on serum growth hormone or IGF-1 concentration and/or changes in clinical symptoms of acromegaly.

Table 2.1.1: Somatuline (lanreotide acetate) dosing regimen after 3 months of treatment

GH	Symptoms	Dose
>1 to \leq 2.5 ng/mL	IGF-1 normal and clinical symptoms controlled	Maintain dosage at 90 mg every 4 weeks
> 2.5 ng/mL	IGF-1 elevated and/or clinical symptoms uncontrolled	Increase dosage to 120 mg every 4 weeks
\leq 1	IGF-1 normal, and clinical symptoms controlled	Decrease dosage to 60 mg every 4 weeks

Lanreotide acetate's proposed indications are for:

- the long-term treatment of adult patients with acromegaly who have had inadequate response to or cannot be treated with surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option

The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal.

2.2 Currently Available Treatment for Indications

Acromegaly is a rare (incidence: 3 to 4 per million; prevalence 40 to 90 per million), chronic disease caused by excessive secretion of GH from a pituitary tumor and is classified by the Food and Drug Administration (FDA) as an orphan indication. Increased plasma levels of GH cause the symptoms and pathology of the disease, either directly through actions on target tissues, or indirectly by stimulating excess secretion of insulin-like growth factor (IGF-1). All the approaches to therapy — surgery, radiotherapy, and medications — have specific advantages and disadvantages. The goal of a cure should ideally be achieved while minimizing side effects¹² (see Table 2.2.1 below).

Table 2.2.1 Acromegaly Treatment Options

Variable	Surgery	Radiotherapy	Somatostatin Receptor Ligand†	Growth Hormone-Receptor Antagonist	Dopamine Agonist
Type of therapy or dose of drug	Transsphenoidal resection	Conventional or radiosurgery	Octreotide (50–100 µg every 8 hr); octreotide LAR (10–40 mg IM every 4 wk); lanreotide (30 mg IM every 10–14 days); lanreotide gel (60–120 mg deep SC every 4 wk)	Pegvisomant (10–40 mg SC daily)	Cabergoline (1–4 mg orally weekly)
Biochemical control					
Growth hormone <2.5 µg/liter	Macroadenomas, <50%; microadenomas, >80%	Approximately 35% in 10 yr	Approximately 70%	Level increased	<15%
Normalization of IGF-1	Macroadenomas, <50%; microadenomas, >80%	<30%	Approximately 70%	>90%	<15%
Onset of response	Rapid	Slow (years)	Rapid	Rapid	Slow (weeks)
Compliance of patient	One-time consent	Good	Must be sustained	Must be sustained	Good
Tumor mass	Debulked or resected	Ablated	Growth constrained or tumor shrunk, about 50%	Unknown	Unchanged
Disadvantages					
Cost	One-time charges‡	One-time charge	Ongoing	Ongoing	Ongoing
Hypopituitarism	Approximately 10%	>50%	None	Very low IGF-1 level if overtreated	None
Other	Tumor persistence or recurrence, 6%; diabetes insipidus, 3%; local complications, 5%	Local nerve damage, second brain tumor, visual and CNS disorders, approximately 2%; cerebrovascular risk	Gallstones, 20%; nausea; diarrhea	Elevated liver enzymes	Nausea, approximately 30%; sinusitis; high dose required

* The goals of acromegaly management include the control of tumor growth and the secretion of growth hormone and IGF-1, the relief of any central compressive effects, the preservation or restoration of pituitary trophic hormone function, the treatment of coexisting illnesses, the prevention of death, and the prevention of biochemical recurrence. Percentages denote the proportion of patients who have the result after treatment. LAR denotes long-acting-release, IM intramuscular, SC subcutaneous, and CNS central nervous system.

† For details, see Table J of the Supplementary Appendix.

‡ There may be additional costs if the patient requires repeated surgery.

Source: Table 2 Melmed S. Acromegaly. N Engl J Med 2006; 355:2558-73.

Based on Dr. Melmed's review on acromegaly, surgery is indicated for growth hormone-secreting microadenomas, as well as for decompressing mass effects on vital structures, particularly the optic tracts. Surgery may not be indicated as first-line therapy if it appears that the tumor mass is unlikely to be resectable and it does not endanger vital structures or if the patient declines surgery. Radiotherapy is generally reserved for tumors that have recurred or persisted after surgery in patients with resistance to or intolerance of medical treatment.

Somatostatin analogs (SSAs) such as octreotide and lanreotide can reduce various measures of GH and IGF-1 levels in up to 50 to 70% of patients, and normalize IGF-1 in approximately 30 to 65% of patients^{13,14,15}. SSAs alleviate many symptoms related to acromegaly, improve acromegaly related comorbid complications and may reduce tumor size in a subset of patients. The main adverse events following use of SSAs are gastrointestinal, including abdominal cramps, diarrhea, and an increased incidence of gallbladder sludge and/or stones.

Best Possible Copy

The first-generation SSAs required subcutaneous administration at least three times a day. Newer formulations of SSAs in a biodegradable polymer matrix have been developed with more extended durations of action.

2.3 Availability of Proposed Active Ingredient in the United States

Lanreotide acetate is a new chemical entity and, while marketed in 40 countries worldwide, is not currently marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

Lanreotide is a polypeptide analogue of somatostatin that shares a common mechanism of action with two previously approved products containing octreotide acetate, Sandostatin and Sandostatin LAR (approved 1992 and 1998, respectively). Sandostatin LAR® (octreotide acetate for injectable suspension), NDA 21-008, is a long-acting somatostatin analog and is indicated for long-term maintenance therapy in acromegalic patients for whom medical treatment is appropriate and who have been shown to respond to and can tolerate Sandostatin® (octreotide acetate) Injection. Adverse events that have been reported with Sandostatin LAR® Depot include gallbladder abnormalities (gallstones, sludge without stones, biliary duct dilatation), hypoglycemia or hyperglycemia (due to alteration in the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone), hypothyroidism, depressed vitamin B12 levels (due to altered absorption of dietary fats), cardiac conduction abnormalities, and gastrointestinal symptoms (diarrhea, abdominal pain, flatulence, constipation, nausea, vomiting).

Efficacy:

Sandostatin LAR® Depot was evaluated in three clinical trials in acromegalic patients. In two of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level <5 ng/mL on Sandostatin® Injection given in doses of 100 mcg or 200 mcg t.i.d. Most patients were switched to 20 mg or 30 mg doses of Sandostatin LAR® Depot given once every 4 weeks for up to 27 to 28 injections. Growth hormone and IGF-1 levels were at least as well-controlled with Sandostatin LAR® Depot as they had been on Sandostatin® Injection and this level of control remained for the entire duration of the trials.

Table 2.4.1 Hormonal Response in Acromegalic Patients Receiving 27 to 28 Injections During Treatment with Sandostatin LAR® Depot

Mean Hormone Level	Sandostatin® Injection S.C		Sandostatin LAR® Depot	
	N	%	N	%
GH <5.0 ng/mL	69/88	78	73/88	83
<2.5 ng/mL	44/88	50	41/88	47
<1.0 ng/mL	6/88	7	10/88	11
IGF-1 normalized	36/88	41	45/88	51
GH <5.0 ng/mL + IGF-1 normalized	36/88	41	45/88	51
<2.5 ng/mL + IGF-1 normalized	30/88	34	37/88	42
<1.0 ng/mL + IGF-1 normalized	5/88	6	10/88	11

1 Average of monthly levels of GH and IGF-1 over the course of the trials

A third trial was a 12-month study that enrolled 151 patients who had a GH level <10 ng/mL after treatment with Sandostatin® Injection (most had levels <5 ng/mL). The starting dose of Sandostatin LAR® Depot was 20 mg every 4 weeks for 3 doses. Thereafter, patients received 10 mg, 20 mg or 30 mg every 4 weeks, depending upon the degree of GH. For the 122 patients who received all 12 injections in the third trial, a mean GH level of <2.5 ng/mL was observed in 66% receiving Sandostatin LAR® Depot. Over the course of the trial 57% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels.

Safety:

Gastrointestinal Symptoms

The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 2.4.2. Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

Table 2.4.2 Number (%) of Acromegalic Patients with Common G.I. Adverse Events

Adverse Event	Sandostatin® Injection S.C t.i.d n=114		Sandostatin LAR® Depot q. 28 days n=261	
	N	%	N	%
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
Nausea	34	(29.8)	27	(10.3)
Vomiting	5	(4.4)	17	(6.5)

Gallbladder Abnormalities

In clinical trials with Sandostatin® Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin® Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure. In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR® Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

Glucose Regulation

In non-diabetics and Type II diabetics with partially intact insulin reserves, Sandostatin Injection or Sandostatin LAR Depot administration may result in decreases in plasma insulin levels and hyperglycemia. In acromegaly patients treated with either Sandostatin® Injection or Sandostatin LAR® Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients. It is recommended that glucose tolerance and antidiabetic treatment be periodically monitored during therapy with these drugs.

Thyroid Function

Hypothyroidism has been reported in acromegaly and carcinoid patients receiving octreotide therapy. In acromegaly patients receiving Sandostatin® Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin® Injection. In acromegalics treated with Sandostatin LAR® Depot hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR® Depot, required initiation of thyroid hormone replacement therapy. Baseline and periodic assessment of thyroid function (TSH, total and/or free T4) is recommended during chronic octreotide therapy.

Cardiac Function

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin® (octreotide acetate) Injection therapy. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease. Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary.

Pain At the Injection Site

Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose-related, being reported by 2%, 9%, and 11% of acromegalics receiving doses of 10 mg, 20 mg and 30 mg, respectively, of Sandostatin LAR® Depot.

Nutrition

Octreotide may alter absorption of dietary fats in some patients. Depressed vitamin B12 levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B12 levels is recommended during therapy with Sandostatin LAR® Depot.

Drug Interactions

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection. Patients receiving insulin, oral hypoglycemic agents, beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents. Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine. Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.

2.5 Presubmission Regulatory Activity

Concerns regarding a possible class effect of somatostatin analogues in association with abnormalities of cardiac valves originated in _____

_____ The safety database for _____ derived from open-label, uncontrolled trials involving a total of 326 patients with acromegaly. In addition, safety data were reported from 1358 additional patients exposed to lanreotide in Phase 1, 2, and 3 protocols involving normal volunteers and patients (most with other than acromegaly). One hundred fifteen patients with acromegaly were treated for more than 15 months. With a notable exception, the safety profile for lanreotide was similar to that of the octreotide-containing drug products for the same indication. Specifically, non-serious gastrointestinal events attributed to the pharmacology of the drug and the occurrence of gallstones and biliary sludge dominate the safety profile. Between 25 and 35% of patients with acromegaly treated with lanreotide in clinical trials developed new gallstones or sludge, though only 1% of total patients underwent cholecystectomy. Serious GI AEs occurred in 3-4% of patients with diarrhea the most common cause for discontinuation (9.6%). Discontinuation for cholelithiasis occurred in 4 patients overall (1.3%)¹⁶.

Most troubling with regard to safety was the finding of valvular heart disease in patients treated with lanreotide. This was the major safety issue raised _____ The _____ study (_____ #705) included one center at which a substudy involving echocardiographic follow up to assess changes in myocardial hypertrophy and cardiac function was conducted. Over the course of the 18-month study (including extension), of the 22 patients enrolled at this center, 18 (82%) developed *de novo* or worsened retrograde transvalvular flow on echo during

the course of treatment, often affecting multiple valves and with no obvious pattern of valvular involvement across affected patients. Dr. Temeck emphasized in her review that the incidence of regurgitation on echo increased with time, that the severity of the regurgitation increased in 11 of 18 patients and that there was an associated increase in LV size in 10 of 18 affected patients. However, the majority of these patients were asymptomatic and the degree of regurgitation was described as trace to mild. This was an open-label study, there was no comparator group and there was no standardization of the performance or the interpretation of these echocardiograms. In sum, the study was inconclusive with regard to an effect of lanreotide on cardiac valve function.

Echocardiographic investigations in other studies of — were inconsistent with respect to detection (or note) of valvular regurgitation, although in one study (8065), 11 out of 80 patients treated for one year with — showed new-onset or worsening valvular regurgitation based on paired echo studies. These supportive studies did not have rigorous protocol-defined criteria for evaluation of echocardiograms, so that the absence or lower rate of adverse valvular findings in these trials could not be taken as definitively contradicting the findings in study 705 and thus provided no reassurance with regard to the cardiovascular safety of lanreotide in acromegalics.

Summary of Issues

1. Clinical: The rate of valvular regurgitation observed in the echocardiograms performed in Study 705 raise significant concerns regarding the cardiac safety of lanreotide in patients with acromegaly.
2. Pharm/Tox: Need to conduct carcinogenicity evaluations in two species using adequate exposures relative to clinical dosing.
- 3.
- 4.
5. Biopharm: In the study with hepatically impaired patients, the majority of patients recruited were only mildly hepatically impaired. The hepatically impaired patient population should have included moderately to severely impaired patients as specified in the protocol. The evaluation of hepatic function should also be based on CHILD PUGH classification. Therefore, the hepatic population study and conclusion are not acceptable.

Under IND 53,993 in DFS dated 06 Sept 2002 DMEP provided a written response to the company's proposed prospective cardiac safety study. DMEP agreed with the sponsor that the proposed design was acceptable. We commented that this study was an observational treatment protocol of a size and duration adequate to detect nothing less than a marked difference in the

cardiovascular adverse event profiles of the two drugs, which is not expected. The company asked if the proposed study could be used to support the cardiac safety of prolonged release formulation of lanreotide acetate and DMEP replied that the study would not “support” the cardiac safety of lanreotide, but would permit characterization of the valvular changes expected among patients of the type recruited during courses of therapy with lanreotide or octreotide. In the absence of a control group not treated with somatostatin analogue but otherwise matched for variables related to the underlying disease, no inferences would be possible regarding a causal role of drug in any observed valvular changes.

Additional comments included:

1. A control group of patients with acromegaly, matched with regard to extent and estimated duration of disease, degree of hormonal control, and metabolic and anatomic sequelae would provide a context in which to permit inference as to the role of drug in any observed differences in the adverse event experiences between treatment groups.
2. Both normal subjects and those with severe valvular regurgitation should undergo echocardiography and their studies should be included at random among those collected from the study subjects. These are to serve as controls (both positive and negative) for the reading and interpretation of the echocardiograms.
3. Submit your definition of “significant regurgitation” for each valve, as well as a prespecified study procedure for obtaining the desired echocardiographic views, a list of the parameters to be analyzed, reference ranges for each value, and sample case report forms.
4. Depending upon the findings of this prospective observational study, labeling may need to include clinical guidance to physicians regarding monitoring of acromegalics with regard to cardiac valvular disease.
5. Should a non-somatostatin-analogue effective medical therapy for acromegaly become available, a comparative safety study with lanreotide should be considered.

On 06 July 2004 a pre-NDA meeting was held to discuss filing an NDA for IND 53,993 Lanreotide Acetate. The minutes from this meeting are in DFS under IND 53,993 dated 20 May 2004.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to Chemistry review by Dr. Chien-Hua Niu

Lanreotide is a new chemical entity. Lanreotide acetate is manufactured by Ipsen Manufacturing Ireland Ltd (IMIL), the DMF holder.

- International Non-proprietary Name: Lanreotide (I.N.N.) acetate
- Chemical name : (cyclo S-S)- 3-(2-naphthyl)- D-alanyl-L-cysteinyl- L-tyrosyl- D-trptophyl- L-lysyl-L-valyl- L-cysteinyl--threoninamide, acetate
- USAN: lanreotide acetate

It is supplied in a single, sterile, pre-filled, ready-to-use polypropylene syringe fitted with a needle covered by a dry natural rubber sheath. Each prefilled syringe is packed in a laminated pouch. Lanreotide acetate must be stored in a refrigerator at 2° C to 8° C (36° F to 46° F) in its original package.

Investigational studies were performed under Ipsen Biotech's IND 53,993

Initially, the product was developed as an immediate release formulation then as a micro-particle formulation. The micro-particles were manufactured

Subsequently, a new lanreotide acetate (Somatuline) formulation was developed. This manufacturing process for the new formulation does not use

A pre-NDA meeting pertaining to the Somatuline was held on 06-July-2004. Included in the discussion was a novel *in vitro* release test involving

The Agency agreed that although the approach was novel it was acceptable. The Agency recommended using both clinical and commercial batches to set the specifications for the *in vitro* release test. The Agency agreed that physicochemical characterization was acceptable to demonstrate comparability; however, a bioequivalence study may also be needed. of the pre-filled syringes was also discussed. The Agency requested inclusion of information on the effect of the

The Agency indicated that the proposed physicochemical characterization and quality control testing appeared acceptable. A change in the manufacturing site for investigational drug product from Ipsen, Dreux, France to Ipsen, Pharma Biotech, Signes, France for commercialization was also discussed.

3.2 Animal Pharmacology/Toxicology

Please refer to Pharm/Tox review by Dr. Da-lin Yao

The basic preclinical pharmacology, toxicology and pharmacokinetics were initially performed the MPF formulation. Pharm/Tox Issues from

are:

- Conduct carcinogenicity evaluations in two species using adequate exposures relative to clinical dosing.

The company's dose selection and carcinogenicity assay protocols were submitted to the Executive Carcinogenicity Assessment Committee (ECAC) for review. These were discussed with the ECAC during an April 11, 2002 teleconference and the protocols (77005 and 77006) were submitted to FDA on September 16, 2002, (IND 53,993, Serial 100, 101). These studies were conducted; _____ out FDA stated in their September 4, 2001 letter that carcinogenicity studies conducted with the active component are considered sufficient.

The following excerpts are from Ipsen's pharm/tox submission.

Effects of Lanreotide on the Cardiovascular System

According to the sponsor, the results from the *in vitro* electrophysiological studies in the HERG and in isolated canine Purkinje fibers, the *in vivo* QT assessment in dogs and the results from the ECGs performed in dogs in the 26-week toxicity study with lanreotide acetate at plasma concentrations of approximately 16 to 23-fold the exposure observed at the MRHD demonstrated that lanreotide did not induce cardiovascular toxicity.

In the patch-clamp assay in which the HERG tail current (I_{Kr}) is measured in human embryonic kidney cells (HEK-293) stably transfected with HERG-1 cDNA, lanreotide at 10⁻⁵ M produced no statistically significant inhibition of HERG tail current. Lanreotide was tested for adverse effects on cardiac action potential in isolated canine Purkinje fibres. Lanreotide, at concentrations of 10⁻⁷, 10⁻⁶ and 10⁻⁵ M, had no statistically significant effect on action potential parameters under either normal (1 Hz) or low (0.33 Hz) stimulation rates.

Lanreotide (5, 20, or 80 mcg/kg) was administered by the intravenous route to normotensive, anaesthetized (pentobarbital) rats and the effects of the drug on blood pressure, heart rate and electrocardiogram (ECG) were observed. In addition, effects of the drug on cardiovascular responses to adrenalin, noradrenalin, isoprenaline and acetylcholine were monitored. Lanreotide (and somatostatin (80 mcg/kg) produced transient, non-dose dependent hypotensive responses immediately after injection. Somatostatin caused bradycardia of about 10 minutes duration but lanreotide did not. Lanreotide did not affect the blood pressure response to the standard agents tested.

Cardiovascular effects of intravenous doses (20 or 80 mcg/kg) of lanreotide were assessed in anaesthetized (pentobarbital) dogs. Groups of three male and three female Beagle dogs were used. Lanreotide was administered by intravenous infusion over periods of two minutes. Cardiovascular parameters monitored included arterial blood pressure, heart rate, femoral and arterial flow, respiration rate and amplitude, ECG, and blood gases (PO_i, PCO₂, HC0₃) and pH. Lanreotide caused no significant changes in blood pressure or venous or arterial flow. At the dose of 80 mcg/kg, a transient bradycardia was observed for one minute.

The *in vivo* evaluation of lanreotide infused at 1, 3 and 10 mg/kg over a 24 hour period in six conscious, radio-telemetry instrumented dogs showed no statistically significant change in arterial blood pressure, heart rate, QRS complex duration and QT interval corrected for heart rate using Bazetts and Fridericia's formulas or Sarma's method.

lanreotide acetate in 108 acromegalic patients. The study was conducted in several centers located in the US, Europe and Hong-Kong.

2. The second study, E-54-52030-081 (referred to as Study 081) was a baseline-controlled study evaluating the effect of lanreotide acetate on GH/IGF-1 levels compared to pre-treatment values, in 63 acromegalic patients.

A supportive study, the self-administration study Y-97-52040-150 (referred to as Study 150) assessed the feasibility of patient self-administration of lanreotide acetate, either by themselves or by their partners.

Additionally, there were five studies with lanreotide MPF that provided supportive data on the long term treatment of acromegalic patients with lanreotide. These were long term efficacy studies (of more than 6 months duration) in which the aim was for acromegalic patients to achieve optimal control of their disease by titrating their monthly dose of lanreotide. In these studies, 30 mg lanreotide MPF was administered; the dosing interval could be adjusted from one dose every 14 days to one dose every 10 or 7 days, corresponding to equivalent monthly doses of 60, 90, and 120 mg lanreotide acetate, respectively. These studies were reviewed by Dr. Temeck,

The evaluation for safety is based on the following studies:

1. Study 717
2. Study 081
3. Study E28-52030-709 (Study 709) and the long-term follow up study E28-52030-710
4. Study 710 with a primary objective to demonstrate that lanreotide acetate is not less effective than the MPF formulation in controlling GH and IGF-1 levels. Study 709 employed a "switch" design in which patients adequately controlled on the MPF formulation were switched to the lanreotide acetate formulation to demonstrate maintenance or improvement of GH and IGF-1 levels. Study 710 allowed dose titration to optimize GH and IGF-1 control.
5. Study 721: A multicenter prospective controlled observer blinded cohort study in patients with acromegaly to evaluate the risk of cardiac valvular regurgitation in patients treated with lanreotide relative to patients treated with octreotide
6. Study 076: A Phase II, randomized, parallel groups, double-blind pharmacokinetic study of lanreotide acetate (60, 90, or 120 mg) after 4 deep subcutaneous injections (administered every 28 days) in acromegalic patients
7. Study 087: A Phase II multi-center, open-label study, evaluating the safety and efficacy of multiple deep subcutaneous administrations of lanreotide acetate (60, 90, 120 mg) in acromegalic patients with IGF-1 level abnormal

Foreign postmarketing safety data is also reviewed in this submission.

4.2 Tables of Clinical Studies

Table 4.2.1. Pivotal Efficacy Studies

Study Identifier	Pretreatment at Baseline	Study Design and Type of Control	Lanreotide Dose	Number of Subjects	Duration of Treatment
E28-52030-717					
Placebo-controlled period	SSAs and dopamine agonists washed out, last surgery > 3 months, last radiotherapy > 3 years before study start	Parallel group, double-blind, randomized, placebo-controlled	Fixed (60, 90, or 120 mg, or Placebo)	108	4 weeks
Fixed dose period	SSAs and dopamine agonists washed out, last surgery > 3 months, last radiotherapy > 3 years before study start	Parallel group, single-blind*, randomized	Fixed (60, 90, or 120 mg)	107	16 weeks
Dose titration period	SSAs and dopamine agonists washed out, last surgery > 3 months, last radiotherapy > 3 years before study start	Open label	Titrated (60, 90, or 120 mg)	105	32 weeks
E54-52030-081					
	SSAs and dopamine agonists washed out, last surgery > 3 months, last radiotherapy > 3 years before study start	Open label	Titrated (90 mg starting dose with titration to 60, 90 or 120 mg)	63	48 weeks

*During the Study 717 fixed dose period investigators were blinded to dose but not to treatment. However, this blind was broken prior to the dose titration phase to allow and appropriate choice of titrated dose.

Table 4.2.2. Pivotal Safety Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Regimen; Route of Administration	Number of Subjects	Duration of Treatment
Efficacy and safety	E-28-52030-717	Investigate the PK, PD, efficacy and safety profile of lanreotide acetate	Phase II multi-centre randomized double-blind	Lanreotide acetate 60 mg, 90 mg, 120 mg or equivalent placebo for 4 weeks then 16 week fixed dose phase of treatment at 60 mg, 90 mg or 120 mg and then 32 week dose titration phase of 8 injections of lanreotide acetate. All deep s.c. into the buttock.	108	52 weeks
Efficacy and safety	E-54-52030-081	Efficacy and safety	Phase III multicenter open label	Lanreotide acetate. Fixed dose phase: 4 times 90 mg s.c. injections at 4-week intervals. Titrated dose phase: 8 times 60 mg, 90 mg or 120 mg s.c. injections at 4-week intervals according to clinical response.	entered: 63 completed: 57	48 weeks
Safety	E-28-52030-709	Efficacy and safety	Phase III multicenter open label comparative	Five lanreotide MPF 30 mg 5 i.m. at 5- to 16-day intervals followed by 3 deep s.c. injections of lanreotide acetate (60, 90 and 120 mg) every 28 days. Each dosing interval was based on the last dosing interval of lanreotide MPF 30 mg before study entry (between 5 and 16 days).	safety: 144 ITT: 132 PP: 107	Lanreotide MPF for 3.6 to 11.4 weeks followed by a lanreotide acetate for 12 weeks

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Safety	E-28-52030-710	Efficacy and safety	Phase III multicenter open label comparative extension of study E-28-52030-709	Lanreotide acetate at titrated doses 60 mg, 90 mg or 120 mg every 28 days for 48 weeks. All deep s.c. injections.	safety: 130 ITT: 124 PP: 88	48 weeks.
Safety	E-91-52030-087	Efficacy and safety	Phase II multicenter open label dose titration	Lanreotide acetate 60 mg, 90 mg and 120 mg deep s.c. injections. Fixed dose phase: 5 injections of lanreotide acetate 90 mg at 28-day intervals. Open label dose-titration phase: 7 injections of lanreotide acetate; dose adjusted to 60 mg or 120 mg according to GH and IGF-1 levels before the fifth injection.	entered: 11 completed: 9	56 weeks
Safety	2-47-52030-721	Determine the risk of new or worsening valvular regurgitation in any valve in patients with acromegaly treated with lanreotide, relative to patients treated with octreotide	Phase IV multicenter prospective observer-blinded	Patients continued to receive either lanreotide MPF or octreotide as prescribed. <i>De novo</i> patients commenced treatment with either lanreotide or octreotide within the 2 weeks following their baseline echocardiography.	Lanreotide: entered: 107 completed: 99 Octreotide: entered: 118 completed: 102	48 weeks
Safety	E-28-52030-076	Evaluate PK profile, efficacy and safety	Phase II randomized double blind parallel group	Lanreotide acetate 60 mg, 90 mg or 120 mg as deep s.c. in the upper quadrant of the buttock. 4 fixed doses at 28 day intervals.	18	16 weeks 27 weeks including screening

Additional clinical studies with lanreotide are in Section 10.3 and include the following tables:

- Table 10.3.1 Clinical studies with lanreotide in acromegalic patients, intrinsic factor studies or studies in healthy subjects
- Table 10.3.2. Studies with lanreotide in other indications

4.3 Review Strategy

The clinical reviewer conducted an independent review, but collaborated on areas of controversy and individual questions. The focus of this review is the seven clinical studies listed in Section 4.1.

4.4 Data Quality and Integrity

A number of provisions were included to enhance data integrity:

- A Clinical Research Associate assigned by the sponsor via the CRO conducted regular visits (every 4 to 6 weeks) to the trial centers to monitor various aspects of the study, including the dispensing and storage of clinical supplies and study files.
- A centralized analysis of ECG and echocardiography data was conducted in addition to review at the local study sites.

- Audits were performed at clinical study sites, at the contract research organization, at the central laboratories, and at the drug storage location. All audits were performed by the R&D IQA department of the Ipsen group.

The Division of Scientific Investigations was consulted on 9 February 2007 to audit the following protocols/sites essential for approval:

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site 701 Investigator Shlomo Melmed, MD ** Pituitary Center 8635 West Third Street, Suite 490 Los Angeles, CA, USA 90048	Study E-28- 52030-717	16	Treatment of acromegaly
Site 6 Pr Philippe Caron C.H.U. de Rangueil Service d'Endocrinologie 1, Avenue Jean Poulhes 31403 Toulouse, Cedex	Study E-54- 52030-081	13	Treatment of acromegaly
Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site 301 Josef Marek, Professor 1st School of Medicine Charles University Prague Czech Republic	Study 2-47- 52030-721	10	Treatment of acromegaly

Sites were selected based on the number of study subjects enrolled and due to

The DSI inspection audited Protocol #E-28-52030-717 and focused on the following clinical investigators: Shlomo Melmed, M.D. (site 701) and David Cook, M.D. (site 703). The inspection reviewed the following: quality assurance and clinical operations, study monitoring procedures, informed consents, participating clinical investigators, monitoring reports, IRB documentation, CRFs, data collection, and study drug accountability. The inspector also compared selected subject CRFs with the firm's data listings.

An audit of 3 subjects' records for site 701 and 3 subjects' records for site 703 was conducted.

Inspection of Dr. David Cook, Study site 703, revealed that 19 subjects were screened; 9 subjects were randomized and 8 subjects completed the study. Subject 703.0001 experienced an SAE of a fractured hip and was withdrawn from the study. An audit of all randomized subjects' records was conducted. Significant findings are as follows:

- 1) For Subjects (0003, 0009, 0011, and 0014), the nurse who was the unblinded administrator of study drug performed study assessments at several subsequent visits during the single-blind phase of the study.
- 2) Subject 703.0011 received the first injection of study drug before all safety assessments were completed.
- 3) Echocardiogram tapes were not maintained for subjects 703.0016 and 703.0017.
- 4) Subject 703.0016 did not sign an IRB-approved Spanish language version of the consent form.

DSI conclusion was that the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Inspection of Dr. Shlomo Melmed, Study site 701, revealed that at this site, 17 subjects were randomized into the study. An audit of 17 subjects' records was conducted. No regulatory violations were noted. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4.5 Compliance with Good Clinical Practices

The applicant asserts that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with the International Congress on Harmonization Good Clinical Practice guidelines. Each investigational center obtained approval from its Institutional Review Board or Independent Ethics Committee. All patients gave informed written consent before entering the trials. In addition, all local regulatory requirements were followed.

Protocol violations were common with the primary reason for exclusion from the per-protocol group being related to assessments or study visits not conducted within the required windows for analysis. This reviewer does not believe the protocol violations affected the studies conclusions regarding the efficacy or safety of lanreotide. Protocol violations for the pivotal efficacy study, Study 717, are detailed below:

Of the 108 patients included in the ITT population, 14 (13%) did not fulfill the criteria to be included in the PP population for analysis of efficacy data from the double-blind study phase (Table 4.5.1). A lower proportion of patients in the lanreotide acetate 60 mg treatment group were excluded from the PP population (4%) as compared to the other 3 treatment groups ($\geq 14\%$). The primary reason patients were excluded from the PP population during the double-blind phase was that the interval between the first injection of study medication (visit 3) and the GH assessment at visit 4 was not 28 ± 3 days ($N = 10$).

Table 4.5.1. Reasons for Exclusion from the Per Protocol Populations in the Double-blind Study Phase (by Dose as received in Double-blind) and Double/Single-blind Study Phase (by Dose as received in Single-blind)

Study Phase Reason for Exclusion	Lanreotide Autogel:			Placebo	Total
	60 mg	90 mg	120 mg		
Double-blind Study Phase¹					
ITT population	27 (100%)	27 (100%)	29 (100%)	25 (100%)	108 (100%)
Total excluded	1 (4%)	5 (19%)	4 (14%)	4 (16%)	14 (13%)
< 25 or >31 days between injection at V3 and GH assessment at V4	0	4 (15%)	4 (14%)	2 (8%)	10 (9%)
Received dopamine agonist after study entry	1 (4%)	0	0	1 (4%)	2 (2%)
No further efficacy assessments	0	0	0	1 (4%)	1 (1%)
No GH at V1	0	1 (4%)	0	0	1 (1%)
Double/Single-blind Study Phase¹					
ITT population	34 (100%)	36 (100%)	37 (100%)	--	107 (100%) ¹
Total excluded	3 (9%)	9 (25%)	6 (16%)	--	18 (17%)
Excluded from PP in Double-blind phase	2 (6%)	5 (14%)	6 (16%)	--	13 (12%) ¹
No efficacy assessment at V10	0	2 (6%)	0	--	2 (2%)
At least one interval ≥35 days between injections 2 to 5	1 (3%)	1 (3%) ²	0	--	2 (2%) ²
GH assessment at V10 >35 days after previous injection	0	1 (3%)	0	--	1 (1%)

Data source: Sponsor Section 14.1, Table 2.3B1.

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

¹ One patient excluded from the PP population during the double-blind phase withdrew from the study prior to entry into the single-blind phase.

² Two additional patients (701.0016 and 721.0006) who were excluded from the PP population during the double-blind phase, and also had at least one interval ≥35 days between injection 2 to 5.

Of the 107 patients included in the ITT population for the double/single-blind study phase, 18 patients (17%) did not fulfill the criteria to be included in the PP population for this phase (Table 4.5.1). A total of 3 (9%), 9 (25%) and 6 (16%) patients were excluded from the lanreotide acetate 60 mg, 90 mg and 120 mg dose groups, respectively. The primary reason for exclusion from the PP population for the double/single-blind study phase was exclusion from the double-blind phase (N = 13); 5 additional patients were excluded from the double/single-blind phase for reasons as presented in Table 4.5.1. Table 4.5.2 presents the reasons for exclusion across all study phases; results are displayed by last dose of lanreotide administered during the study and all reasons for exclusion from all study phases are presented.

Table 4.5.2. Reasons for Exclusion from the Per Protocol Populations in the Double/Single-blind and Open-label Study Phases by Last Dose Administered

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

Data source: Sponsor Section 14.1, Table 2.3B2.

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

Note: Patients may have had more than one reason for exclusion and may therefore appear in more than one category.

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

Of the 107 patients included in the ITT population for the double/single-blind and open-label phases, 31 (29%) were not included in the PP population for the 3 study phases for reasons as presented in Table 4.5.2. The 31 patients included 5 (24%) of 21 patients in the 60 mg last dose group, 8 (47%) of 17 patients in the 90 mg last dose group, and 18 (26%) of 69 patients in the 120 mg last dose group. The primary reasons for exclusion were related to assessments or study visits not conducted within the required windows for analysis.

4.6 Financial Disclosures

In accordance with 21 CFR § 54.4(a)(3)(i)-(iv) the applicant provided a list of all Clinical Investigators with disclosable financial interests and/or arrangements who participated in the Covered Clinical Studies supporting this New Drug Application. The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators.

Table 4.6.1. Clinical Investigators Participating in Covered Clinical Study for this New Drug Application for whom a Disclosable Financial Interest Exists

Covered Clinical Study(ies)	Clinical Investigator	Type of Financial Interest / Arrangement	Payor	Applicable Contract Period	Amount
		Consulting Agreement	Henri Beaufour Institute USA* / Biomeasure Incorporated* 27 Maple Street Milford, MA	/	\$175,000
		Consulting Agreement	Ipsen Limited* Maidenhead Berkshire, SL6 4UH UK	/	\$8,000
		Travel		/	\$14,801
		Consulting Agreement	Speywood Pharmaceuticals, Inc.* 27 Maple Street Milford, MA	/	\$15,625
		Educational Grants (travel and expenses)	Ipsen, S.p.A.* Via G. Ripamonti, 332/4 20141 Milan Italy	/	\$12,375
				/	\$11,140
		Research Funding Agreement	Biomeasure Incorporated* 27 Maple Street Milford, MA	/	\$160,000

* Beaufour Ipsen Pharma (Paris, France) is the NDA applicant and is part of the Ipsen Group of companies. All companies listed as payors are affiliates of Beaufour Ipsen Pharma and are part of the Ipsen Group of companies.

Steps taken to minimize bias include:

- The efficacy of the Covered Clinical Studies in which the Clinical Investigators identified in Table 4.6.1 above participated was based on evaluating objective biochemical laboratory values. These values were determined from blood samples evaluated by a central clinical laboratory.
- The normal laboratory values used for these laboratory parameters are based on published literature.
- The statistical analysis plan to evaluate the results includes a center by center evaluation to identify any potential biases.
- The clinical trials were monitored by a Contract Research Organization according to the principles of Good Clinical Practice.

5 CLINICAL PHARMACOLOGY

Please refer to Clin Pharm review by Drs. Jayabharathi Vaidyanathan and Hao Zhu.

Clinical Pharmacology issues
 — involved

Additionally, in the study with hepatically impaired patients, the majority of patients recruited were only mildly hepatically impaired. The hepatically impaired patient population should have included moderately to severely impaired patients as specified in the protocol. The evaluation of hepatic function should also have been based on CHILD PUGH classification. Therefore, the hepatic population study and conclusion were not acceptable.

Data from 5 different studies were used to evaluate the bioavailability of lanreotide acetate. The critical study with the intended market formulation is A-93-5200-149. No change in formulation was made from Phases 2 to 3.

Table 5.1 Overview of Bioavailability Studies

Study	Study Design	Treatment	Population
149	Single center, open label, randomized, parallel group*	Lanreotide IR 7 µg/kg i.v. then lanreotide acetate (0.246 mg/mg) 60, 90 or 120 mg dose strength, deep s.c., superior-external quadrant of the buttock	50 healthy subjects received lanreotide IRF, of whom 38 then received lanreotide acetate
038	Single center, Double blind, randomized, parallel group*	Lanreotide IRF 1 mg i.v. then one of the following: lanreotide acetate (0.246 mg/mg) 60, 90 or 120 mg dose strength i.m. or 60 mg s.c.; lanreotide acetate (0.287 mg/mg) 60 mg dose strength i.m.; lanreotide acetate (0.205 mg/mg) 60 mg dose strength i.m. or s.c.	42 healthy subjects received lanreotide IRF and lanreotide acetate
032	Single center, Double blind, randomized, parallel group*	Lanreotide IRF 1 mg i.v. then either lanreotide acetate (0.287 mg/mg) 30, 40 or 60 mg s.c. or lanreotide MPF 30 mg i.m.	24 healthy subjects received lanreotide IRF, of whom 18 then received lanreotide acetate and 6 received lanreotide MPF
175	Single center, open label, randomized, cross-over	Lanreotide IRF 7 µg/kg (s.c. vs. i.v.) then lanreotide IRF s.c. (7, 21 and 42 µg/kg) and i.v. (7 µg/kg), then lanreotide MPF 30 mg i.m.	12 healthy subjects received lanreotide IRF and lanreotide MPF
180	Multicenter, Open label, Non comparative*	Lanreotide IRF 7 µg/kg i.v. then lanreotide IRF 7 µg/kg s.c. then lanreotide MPF 30 mg dose strength i.m. first as a single dose, then every 14 days up to the third month and then every 10 or 14 days from the third month until study completion (6 months)	14 acromegalic patients received lanreotide IRF, of whom 13 then received lanreotide MPF

* = The initial dose of lanreotide IRF was administered to determine bioavailability and so these studies are not considered crossover studies.

Lanreotide acetate forms a drug depot at the injection site due to the interaction of the formulation with physiological fluids. The most likely mechanism of the prolonged sustained release demonstrated with lanreotide acetate is by prolonged passive diffusion. The release

profile of lanreotide acetate is characterized by a limited initial burst release of approximately 8%, followed by a sustained release. The apparent terminal half-life of lanreotide acetate of 23 to 30 days is due to the slow release of lanreotide from the drug depot at the injection site, and not due to the $T_{1/2}$ of the peptide itself.

The following is an excerpt from Dr. Zhu's review:

The major pharmacometric findings are:

- Diarrhea is the most common adverse effect (AE). After initialization of Somatuline Autogel treatment, the probability of a patient to develop diarrhea is driven by dose. The probability for a patient to develop diarrhea is about 28% at the dose of 60 mg, and is increased to 46% at the dose of 120 mg.
- Diarrhea appears to be a transient AE. 64% patients who received 120 mg dose for 3 consecutive periods had diarrhea in the first dosing period, whereas, only 21%, 11% had it in the 2nd and 3rd periods.
- The other major adverse events (bradycardia, hypertension, diabetics, and anemia) were not dose related, based on the first treatment period of Studies E28 52030 717, E28 52030 709/710, and E28-52030-076. No obvious trend is identified cross the dose range from 60 mg to 120 mg.
- Following long term therapy at the highest dose (120 mg), no trend in the incidence of other major adverse events (bradycardia, hypertension, diabetics, and anemia) is identified over time.

The following is an excerpt from Dr. Vaidyanathan's review:

- The pharmacokinetics of lanreotide was only obtained in end stage renal impaired patients, who had increased lanreotide half-life (2 times) and exposure (2-4 times) as compared to normal subjects. There is no information regarding exposure in mild, moderate and severe renal impaired patients. Also there were very few renal impaired patients (N= ~3) in the clinical trials to draw conclusions regarding safety. Although the mechanism of increase in exposure in ESRD is unknown, it is reasonable to assume similar increase in exposure in moderate and severe renal impaired patients. Therefore, it is recommended to start dosing at 60 mg in moderate and severe renal impaired patients.
- The clearance of lanreotide was about 30% lower in moderate and severe hepatic impaired patients as compared to healthy subjects. This hepatic impairment study also showed a trend of increase in exposure in moderate as compared to mild hepatic impairment. No dose adjustment is needed in case of mild hepatic impairment. However, it is recommended to start dosing at 60 mg, in moderate and severe hepatic impaired patients.
- *Efficacy*: The sponsor's analysis of the pharmacodynamic model based on pivotal clinical study E28-52030-717 was found acceptable to describe the growth hormone change over time. The conclusions from this analysis were as follows:
 - Based on the population pharmacodynamic model developed by the sponsor, the therapeutic doses selected by the sponsor (60 mg, 90 mg, 120 mg) are close to the E_{max} of growth hormone reduction in the responder population.
 - Based on the modeling outcome, the proposed dosing appears to be acceptable.

Safety: The major pharmacometric findings are:

- Diarrhea was the most common adverse effect (AE). After initialization of Somatuline Autogel treatment, the probability of a patient to develop diarrhea was driven by dose. The probability for a patient to develop diarrhea was about 28% at the dose of 60 mg, and was increased to 46% at the dose of 120 mg.
- After initialization of Somatuline Autogel treatment,
 - Elder patients (≥ 65 years) do not appear to have a higher incidence of diarrhea.
 - Within the elder patients, diarrhea does not appear to be dose-dependent.
 - Within the younger patients (age < 65 years), the incidence for diarrhea is about 50% at the dose of 120 mg after initialization of Somatuline Autogel treatment. However, under current proposed initial dosing regimen (i.e. 90 mg every 28 days), the incidence of diarrhea is about 30% in the younger patients.
- Diarrhea appeared to be a transient AE. 64% patients who received 120 mg dose for 3 consecutive periods had diarrhea in the first dosing period, whereas, only 21%, 11% had it in the 2nd and 3rd periods.
- The other major adverse events (bradycardia, hypertension, diabetes, and anemia) were not dose related, based on the first treatment period of Studies E28-52030-717, E28-52030-709/710, and E28-52030-076. No obvious trend was identified across the dose range from 60 mg to 120 mg.
- Following long term therapy at the highest dose (120 mg), no trend in the incidence of other major adverse events (bradycardia, hypertension, diabetes, and anemia) was identified over time.

5.1 Pharmacokinetics

No new PK studies were conducted in renally impaired patients using lanreotide acetate. Studies were previously conducted under _____ submission. Serum clearance of lanreotide was approximately halved in patients with impaired renal function (patients had end-stage renal function and were on dialysis) compared to healthy subjects, following a single i.v. injection of 7 $\mu\text{g}/\text{kg}$ lanreotide IRF. In discussion with Dr. Vaidyanathan, it appears reasonable to start dosing at 60 mg in renally impaired patients due to the reduced clearance in these patients.

A PK study was conducted in hepatically impaired individuals using the CHILD PUGH scale; there were 6 moderate and 2 severe hepatically impaired patients. Serum clearance of lanreotide was reduced by approximately 30% in patients with moderate to severe hepatic impairment after administration of 7 $\mu\text{g}/\text{kg}$ lanreotide IRF by i.v. infusion. Mean residence time (MRT) and volume of distribution were increased in patients with varying degrees of hepatic insufficiency. As there were very few patients with severe hepatic impairment evaluated in the PK studies and in the clinical studies, dosing should start at the lower 60 mg dose due to the reduced clearance of drug in these patients.

No new PK studies were conducted in elderly patients using lanreotide acetate. Terminal half-life increased 85% and MRT were longer in healthy elderly subjects compared to young healthy subjects following a 7 $\mu\text{g}/\text{kg}$ i.v. infusion of lanreotide IRF, with no significant differences in

clearance. AUC and volume of distribution at steady state in elderly healthy subjects were somewhat higher, but overlapped with the range of values seen in young healthy subjects.

Pharmacokinetic Profile /

Lanreotide acetate is thought to form a drug depot at the injection site due to the interaction of the formulation with physiological fluids. The most likely mechanism of drug release is a passive diffusion of the precipitated drug from the depot towards the surrounding tissues, followed by the absorption to the blood stream.

After a single deep s.c. administration, the mean absolute bioavailability of lanreotide acetate in healthy subjects was 73.4, 69.0 and 78.4%, for the 60, 90 and 120 mg doses respectively. Mean C_{max} values ranged from 4.3 to 8.4 ng/mL during the first day. Single dose linearity was demonstrated with respect to AUC but not C_{max}, which showed high inter-subject variability. Lanreotide acetate showed sustained release of lanreotide with a half-life of 23 to 30 days. Mean serum concentrations were > 1 ng/mL throughout 28 days at 90 mg and 120 mg and > 0.9 ng/mL with 60 mg.

In vivo input profiles show that the release of lanreotide occurs for at least 112 days following administration of lanreotide acetate by deep s.c. injection at doses of 60, 90 or 120 mg in healthy subjects. In a repeated dose administration PK study of lanreotide acetate in acromegalic patients, rapid initial release was seen giving peak levels during the first day after administration. At doses of lanreotide acetate between 60 and 120 mg linear pharmacokinetics were observed in acromegalic patients. At steady state mean C_{max} values were 3.8 ± 0.5 , 5.7 ± 1.7 and 7.7 ± 2.5 ng/mL increasing linearly with dose. The mean accumulation ratio index was 2.7 which is in line with the range of values for the half life of lanreotide acetate. A limited initial burst effect and a low peak to trough fluctuation (81% to 108%) of the serum concentration at the plateau was observed.

In a pharmacokinetic study, patients receiving four administrations of lanreotide acetate every 28 days had steady state trough serum lanreotide levels of 1.8 ± 0.3 ; 2.5 ± 0.9 and 3.8 ± 1.0 ng/mL at 60, 90 and 120 mg dose respectively. For the same doses, similar values were obtained in clinical studies after at least four administrations (2.3 ± 0.9 , 3.2 ± 1.1 and 4.0 ± 1.4 ng/mL respectively).

Lanreotide acetate has not been studied in special populations. For completeness, information on studies with an immediate release formulation (IRF) of lanreotide administered intravenously is provided. Note that although some changes in elimination or distribution have been observed after IRF administration, no changes in the apparent half-life are expected with lanreotide acetate as the terminal phase is controlled by the release of lanreotide from the formulation.

Subjects with severe renal insufficiency showed an approximate 2-fold decrease in total serum clearance of lanreotide, with a consequent increase in half-life and AUC.

Studies in healthy elderly subjects showed an increase in half-life and mean residence time (MRT) of lanreotide compared to those seen in healthy young subjects.

In moderate to severely hepatically-impaired subjects a 30% reduction in clearance of lanreotide was observed. Increase in MRT and volume of distribution occurred in subjects with all degrees of hepatic insufficiency.

In studies evaluating excretion, <5% of lanreotide was excreted in urine and less than 0.5% was recovered unchanged in feces, indicative of some biliary excretion.

Drug-Drug Interactions

The potential for drug-drug interactions with lanreotide has been evaluated in two plasma protein binding studies, one PK interaction study in healthy subjects, and a review of current scientific literature for reported drug interactions with lanreotide or the related SSA octreotide.

No major direct drug-drug interaction was identified, other than a 19% reduction in the relative bioavailability of cyclosporine in the presence of lanreotide. Therefore, concurrent administration of lanreotide acetate and cyclosporine may necessitate adjustment of cyclosporine dosage to maintain therapeutic levels. There was no effect on vitamin K. The gastrointestinal effects of lanreotide acetate may reduce the intestinal absorption of co-administered drugs including cyclosporine.

An indirect PK interaction is possible between lanreotide and drugs metabolized by the cytochrome P450 pathway. Published reports indicate that GH secretion modulates human hepatic cytochrome P450 activity^{18,19}. Thus, the regulation of GH by SSAs such as octreotide and lanreotide may affect cytochrome P450 activity and the metabolism of drugs by this pathway. Octreotide increases bromocriptine bioavailability, possibly through indirect modulation of cytochrome activity²⁰. Therefore, lanreotide may also increase the bioavailability of bromocriptine.

5.2 Pharmacodynamics

The primary pharmacodynamic effect of lanreotide is to suppress GH secretion by normal pituitary somatotroph cells as well as adenomatous somatotroph cells. In the treatment of acromegaly GH secretion is inhibited through lanreotide binding to human somatostatin receptor subtypes 2 and 5 present on the cell surface of the adenoma cells. Decreased GH secretion leads to decreased secretion of IGF-1, mostly by the liver, but also by other GH target tissues.

Pharmacodynamic Profile

Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5 and a reduced binding affinity for human SSTR1, 3 and 4. Activity at human SSTR 2 and 5 is the primary mechanism believed responsible for GH inhibition. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions.

The primary pharmacodynamic effect of lanreotide is a reduction of GH and/or IGF-1 levels enabling normalization of levels in acromegalic patients. In acromegalic patients, lanreotide reduces GH levels in a dose-dependant way. After a single injection of lanreotide acetate, plasma GH levels fall rapidly and are maintained for at least 28 days.

Lanreotide inhibits the basal secretion of motilin, gastric inhibitory peptide and pancreatic polypeptide, but has no significant effect on the secretion of secretin. Lanreotide inhibits post-prandial secretion of pancreatic polypeptide, gastrin and cholecystokinin (CCK). In healthy subjects, lanreotide produces a reduction and a delay in post-prandial insulin secretion, resulting in transient, mild glucose intolerance. Lanreotide inhibits meal-stimulated pancreatic secretions, and reduces duodenal bicarbonate and amylase concentrations, and produces a transient reduction in gastric acidity.

Lanreotide has been shown to inhibit gallbladder contractility and bile secretion in healthy subjects.

In healthy subjects, lanreotide inhibits meal-induced increases in superior mesenteric artery and portal venous blood flow, but has no effect on basal or meal-stimulated renal blood flow. Lanreotide has no effect on renal plasma flow or renal vascular resistance. However, a transient decrease in glomerular filtration rate (GFR) and filtration fraction has been observed after a single injection of lanreotide.

In healthy subjects, non-significant reductions in glucagon levels were seen after lanreotide administration. In diabetic non-acromegalic subjects receiving a continuous infusion (21 day) of lanreotide, serum glucose concentrations were temporarily decreased by 20-30% after the start and end of the infusion. Serum glucose concentrations returned to normal levels within 24 hours. A significant decrease in insulin concentrations was recorded between baseline and Day 1 only.

Lanreotide inhibits the nocturnal increase in TSH seen in healthy subjects. Lanreotide reduces prolactin levels in acromegalic patients treated on a long-term basis.

5.3 Exposure-Response Relationships

To correlate lanreotide levels with GH reductions in acromegalic patients, the sponsor developed a maximum effect on GH concentration model to adequately describe the relationship between lanreotide and GH concentrations. Based on this model, the median lanreotide acetate concentration required to decrease GH concentrations to 2.5 ng/mL among responders was 0.95 ng/mL. A mixture model showed that 13.7% of patients were non-responders.

The suggested interval between titration steps allows the lanreotide serum concentrations to stabilize close to steady state. After three injections (12 weeks), minimum serum concentration (C_{min}) values were maintained above the median lanreotide serum concentration needed to decrease GH levels to 2.5 ng/mL in the majority of patients treated with 90 mg lanreotide acetate. Median serum levels of lanreotide sufficient to provide control of acromegaly (0.95 ng/mL) were achieved after a single 90 or 120 mg injection of lanreotide acetate in Study 076. These results were confirmed by the minimum serum lanreotide levels obtained in Study 717. Therefore 90 mg appears to be the minimal effective starting dose strength.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is:

Somatuline (lanreotide acetate) Injection 60 mg, 90 mg and 120 mg is indicated for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.

6.1.1 Methods

The efficacy of lanreotide in the treatment of acromegaly was examined in a number of clinical studies. Studies were divided into several categories: pivotal studies; supportive studies with lanreotide acetate; supportive studies with lanreotide MPF; and a supportive study of lanreotide acetate self-administration.

The two pivotal efficacy studies are Study 717 and Study 081. The primary efficacy data for lanreotide acetate in the treatment of acromegaly are derived from the 4-week, placebo-controlled period of randomized study, 717. In the initial placebo-controlled part of the study, three doses of lanreotide acetate (60, 90, and 120 mg) were compared to placebo. Study E28-52030-717 (Study 717) is reviewed in detail in Section 10.1.1 and Study E-54-52030-081 (Study 081) is reviewed in detail in Section 10.1.2. Supportive efficacy studies using Lanreotide acetate include Studies 709, 710 and 150. This section will provide a summary of the efficacy of lanreotide acetate.

All efficacy data for this review were obtained from the sponsor's submitted NDA, which may be accessed through the FDA electronic Document Room path:

\\CDSESUB1\N22074\N_000\2006-11-29 and \\CDSESUB1\N22074\N_000\2006-10-27

6.1.2 General Discussion of Endpoints

The primary parameters for the evaluation of lanreotide efficacy were reductions in GH and IGF-I concentrations in acromegalic patients. Clinical studies of acromegaly have generally not evaluated morbidity and mortality since such studies would require long durations (years) and a large number of patients, while the numbers of patients available to be recruited into such studies are relatively small. None of the clinical studies in this submission evaluated mortality. However, multivariate analysis of determinants of survival in long-term studies indicate that GH < 2.5 µg/L, a younger age, a shorter duration of disease, and the absence of hypertension independently predict longer survival.^{21,22}

Biochemical diagnosis is made by measuring GH during a 2-hour period after a standard 75-g oral glucose load (glucose-tolerance test), as well as by assessing the peripheral biologic effect of hypersecretion of growth hormone, as reflected by changes in IGF-1.²³ During the lanreotide development program GH has generally not been assessed during OGTT. The sponsor states that this method is unreliable in diabetes mellitus where loss of normal GH suppression may be seen²⁴. It is noteworthy that GH and IGF-1 assays varied between the clinical studies, and age-adjusted normal ranges for IGF-1 also differed. Therefore, results from individual studies may not systematically be directly comparable.

Reduction of GH concentrations in acromegalic patients can lead to reversal of disease complications²⁵. Therefore, symptoms of acromegaly such as headache, perspiration, fatigue, swelling of extremities, joint pain, impotence (in male patients) and oligomenorrhea (in female patients) were examined both before and after treatment with lanreotide.



6.1.3 Study Design

The basic study design used in the majority of studies in the clinical development program was the baseline-control design in which efficacy measures obtained during the study were compared to values obtained at baseline. Baseline-control was used for Studies 717 (dose titration/optimal control period) and 081. Studies 709, 710, and 150 were "uncontrolled" with respect to baseline, i.e. at study start the patients were being treated with lanreotide. A double-blind, placebo-controlled period of one month was incorporated into the design of pivotal study 717 to allow for the demonstration of the initial treatment effect versus placebo. The majority of the studies were open-label; blinding techniques were only used in Studies 717 and 076.

Reasons for using the open-label, baseline-control design are:

- 1) Long term placebo trials are considered unethical in allowing half or some patients to continue with untreated acromegaly.
- 2) Differences between acromegaly treatments make blinding difficult.
- 3) Acromegaly is a stable or slowly progressive disease that does not improve spontaneously thus the baseline-control design can be considered adequate to demonstrate efficacy.

6.1.3.1 Study 717 (detailed review is in Section 10.1.1)

Study E-28-52030-717: Phase II, Multi-Center, Randomized, Double-Blind Study, in Acromegalic Patients Evaluating the Efficacy and Safety of a Single Deep Subcutaneous Administration of Lanreotide Acetate (60, 90, or 120 mg) versus Placebo, Followed by a Single Blind Fixed Dose Phase Evaluating the Pharmacokinetic, Pharmacodynamic, Efficacy and Safety

Profile of Multiple Deep Subcutaneous Administrations of Lanreotide Acetate (60, 90 and 120 mg) Ending in Open Label Dose Titration Phase.

This multicenter study was conducted in a total of 108 acromegalic patients in the US, Europe and Hong Kong. The study investigated the efficacy and safety of lanreotide acetate administered as a deep s.c. injection and consisted of four periods:

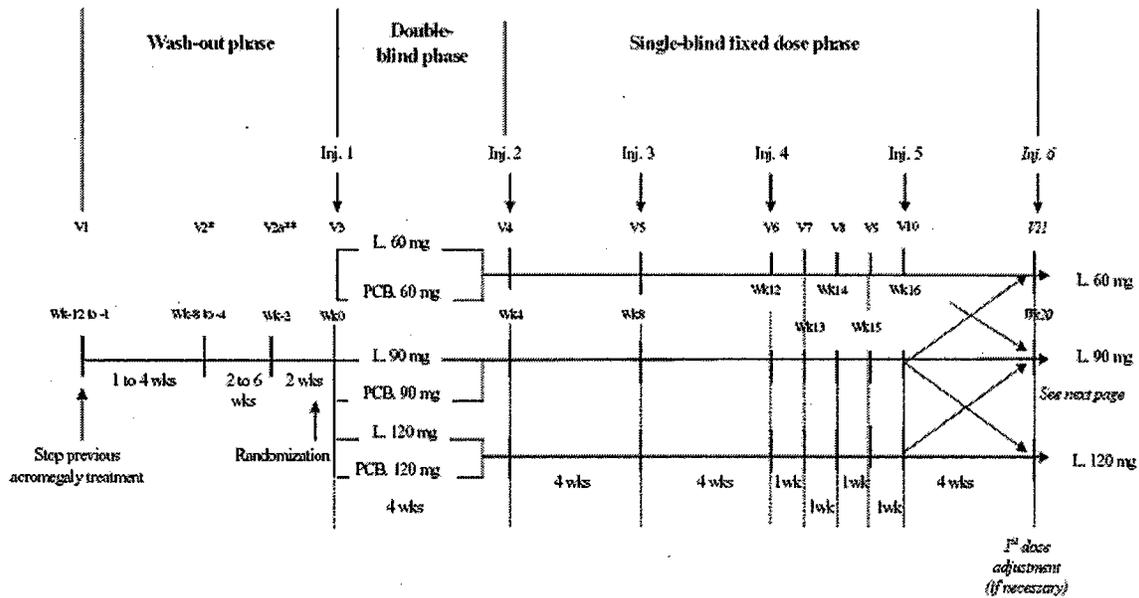
- Washout period of up to 12 weeks,
- 4-week double-blind, placebo-controlled period,
- 16-week single-blind, fixed-dose period (during the fixed-dose period both patients and investigators were blinded to dose strength, although the investigators were informed of the dose strength prior to the first visit of the dose-titration period in order to determine the appropriate dose-titration for each patient),
- 32-week open-label dose-titration period.

The primary objective of the study was to show whether a single injection of lanreotide acetate (60, 90, or 120 mg) had a greater effect on GH concentration than placebo. A secondary objective was to investigate the effect of lanreotide acetate at these doses on IGF-1 concentrations. In addition, the effect of repeated lanreotide acetate injections over time on GH and IGF-1 concentrations, as well as on acromegaly symptoms, was determined.

At study entry, adults with acromegaly had a mean GH concentration >5 ng/mL before treatment. Patients receiving a SSA or a dopamine agonist at entry were to have a mean GH concentration >3 ng/mL and at least a 100% increase in mean GH concentration after washout of medication. Patients could not have had radiotherapy for acromegaly within 3 years, pituitary surgery within 3 months, or received lanreotide acetate or a GH antagonist at any time. Excluded concomitant treatments during the study were SSA (besides the study drug), dopamine agonists, cyclosporine, as well as pituitary surgery or radiotherapy.

Patients were randomized at the start of the study to the 60, 90, or 120 mg lanreotide acetate/placebo treatment groups in a 3: 1 ratio (active: placebo) per dose level. During the 4-week double-blind, placebo-controlled period, 25% of the patients in each of these three dose groups received placebo. For the double-blind, placebo-controlled period (Weeks 0 to 4), patients received one single dose of their assigned treatment. During the fixed-dose period (Weeks 4 to 20), four doses of the study treatment were administered. The open-label treatment (Weeks 20 to 52) consisted of eight injections; the first and the fifth of these doses could be titrated according to the patients' GH and IGF-1 concentrations; however, once increased, the dose was not to be reduced again.

Figure 6.1.3.1 Study 717 Schema



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GH and IGF-1 concentrations were measured at screening, at Weeks 4, 13, 14, 15, 16, 32, and 52, and in the event of early withdrawal. Serum GH concentrations were given as means from serial measurements; IGF-1 concentrations were determined from a single serum sample. Acromegaly symptoms were assessed at screening and Weeks 0, 4, 16, 32, 52 and in the event of early withdrawal.

Of the 220 patients screened, 111 patients were randomized to the double blind period, 108 of whom went on to receive treatment. Of the 108 patients receiving treatment, one patient (from the placebo group) withdrew during the 4-week double-blind placebo-controlled period due to an AE, two patients (both from the 90 mg lanreotide group) withdrew during the 16-week single-blind fixed-dose period due to AEs, and six patients (two from the 90 mg group and four from the 120 mg dose group) withdrew during the 32-week open-label dose-titration period, two due to AEs and four due to lack of efficacy. For details of AEs leading to study withdrawal see Section 10.1.1.

6.1.3.2 Study 081 (detailed review is in Section 10.1.2)

Study E-54-52030-081: Phase III, Multicenter, Open Study to Assess the Efficacy and Safety of Lanreotide Autogel (60, 90 or 120 mg) in Acromegalic Patients Previously Treated or not by Somatostatin Analogues.

Study 081 was an open-label multicenter study, designed to assess efficacy and long term safety of lanreotide acetate administered as a deep s.c. injection in acromegalic patients over a treatment period of 48 weeks. The study was conducted in a total of 63 acromegalic patients in

France (16 centers) and Switzerland (one center). The study design included three distinct study periods:

- Washout period of up to 12 weeks (where appropriate),
- 16-week open-label fixed-dose period in which patients received four injections of 90 mg lanreotide acetate (Visits 1 to 4),
- 32-week open-label dose-titration period in which patients received eight injections (Visits 5 to 8). During the latter period, two dose adjustments based on hormonal response (as measured by GH and IGF-1 concentrations) could be made.

The primary objective of this study was to evaluate the long term efficacy of repeated injections of lanreotide acetate administered at titrated doses in acromegalic patients, by assessing response in terms of the primary efficacy parameter, i.e. the percentage of patients with a normal (age-adjusted) serum IGF-1 concentration at the end of treatment. Secondary objectives included assessment during the study of IGF -1 and GH concentrations and clinical signs of acromegaly.

At study entry, adults with acromegaly had an IGF-1 concentration at least 1.3 times the upper limit of the age-adjusted normal range. Those patients receiving a SSA (other than lanreotide acetate) or a dopamine agonist when attending the first visit had to attain this IGF-1 concentration following an appropriate washout period. Patients could not have had radiotherapy for acromegaly within 3 years, pituitary surgery within 3 months, or received lanreotide acetate at any time. Excluded concomitant treatments during the study were SSA (besides the study treatment), or cyclosporine, dopamine agonists, pituitary surgery or radiotherapy.

All patients started the 16-week open-label treatment period on 90 mg lanreotide acetate. Study treatment was administered every 4 weeks as a deep s.c. injection. The open-label dose-titration period (Weeks 16 to 48) consisted of eight injections; the first and the fifth of these doses could be titrated according to the patients' GH and IGF-1 concentrations. Patients who titrated up to the 120 mg dose were not allowed to titrate back down.

GH and IGF-I concentrations were measured at screening, Weeks 12 and 28 (to titrate the dose of study treatment at Weeks 16 and 32, respectively), at the end of the study (Week 48) and in the event of early withdrawal. Serum GH concentrations are given as means from serial measurements; IGF-I concentrations were determined from a single serum sample. Acromegaly symptoms were documented at screening, at baseline at each visit (Weeks 4, 8, 12, 16, 28, 32 and 48) and in the event of early withdrawal. Of the 68 patients screened, 63 entered the fixed dose period of the trial and 57 of these completed the 48 weeks' treatment. Six patients withdrew from the study, two due to AEs, two for 'other reasons', one due to lack of efficacy and one withdrew consent.

6.1.3.3 Study 709 (detailed review is in Section 10.1.6)

Study E-28-52030-709: Open, Comparative Multicenter Phase III Study Evaluating the Efficacy of Three Repeated Deep Subcutaneous Administrations of Lanreotide Autogel (60, 90 or 120 mg) at Fixed Doses in Acromegalic Patients Previously Treated with Lanreotide 30 mg MPF.

This open-label multicenter study investigated the switch from lanreotide MPF to equivalent doses of lanreotide acetate with respect to efficacy and safety. The primary objective of the study was to compare the lanreotide acetate regimen to the patients' previous lanreotide MPF regimen with regard to GH concentration. A secondary objective was to compare lanreotide acetate to lanreotide MPF based on IGF-1. The following variables were assessed after one and three repeated administrations of lanreotide acetate every 4 weeks and were compared to the values seen directly before the last injection of 30 mg lanreotide MPF i.e. before the formulation switch:

- Percentage of patients with normalization of GH (≤ 5 ng/mL or ≤ 2.5 ng/mL) or IGF-I concentrations,
- Serum GH and IGF-1 concentrations,
- Changes in acromegaly symptoms,
- Antibodies to lanreotide,
- Safety\Lanreotide serum concentrations.

To qualify for the study, adult patients treated with lanreotide 30 mg MPF for at least 3 months before the study were to have a documented diagnosis of active acromegaly (basal GH > 5 ng/mL, or age and sex adjusted IGF-1, or GH concentration > 2 ng/mL after OGTT measured after the most recent surgical or radiation treatment) within the previous 5 years. Only patients with a GH concentration ≤ 10 ng/mL directly before the last injection of lanreotide 30 mg MPF before the switch were eligible for the study period with lanreotide acetate treatment. Pituitary surgery within 6 months before the study and radiotherapy for acromegaly within 1 year before the study constituted exclusion criteria.

6.1.3.4 Study 710 (detailed review is in Section 10.1.7)

Study E-28-52030-710: Open, Comparative Multicenter Phase III Study Evaluating the Efficacy of Repeated Deep Subcutaneous Administrations of Titrated Doses of Lanreotide Autogel (60, 90 or 120 mg) in Acromegalic Patients Previously Treated with Lanreotide 30 mg MPF and with Lanreotide Autogel at Fixed Doses.

Study 710 was an open-label, multicenter, long term follow-up study in which the lanreotide acetate dose which patients were receiving at the end of Study 709 was titrated three times according to GH and IGF-1 concentrations, so that patients received a further 12 deep s.c. injections of lanreotide acetate. The study investigated whether the effect of lanreotide acetate on mean GH concentrations was greater at the end of Study 710 than at end of Study 709 (primary objective), and whether there was a difference in GH concentrations between the end of Study 710 and the end of lanreotide MPF treatment in Study 709 (secondary objective).

To qualify for the study, patients had to complete the preceding Study 709. Patients received 12 injections of 60, 90, or 120 mg lanreotide acetate and the second, sixth, and tenth dose could be titrated according to the patients' GH concentrations. Once increased, a patient's dose was not to be reduced again. The same efficacy and safety variables as those measured in Study 709 were assessed directly before each dose titration.

Design concerns with Study 710 are that the study is 'enriched for completers' and combines data on all dose strengths.

6.1.3.5 Study 150

Study Y-97-52030-150: A Phase IV, Multicenter, Open Label, Controlled Study to Assess the Ability of Patients with Acromegaly, or their Partners, to Administer Somatuline Autogel

This open-label, multicenter study investigated the ability of patients to self administer, or receive from their partners, unsupervised injections of lanreotide acetate. The safety and efficacy of treatment in this Test Group was compared with a Control Group of patients who continued to receive lanreotide acetate injections from a healthcare professional.

The primary objective of the study was:

- To assess the ability of patients with acromegaly or their partners to competently perform unsupervised lanreotide acetate injections.

Secondary study objectives were to assess:

- Whether administration of unsupervised injections of lanreotide acetate had any effect on GH and IGF-I control or serum lanreotide concentrations,
- Patient/partner and healthcare professional experience with unsupervised injections,
- The safety of unsupervised lanreotide acetate injections performed by patients or their partners.

To qualify for the study, adult patients with a clinical diagnosis of acromegaly had to have been established on lanreotide acetate treatment (60, 90 or 120 mg every 4 weeks) for at least 4 months prior to the screening visit. Patients had to have a GH concentration ≤ 10 ng/mL within 28 days prior to the baseline visit, and they were excluded if they had received pituitary surgery within 6 months or pituitary radiotherapy within one year prior to screening, or were receiving a GH antagonist or a SSA other than lanreotide acetate at the start of the study.

Patients, who were willing to be involved in the trial but did not wish to attempt self/partner injections, were enrolled in the Control Group. Patients who were motivated and willing to try unsupervised administration of lanreotide acetate with/without the aid of a partner were enrolled in the Test Group and given appropriate training. Lanreotide acetate was therefore administered in one of three ways:

- Patients self-injected (into the outer thigh, into alternate thighs each month),
- Patients were injected by their partners via the usual site (perpendicularly in the superior external quadrant of the buttock),
- Patients continued to receive injections from a health professional (perpendicularly in the superior external quadrant of the buttock).

All patients received or self-injected doses of lanreotide acetate every 4 weeks for six months at the same dose of lanreotide acetate they were taking on entry. GH, IGF -1 and serum lanreotide concentrations were assessed at the baseline visit, interim visit (after three injections) and study

completion visit. Thirty patients (15 Test Group, 15 Control Group) were screened for inclusion into the study; all were successfully enrolled and all 30 patients completed the study.

6.1.4 Efficacy Findings

6.1.4.1 Study 717:

Results of Double Blind Placebo Controlled Period

The results based on GH and IGF-1 for the double blind, placebo controlled period are summarized in Table 6.1.4.1.1. Mean concentrations of GH and IGF-1 decreased in each of the lanreotide dose groups and increased in the placebo group. The differences between the mean concentrations of GH and IGF-1 in patients on active treatment and placebo were statistically significant ($p < 0.001$) for each of the three lanreotide dose groups and the combined lanreotide dose group.

The percentages of patients with a $>50\%$ decrease in GH (primary variable) and $\text{GH} \leq 2.5 \text{ ng/mL}$ were statistically significantly higher in each of the three lanreotide dose groups, and in the combined lanreotide group compared to the placebo group ($p < 0.001$). Not unexpectedly, the hormonal response, as measured by the percentage of patients with $>50\%$ decrease in GH and by $\text{GH} \leq 2.5 \text{ ng/mL}$, was greater in the 120 mg group compared to the other two dose groups.

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Table 6.1.4.1.1 Efficacy Based on GH and IGF-1 for the Double Blind, Placebo Controlled Period (ITT Population, Week 4): Study 717

Variable (ITT)	Lanreotide Autogel				Placebo (n=25)	p-value ³	p-value overall
	60 mg (n=27)	90 mg (n=27)	120 mg (n=29)	Overall (n=83)			
Patients with decrease in GH >50%	52%	44%	90%	63%	0%	<0.001 ²	<0.001 ³
Patients with GH ≤2.5 ng/mL	19%	30%	52%	34%	0%	≤0.019 ⁴	<0.001 ⁴
% change in GH (mean±SD)	-44.9 ± 31.0	-40.9 ± 38.5	-70.2 ± 22.0	-52.4 ± 33.4	+55.5 ± 171.6	<0.001 ⁵	<0.001 ⁵
Patients with IGF-1 normal ⁸	30%	30%	17%	25%	4%	>0.05 ^{4,6}	0.021 ⁴
% change in IGF-1 (mean±SD)	-19.7 ± 33.1	-23.3 ± 36.5	-38.6 ± 19.2	-27.4 ± 27.6	+7.2 ± 19.5	<0.001 ⁵	<0.001 ⁵
Patients with GH ≤2.5 ng/mL and IGF-1 normal ⁸	11%	19%	17%	16%	0%	>0.05 ^{4,7}	0.033 ⁴

Data source: Sponsor Table 2.7.3-8

% change relates to last value obtained prior to the first injection of study medication compared to Week 4; missing values included as non responses.

1Largest p-value for comparing an individual dose of lanreotide acetate to placebo.

2 Adjusted p-value - Fisher's exact test with permutation resampling.

3Unadjusted p-value for comparison of combined dose group with placebo using Fisher's exact test.

4Cochran-Mantel-Raenszel test.

5 Analysis of covariance.

6 60 mg (p=0.015) and 90 mg (p=0.019) dose groups were statistically significant.

7 90 mg (p ≤0.027) and 120 mg (p=0.028) dose groups were statistically significant.

8 Age-adjusted.

The percentage of lanreotide treated patients with a >50% decrease in mean GH was similar for the two regions examined, US 19/32 patients (59%) and Europe/Hong Kong 33/51 patients (65%).

The percentages of patients with normalized IGF-1 levels at Week 4 were higher in patients on active treatment compared to placebo. However, the differences were only statistically significant in the 60 mg (p=0.015), 90 mg (p=0.019), and combined dose groups (p=0.021), but not in the 120 mg dose group. The low percentage of patients with normal IGF-1 after receiving the 120 mg dose may be related to baseline differences in the proportion of patients with normal IGF-1 (15%, 11 %, 3% and 8% on 60, 90 and 120 mg lanreotide, and placebo, respectively).

The percentages of patients with GH ≤2.5ng/mL and IGF-1 normal at Week 4 were higher in patients on active treatment compared to placebo. These differences were statistically significant in the 90 mg (p=0.027), 120 mg (p=0.028), and combined dose groups (p=0.033), but not in the 60 mg dose group.

Higher rates of improvement in acromegaly symptoms for lanreotide (total dose group) over placebo was seen for headache (22% versus 13%) and fatigue (30% versus 13%). Higher rates of improvement in acromegaly symptoms for placebo over lanreotide (total dose group) was seen for perspiration (38% versus 30%), impotence (8% versus 3%), and oligomenorrhea (33% over

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10%). Lanreotide and placebo dose groups showed similar rates of improvement in swelling of extremities and joint pain. The numbers of patients with changes related to impotence (n=36 for lanreotide and 12 for placebo) and oligomenorrhea (n=20 for lanreotide and 3 for placebo) were small and should be interpreted with caution.

Overall Results for Study 717

Table 6.1.4.1.2 displays GH and IGF-I results for the overall data set following the dose titration period. The values at end of study reflect two possible dose titrations. The majority of subjects were taking the 120 mg dose by the end of the study. At LVA (last value available), 21 (20%), 17 (16%), and 69 (64%) patients had received 60, 90, and 120 mg lanreotide acetate, respectively:

The overall proportions of patients with a decrease in GH of >50% or who had age-adjusted normalized IGF-1 concentrations increased throughout the study. Similarly, the percent change from baseline in both GH and IGF-1 concentrations also increased. The overall percentages of patients with GH ≤2.5 ng/mL, and patients with both GH≤2.5 ng/mL and IGF-1 normal were slightly lower after the second dose titration but were still higher at Week 52 than before dose titration.

Table 6.1.4.1.2. Overall Efficacy Results Based on GH and IGF-I for the Overall Data Set (ITT Population): Study 717

Variable (ITT)	Week 16	Week 32	Week 52	LVA
	Before Titration 1 (n=105 ¹)	Before Titration 2 (n=103)	End of Study (n=98)	(N=107)
Patients with decrease in GH >50%	73%	80%	82%	77%
Patients with GH ≤2.5 ng/mL	50%	57%	54%	51%
% change in GH [mean±SD]	-62.3±36.6	-65.5±36.9	-67.1±32.0	-62.7±38.4
Patients with IGF-1 normal ²	55%	55%	59%	57%
% change in IGF-1 [mean±SD]	-44.5±29.6	-48.0±27.1	-48.9±28.6	-47.0±29.4
Patients with GH ≤2.5 ng/mL and IGF-1 normal ²	39%	45%	43%	41%

Data source: Sponsor's Table 2.7.3-11

% change relates to last value obtained prior to the first active drug injection.

Missing values were excluded.

1 Two of the 107 study patients who entered the dose-titration period withdrew during the single blind period.

2 Age-adjusted.

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

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

For the primary endpoint in study 717, the proportion of patients with a greater than 50% decrease in mean GH from baseline, the results were similar in all patient subpopulations. Similar results were seen for a median reduction in mean GH. For all other efficacy parameters, there was a general trend towards a higher response rate within the previously treated population compared to the naïve patient group. The difference in responses between patients previously treated and those patients in the naïve group may be due to a selection bias, as the naïve patient group may include responders as well as non-responders, while the previously treated non-responders would be less likely to enroll in the study. Naïve patients were receiving lanreotide as first line medical therapy. Section 10.1.1 has additional information on mean GH and IGF-I levels at different time-points of the study by treatment group and previous somatostatin analog history.

Table 6.1.4.1.3 Revised Efficacy Data for Study 717: All Doses from Last Value Available (LVA) by Previous Somatostatin Analog History

Endpoint	Measurement	Naïve	Not treated within 3 months	Previously treated
GH[a]				
>50% reduction	%	13/15 (86.7)	25/39 (64.1)	42/51 (82.4)
≤5.0 ng/mL	n/N (% of patients)	8/15 (53.3)	23/39 (59.0)	43/51 (84.3)
≤2.5 ng/mL	n/N (% of patients)	5/15 (33.3)	15/39 (38.5)	35/51 (68.6)
≤1.0 ng/mL[b]	n/N (% of patients)	0/15 (0)	6/39 (15.4)	11/51 (21.6)
Median GH	ng/mL	3.29	3.17	1.91
Median % change in GH [c]	%	68.6	78.0	74.9
IGF-1				
Normal	n/N (% of patients)	6/15 (40.0)	19/39 (48.7)	36/51 (70.6)
Median IGF-1	ng/mL	450.0	392.0	259.0
Median % change in IGF-1 [b]	%	44.8	52.5	58.6
IGF-1 normal + mean GH	n/N (% of patients)			
≤2.5 ng/mL		3/15 (20.0)	13/39 (33.0)	28/51 54.9

(a) GH is reported as a mean of at least five GH values (ng/mL)

(b) Not part of original 717 efficacy analyses, added for comparison across pivotal efficacy studies

(c) % change reduction from baseline

Acromegaly symptoms

Improvement from baseline or stability in the acromegaly symptoms headache, perspiration, fatigue, swelling of extremities, and joint pain was seen in 92 to 93% of patients at Week 16. No apparent trend was noted for improvement in acromegaly symptoms with increasing lanreotide

dose. The LVA analysis also showed the acromegaly symptoms of headache, perspiration, fatigue, swelling of extremities, and joint pain had either improved from baseline or were stable in 88 to 94% of patients.

6.1.4.2 Study 081

After treatment with lanreotide acetate every 4 weeks, 43% (27/63) of the acromegalic patients in this study achieved normal age-adjusted IGF-1 concentrations (ITT population; LVA). A similar proportion of patients (42% (24/57)) who continued treatment up to Week 48 also achieved normal age-adjusted IGF-1 concentrations.

The proportion of patients with mean GH concentrations below 2.5 ng/mL (a baseline status which excluded patients from Study 717, but not from 081, where the primary endpoint was IGF-1 concentration) increased during the fixed dose period from 35% (95% CI: 23.2, 46.7) to 77% (95% CI: 66.5, 87.6) after the first four injections and reached 85% (95% CI: 76.7, 94.3) at the end of the study. Similarly, the proportions of patients with mean GH concentrations <1 ng/mL increased throughout the treatment period from 11% (95% CI: 3.4, 18.9) at baseline to 31% (95% CI: 19.5, 42.8) at Week 12. During the dose titration period the proportions of patients with mean GH concentrations <1 ng/mL remained stable over four titrated doses but had increased to 45% (95% CI: 32.8, 57.6) by the end of the study.

At the end of treatment, 24/63 (38%) of patients had both normal IGF-1 concentrations and a GH concentration of ≤ 2.5 ng/mL, and 17/63 patients (27%) had both normal IGF-1 concentrations and a GH concentration of < 1 ng/ml.

The incidence and intensity of clinical symptoms of acromegaly are summarized in the table below.

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Table 6.1.4.2.1. Incidence and Intensity of Symptoms of Acromegaly during the Study (ITT Population, by Visit): Study 081

Symptom	Number of Patients with Symptom (%)					
	Baseline n=63	Week 4 n=63	Week 12 n=61	Week 28 n=59	Week 48 n=63	
Headache	None	37 (59%)	45 (71%)	41 (67%)	40 (68%)	47 (75%)
	Mild	12 (19%)	11 (17%)	15 (25%)	16 (27%)	12 (19%)
	Moderate	11 (17%)	6 (10%)	5 (8%)	3 (5%)	3 (5%)
	Severe	2 (3%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Excessive Perspiration	None	38 (60%)	45 (71%)	47 (77%)	48 (81%)	51 (81%)
	Mild	15 (24%)	13 (21%)	11 (18%)	10 (17%)	9 (14%)
	Moderate	5 (8%)	2 (3%)	2 (3%)	0 (0%)	2 (3%)
	Severe	4 (6%)	3 (5%)	1 (2%)	1 (2%)	1 (2%)
Asthenia	None	21 (33%)	27 (43%)	33 (54%)	36 (61%)	36 (57%)
	Mild	18 (29%)	25 (40%)	18 (30%)	18 (31%)	18 (29%)
	Moderate	18 (29%)	10 (16%)	9 (15%)	4 (7%)	5 (8%)
	Severe	5 (8%)	1 (2%)	1 (2%)	1 (2%)	4 (6%)
Swelling of Extremities	None	35 (56%)	41 (65%)	48 (79%)	48 (81%)	49 (78%)
	Mild	14 (22%)	16 (25%)	11 (18%)	9 (15%)	12 (19%)
	Moderate	10 (16%)	6 (10%)	2 (3%)	2 (3%)	2 (3%)
	Severe	3 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Joint Pain	None	26 (41%)	40 (63%)	41 (67%)	37 (63%)	42 (67%)
	Mild	20 (32%)	12 (19%)	10 (16%)	13 (22%)	13 (21%)
	Moderate	10 (16%)	6 (10%)	6 (10%)	5 (8%)	5 (8%)
	Severe	6 (10%)	5 (8%)	4 (7%)	4 (7%)	3 (5%)

Source: Sponsor's Table 2.7.3-14

Patients with no data are excluded from this table therefore not all totals sum to 100%.

There was a general trend for the severity of all symptoms to decrease during the study.

6.1.4.3 Study 709

Median GH was similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR. In general, median GH levels were highest in the 120 mg lanreotide acetate group and lowest in the 60 mg lanreotide acetate group. Median IGF-1 was similar at the end of the third interval of lanreotide acetate and at the end of the fourth interval of lanreotide 30 mg PR. In general, IGF-1 levels were highest in the 120 mg lanreotide acetate group and lowest in the 60 mg lanreotide acetate group. The lowest GH and IGF-1 levels were achieved with 60 mg lanreotide acetate and the highest GH and IGF-1 levels were observed with 120 mg lanreotide acetate. This may reflect the nature of the patients who were assigned to each dosing level. Patients who responded well to treatment with lanreotide 30 mg PR were dosed less frequently (12 to 16 days) and were subsequently assigned to low doses of lanreotide acetate (60 mg). On the other hand, patients who did not respond well to treatment with lanreotide 30 mg PR were dosed more frequently (5 to 7 days) and were subsequently assigned to high doses of lanreotide acetate (120 mg).

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

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

6.1.4.4 Study 710

Table 6.1.4.4.1. Efficacy Results Based on GH and IGF-1 (ITT Population): Study 710

Variable (ITT)	Before Formulation Switch in Study 709 (Visit R5) ¹ (N=124)	Start of Study 710 (Week 0) ² (N=124)	End of Study 710 (Week 48) ³ (N=123)
GH ng/mL (mean \pm SD)	2.82 \pm 2.00	3.02 \pm 2.33	2.38 \pm 2.00 *
IGF-1 ng/mL (mean \pm SD)	332.2 \pm 168.2	310.4 \pm 153.8	287.5 \pm 137.1 **
GH ≤ 5 ng/ml (% patients)	86	81	93
GH ≤ 2.5 ng/ml (% patients)	49	55	68
IGF-1 normal (% patients)	44	49	50
GH ≤ 2.5 ng/ml and IGF-1 normal (% patients)	32	39	43

Data source: Sponsor's Table 2.7.3-18.

1 Immediately before the last (fifth) injection of lanreotide 30 mg MPF in Study 709 (Visit R5).

The exact timing of this visit for each patient depended on their lanreotide MPF dosing interval in the run-in period and was 5 to 16 days before start of lanreotide acetate treatment.

2 After 3 monthly injections of lanreotide acetate on Study 709.

3 After 12 monthly injections of lanreotide acetate on Study 710.

*With $p < 0.001$ versus Visit R5 and versus Week 1 (based on 2-sided 95% CIs of the ratios).

**With $p = 0.002$ versus Visit R5; not significant versus Week 1.

The reduction in mean GH concentrations during Study 710 was accompanied by increases in the percentages of patients who had GH concentrations ≤ 2.5 ng/mL, ≤ 5.0 ng/mL, normalized IGF-1 concentrations, and both GH ≤ 2.5 ng/mL and IGF-1 normalized.

At Visit 4 (after three injections of lanreotide acetate) most acromegaly symptoms remained stable compared to the symptoms at the end of treatment with lanreotide MPF (Visit R5) with the same or very similar percentages of patients showing worsening/improvement of symptoms (see Table below). At Visit 16 (after a total of 15 injections of lanreotide acetate) higher percentages of patients showed improved symptoms than worsened symptoms when compared to the symptoms at the end of treatment with lanreotide MPF (Visit R5). The only exception was joint pain where the percentages of patients with improved and worsened symptoms remained unchanged.

Table 6.1.4.4.2. Summary of Changes in Acromegalic Symptoms from Baseline (ITT population): Study 710

Symptom		End of 3 rd Interval on Lanreotide Autogel vs End of 4 th Interval on Lanreotide 30 mg MPF (Week 0 vs Visit R5)	End of 15 th Interval on Lanreotide Autogel vs End of 4 th Interval on Lanreotide 30 mg MPF (Week 48 vs Visit R5)	End of 15 th Interval on Lanreotide Autogel vs End of 3 rd Interval on Lanreotide Autogel (Week 48 vs Week 0)
		Headache	Worsened	14 (11%)
	Stable	95 (77%)	91 (75%)	96 (79%)
	Improved	14 (11%)	20 (16%)	18 (15%)
	Total	123 (100%)	122 (100%)	121 (100%)
Night Sweats	Worsened	13 (11%)	6 (5%)	5 (4%)
	Stable	96 (78%)	102 (84%)	105 (87%)
	Improved	14 (11%)	14 (11%)	11 (9%)
	Total	123 (100%)	122 (100%)	121 (100%)
Asthenia	Worsened	15 (12%)	9 (7%)	10 (8%)
	Stable	92 (75%)	96 (79%)	92 (76%)
	Improved	16 (13%)	17 (14%)	19 (16%)
	Total	123 (100%)	122 (100%)	121 (100%)
Swelling of Extremities	Worsened	8 (7%)	9 (7%)	11 (9%)
	Stable	96 (78%)	84 (69%)	90 (74%)
	Improved	19 (15%)	29 (24%)	20 (17%)
	Total	123 (100%)	122 (100%)	121 (100%)
Joint Pain	Worsened	20 (16%)	20 (16%)	13 (11%)
	Stable	88 (72%)	82 (67%)	91 (75%)
	Improved	15 (12%)	20 (16%)	17 (14%)
	Total	123 (100%)	122 (100%)	121 (100%)

Source: Sponsor's Table 2.7.3-19
 Visit R5 = before last (fifth) injection of lanreotide 30 mg MPF.

6.1.4.5 Study 150

The primary endpoint was the percentage of Test Group patients (or partners) who could perform unsupervised lanreotide acetate injections competently on completion of the study. Competency was declared for each Test Group patient if four criteria were met as below:

Table 6.1.4.5.1. Summary of Competence of Test Group Patients to Perform Unsupervised Injections (ITT Population): Study 150

Competency Criterion	Number (%) of Patients (N = 15)	95% CI
Declared qualified by healthcare professional after up to three supervised training injections	15 (100%)	-
Received adequate treatment, as assessed by healthcare professional at Study Completion visit	15 (100%)	-
GH concentration maintained ¹ at Study Completion visit compared with Baseline visit	14 (93%) ³	-
IGF-1 concentration maintained ² at Study Completion visit compared with Baseline visit	15 (100%)	-
Competence declared	14 (93%)	70% to 99%

Source: Sponsor Table 2.7.3-33

1 Patients' GH concentrations were categorized into three bands at baseline (band A: <2.0 ng/mL; band B: 2.0 to 5.0 ng/mL; and band C: >05.0 ng/mL). A patient's GH concentrations were considered to be maintained if they did not move from either Band A and B to Band C.

2 Patients' IGF-1 concentrations were categorized as low, normal, or elevated at baseline and were considered to be maintained if they did not increase to above the upper limit of the age-related normal range during the study, or if they remained elevated.

3The one patient whose GH concentrations were not maintained had a concentration of 5.01 ng/mL at screening, 2.02 ng/mL at baseline, and 6.72 ng/mL at the completion visit.

Fourteen of the 15 patients met the criteria for competency. One patient failed to meet the criterion for lack of maintenance of GH concentration. All 15 patients in the Test Group remained in the same IGF-1 control band at the Study Completion visit compared to baseline. However, six patients had elevated IGF-1 concentrations at Study Completion. In the Control Group, 14 of the 15 patients were also in the same IGF-1 control band at the study completion visit. Again, nine patients had elevated IGF-1 concentrations at study completion. One patient in the Control Group had concentrations which changed from normal at screening and interim visits to elevated at the study completion visit.

6.1.4.6 Combined analysis of Studies 717 and 081

For these two pivotal Studies 717 and 081 the data from the initial fixed dose period (in Study 081 all patients received 90 mg lanreotide acetate) have not been pooled together since the two studies enrolled slightly different patient populations (based on the respective study inclusion/exclusion criteria) and Study 081 did not have a randomized dose ranging phase.

The combined analysis of the dose titration periods of Studies 717 (starting at doses of either 60, 90 or 120 mg) and 081 (starting at a dose of 90 mg) provides evidence that acromegaly patients in these studies achieved long-term hormonal control as determined by measurement of their GH and IGF-1 concentrations.

Table 6.1.4.6.1 Suppression of GH and IGF-1 in Lanreotide Acetate Pivotal Studies 717 and 081

Study ID	717		081#		717 and 081	
	baseline	LVA	baseline	LVA	baseline	LVA
GH						
≤5.0 ng/mL n/N (%)	20/107 (18.7)	74/107 (69.2)	40/63 (63.5)	62/63 (98.4)	60/170 (35.3)	136/170 (80.0)
≤2.5 ng/mL	0/107 (0.0)	55/107 (51.4)	21/63 (33.3)	54/63 (85.7)	21/170 (12.4)	109/170 (64.1)
≤1.0 ng/mL	0/107 (0.0)	17/107 (15.9)	8/63 (12.7)	28/63 (44.4)	8/170 (4.7)	45/170 (26.5)
IGF-1 normal[†]	9/107 (8.4)	62/107 (57.9)	0/63 (0.0)	27/63 (42.9)	9/170 (5.3)	89/170 (52.4)
IGF-1 normal[‡] +GH ≤2.5 ng/mL	0/107 (0.0)	44/107 (41.1)	0/63 (0.0)	24/63 (38.1)	0/170 (0.0)	68/170 (40.0)

Source: Sponsor's Table 2.5-5

Note that patient 711:0002 was randomized to the 120 mg dose and received such at Weeks 0, 4 and 8, but was mistakenly administered 60 mg at Weeks 12 and 16. Therefore this patient was included in the 60 mg dose group for the analysis of the single-blind, fixed dose period.

some patients had GH ≤ abnormal thresholds at baseline: Study 081 GH ≤5: n=40, GH ≤2.5: n=21, GH ≤1: n=8, compared to Study 717 GH ≤5: n=20, GH ≤2.5: n=0 GH ≤1: n=0.

IGF-1 normal at baseline n=9 patients in Study 717 compared to 0 in Study 081

† Age-adjusted

Results for 2 missing patients were counted as non-response

Results of these two pivotal efficacy studies and other efficacy studies demonstrated efficacy of lanreotide, mainly comparing the GH and IGF-1 values observed after lanreotide administration with those observed at baseline. Strictly speaking, it is not appropriate to pool the data across these completed trials as they had different study designs, different inclusion criteria, different study objectives, and different criteria for defining acromegaly control. A comparison of results across studies needs to take into account differences in overall study design, including: 1) differences across studies in the assay methods and units used to express GH and IGF-1 concentrations; 2) different patient populations with different degrees of acromegaly and different treatment histories; and 3) duration of treatment with lanreotide. Nonetheless, results of all studies consistently demonstrated the efficacy of lanreotide for the treatment of acromegaly.

The applicant did perform an analysis on pooled data to evaluate effectiveness data for gender, age, and racial subgroups. Subgroup responder analyses were performed using pooled data from studies 717 and 081 and with regard to the following criteria: gender, age, body mass index, bodyweight, acromegaly severity at baseline, surgery history, radiotherapy history, SSA history, race, and region (US and non-US). The results of these analyses are summarized below:

Gender and Age

Patients in Studies 717 and 081 were well matched for age (median, 54 and 55 years, respectively), and the distributions of patients by age groups were similar for both studies with the majority being between 40 and 64 years old. 53% of subjects were female in Study 717, while 40% were female in Study 081. After treatment with lanreotide acetate, the percentage of patients with mean GH ≤2.5 ng/mL with normalized IGF-1 was similar in females (42.7%; 95%

CI: 31.8, 54.1) and males (37.5%; 95% CI: 27.4, 48.5). Although the greatest percentage of responders was seen in the oldest group of patients (≥ 75 years), with 63.6% of patients having mean GH ≤ 2.5 ng/mL with normalized IGF-1 after treatment compared to between 30.0% and 40.7% in the other age groups. This difference between the age groups should be interpreted with caution as the 95% confidence intervals were overlapping and there were relatively small numbers of patients in the older age group.

Body Mass Index and Bodyweight

Although there were proportionally more male patients in Study 081, the overall median patient weights were similar between Study 717 and 081 (82.0 kg versus 81.8 kg, respectively) and the median weights of male patients were also similar (89.6 kg versus 90.0 kg, respectively). However, the median weight of female patients in Study 717 was greater than in Study 081 (77.3 kg versus 70.0 kg, respectively). Data regarding height were not collected in Study 081 so results for body-mass index (BMI) are only valid for Study 717. Based on BMI, 38% of subjects with a BMI < 26 kg/m² had a mean GH ≤ 2.5 ng/mL and normalized IGF-1 which increased to 42% at BMI 26 to 32 and 45% at BMI > 32 . The CIs were wide and overlapped significantly making it unlikely that there is any meaningful difference in response rate with regard to body mass index.

Acromegaly Severity at Baseline

A higher proportion of patients in Study 717 had higher baseline GH concentrations compared to patients in Study 081 but patients in Study 081 had higher IGF-1 concentrations. However, it should be noted that patients in Study 081 had to have abnormal IGF-1 at baseline to be eligible to participate in the study. There was a higher percentage of responders (i.e., patients with GH ≤ 2.5 ng/mL and normalized IGF-1) among patients with lower GH concentrations (mean GH < 10 ng/mL) at baseline (44.8% responders; 95% CI: 35.0, 54.8), compared with patients with higher GH concentrations (mean GH ≥ 10 ng/mL) at baseline (32.3% responders; 95% CI: 21.2, 45.1).

Surgery, Radiotherapy, or Somatostatin Analog Treatment History

Patients in Study 081 had a longer time since diagnosis of acromegaly than those in Study 717 [median (range): 6.7 years (0.2 to 33.3 years) versus 3.4 years (0.0 to 42.4)]. 55% of Study 717 subjects and 59% of Study 081 subjects had previous surgery while 11% of Study 717 subjects and 19% of Study 081 subjects had undergone radiotherapy. A comparison between Study 717 and 081 of previous SSA treatment received is not possible since Study 081 did not distinguish the previous treatment used in patients:

There were a higher percentage of responders (i.e., patients with mean GH ≤ 2.5 ng/mL and normalized IGF-1) in the subgroup of patients who had undergone surgery in the past (51.0% responders; 95% CI: 40.6, 61.4), compared with those who had not (25.7% responders; 95% CI: 16.2, 37.2). There was no notable difference in percentage of responders based on whether the patients had a history of radiotherapy (41.7% responders; 95% CI: 22.1, 63.4) compared with those who did not (39.7% responders; 95% CI: 31.7, 48.1). There was a lower percentage of responders in somatostatin-naïve patients (15.0%; 95% CI: 3.2, 37.9) compared to patients previously treated with SSAs (54.9%; 95% CI: 40.3, 68.9). This difference may be influenced by the positive selection of responders in the previously treated group.