

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-074

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	22-074	<i>Submission Date(s)</i>	10/27/06, 11/29/06, 4/18/07 and 6/15/07
<i>Brand Name</i>	Somatuline Autogel		
<i>Generic Name</i>	Lanreotide acetate/ BIM23014		
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<i>OND Division</i>	Division of Metabolic and Endocrinology Products		
<i>Sponsor</i>	Ipsen Group		
<i>Relevant IND(s)</i>	53,993		
<i>Submission Type; Code</i>	Original 505 (b) (1) NME	S	
<i>Formulation; Strengths; Regimen</i>	60 mg, 90 mg, and 120 mg deep s.c. injection q 28 days		
<i>Indication</i>	Treatment of Acromegaly		

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1 Executive Summary

Somatuline® Autogel® (lanreotide acetate) injection 60, 90, 120 mg is a prolonged release formulation of lanreotide, a somatostatin analog intended for deep subcutaneous injection as a treatment for patients with acromegaly. It is supplied in three strengths in ready to use sterile prefilled syringes. Lanreotide was designated as an orphan drug for the treatment of acromegaly on September 11, 2000 by the FDA. Acromegaly is a rare disease in which the pituitary gland produces excessive growth hormone (GH) due to presence of adenoma. It leads to a marked increase in morbidity and mortality notably from cardiovascular, pulmonary, and neoplastic causes. Treatment of acromegaly is very complex using neurological, pharmacological and radiation methods.

Lanreotide was first developed for commercial use as a micro-particle formulation (MPF) administered every 7, 10, or 14 days depending on GH and insulin like growth factor-1 (IGF-1) response. Since 1994, MPF has been approved in over 50 countries according to sponsor.

Subsequently Autogel formulation was developed to further extend the duration of lanreotide release allowing for administration every 4 weeks. Sponsor has stated that the lanreotide Autogel is registered in over 40 countries for the treatment of acromegaly and carcinoid syndrome.

The immediate release formulation (IRF) and MPF of lanreotide were developed prior to Autogel and therefore many studies conducted early in development were with these formulations. Data from studies using these early formulations are included in this NDA to help support establishing pharmacological and pharmacokinetic properties as well as safety and efficacy of lanreotide in Autogel formulation.

1.1 Recommendations

The information in NDA 22-074 (Somatuline Autogel) was reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2). The submission is acceptable from a Clinical Pharmacology perspective. Recommendations and comments including labeling comments should be sent to sponsor as appropriate. An optional inter-divisional level OCP briefing was held on 7/9/07 and the attendees were Drs. Chandra Sahajwalla, Joga Gobburu, Kellie Reynolds, Sally Choe, Partha Roy, Lei Zhang, Tayo Fadiran, Jayabharathi Vaidyanathan, Hao Zhu, Eileen Craig and Project Manager Jennifer Johnson and Ting Ong.

The following comments need to be conveyed:

- The pharmacokinetics of lanreotide was only obtained in end stage renal disease patients on dialysis (ESRD), 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.
- Labeling comments are addressed in page 48.

1.2 Phase IV Commitments

No Phase 4 commitments are recommended.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Exposure (Dose)-Response Relationship

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:

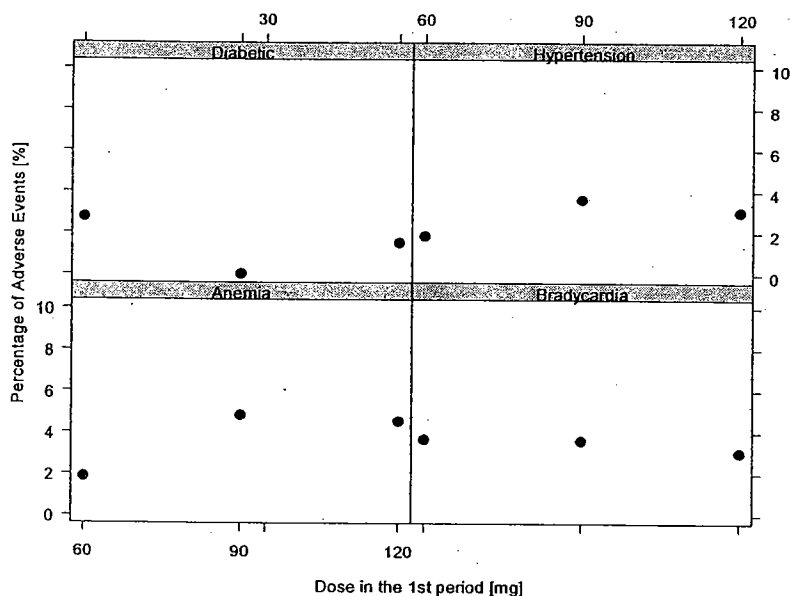
- Diarrhea was the most common adverse effect (AE). After initialization of Somatuline Autogel treatment, the probability of a patient to develop diarrhea was driven by dose. The probability for a patient to develop diarrhea was about 28% at the dose of 60 mg, and was increased to 46% at the dose of 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. The incidences of adverse events are demonstrated in Figure 1. 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.

[To note: No predefined and standardized criteria were used by the sponsor to define the occurrence of adverse events (AEs) of hypertension, bradycardia, diabetes mellitus, diarrhea, or anemia across the seven clinical studies (717, 721, 709, 710, 087, 081, and 076). AEs were determined case by case by the clinical investigators.]

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Figure 1: Incidence of major adverse events (bradycardia, hypertension, diabetes, and anemia) in different dose groups during the first treatment period in studies E28-52030-717, E28-52030-709/710 and E28-52030-076



Pharmacokinetic/ Biopharmaceutics Properties

The release profile of lanreotide Autogel was characterized by an initial burst release on the first day of administration that determines the C_{max} followed by a sustained release to give a long apparent terminal half-life (23-30 days). There was no dose-dumping from the formulation. The apparent terminal half-life of the lanreotide Autogel is limited by release from the depot and not by disposition half-life of the peptide (flip-flop). Following i.v. administration of lanreotide, elimination of lanreotide was fast (1.14 h half life and 23.7 L/h clearance) and the volume of distribution at steady state was low (16 L). The absolute bioavailability of the Autogel formulation when given by s.c route was 73.4%, 69% and 78.4% respectively for the 60, 90 and 120 mg doses.

The overall binding for human serum was 78-83%. Human serum albumin (HSA) accounted for the largest fraction of bound lanreotide despite the low affinity of lanreotide to HSA. The excretion of lanreotide in urine and feces was low. At steady state, the fraction of the amount administered over 24 h that was excreted in urine was approximately 1-5% and 0.3-2.3% for the low and high dose groups respectively. Data on fecal excretion was collected from 4 subjects in the high dose group on Days 3 and 4 of the infusion period. The amount of drug recovered was less than 0.5% of the drug administered over a 24-h period. Lanreotide is a peptide and drug metabolizing enzymes (Phase 1 and Phase 2) are not involved in its metabolism.

After repeated dosing, lanreotide Autogel exhibited linear pharmacokinetics (PK). The PK properties were similar in healthy volunteers and in acromegaly patients. Repeated

administrations produced an accumulation in the body independent of dose level with a mean accumulation index of 2.7. The pattern of serum concentration-time profile curves did not differ to those obtained after single dose administration. The mean minimum serum levels of lanreotide after first, second, third and fourth Autogel administrations (Cmin1, Cmin2, Cmin3, Cmin4) were 0.725, 1.203, 1.546, and 1.822 ng/ml for 60 mg; 0.973, 1.655, 2.083, and 2.511 ng/ml for 90 mg; and 1.406, 2.162, 3.204 and 3.762 ng/ml for 120 mg.

There were no significant differences in AUC and Cmax values between the young vs. elderly subjects. A reduction of total serum clearance and an increased half-life (approximately doubled) were observed in patients with ESRD when treated with a single intravenous dose of lanreotide 7 µg/kg. Similarly there was an increased exposure of lanreotide (2-4 times higher) in end stage renal impaired patients. The initial serum concentrations were also higher in renal impaired patients than in healthy subjects. The differences in CL, Vss, Vz, AUC, MRT and $t_{1/2}$ were statistically significant between healthy and patients with hepatic impairment. Clearance was about 30% lower in hepatic impaired patients than in healthy (0.237 L/Kg·h versus 0.343 L/Kg·h).

Drug interaction study of lanreotide with cyclosporin indicated that the mean AUC and Cmax for cyclosporin were reduced by 19% and 36% respectively. This is clinically significant and the blood levels of cyclosporin in patients concomitantly treated with lanreotide should be monitored leading to dose adjustment if required.

The proposed to-be-marketed formulation of lanreotide Autogel is the same as the formulation used in pivotal clinical trials.

Long term treatment with lanreotide Autogel does not lead to an increase in antibodies to lanreotide in patients.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Lanreotide was first developed for commercial use as a micro-particle formulation (MPF) administered every 7, 10, or 14 days depending on GH and IGF-1 response. Since 1994, MPF has been approved in over 50 countries according to sponsor

Subsequently, Autogel formulation was developed to further extend the duration of lanreotide release allowing for administration every 4 weeks. Sponsor has stated that the

Lanreotide Autogel is registered in over 40 countries for the treatment of acromegaly and carcinoid syndrome.

The immediate release formulation (IRF) and MPF of lanreotide were developed prior to Autogel and therefore many studies conducted early in development were with these formulations. Data from studies using these early formulations are included in this NDA to help support pharmacological and pharmacokinetic properties as well as safety and efficacy of lanreotide in Autogel formulation.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Lanreotide (BIM-23014) is a synthetic cyclic octapeptide structurally related to somatostatin: 3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threonylamide cyclic (2-7)-disulphide acetate. It is presented in free base form (molecular weight = 1096.34 D) and is a ——— Lanreotide is soluble in water. The chemical structure is shown in Figure 2.



.CH₃CO₂H

Lanreotide Autogel is a supersaturated solution of lanreotide acetate in water for injection. Initial clinical studies were performed with various peptide concentrations of lanreotide Autogel (——— 0.246 and ——— mg/mg). The 0.246 mg/mg peptide concentration of lanreotide Autogel was selected for formulation to be used in clinical studies and as the formulation intended for marketing.

The solubility of lanreotide _____ . In physiological medium, *in vitro* solubility of lanreotide is _____. The solubility _____, therefore, changes in local physiological environment of the depot could result in changes in the release profile of lanreotide Autogel.

Therefore, lanreotide is more stable than the native peptide, somatostatin.

Table 1: Unit composition of lanreotide Autogel

Ingredient	Unit Composition (mg)			% w/w	Function
	60 mg	90 mg	120 mg		
(Lanreotide base) Equivalent to weighed lanreotide acetate	79.8	116.4	155.5	(24.6)	Somatostatin analog
Water for injection	186.2	271.6	363.0	QS. to 100	Solvent
Total mass	266	388	518.5		
Injected mass					
Delivered dose (lanreotide base)	60	90	120		

Lanreotide is a somatostatin analog indicated for the treatment of acromegaly. Lanreotide possesses the same pharmacological properties as somatostatin.

8

Somatostatin and its synthetic analogues are used clinically to treat acromegaly and neuroendocrine tumors. Acromegaly is a chronic, progressive disease caused by uncontrolled hyper-secretion of GH from a tumor of the anterior pituitary. The effects of increasing pituitary tumor size include visual defects, headaches and hypopituitarism. The disease is accompanied by increased mortality as a result of cardiovascular, cerebrovascular and respiratory diseases. The treatment of choice is surgery, however, acromegaly remains active in over 50% of patients as defined as increased levels of GH and IGF-1. The short biological half-life of natural somatostatin limits its therapeutic utility. Somatostatin analogs reduce GH and IGF-1 levels in 50-70% of patients and provide an IGF-1 normalization rate of approximately 30-65%.

Lanreotide® Autogel® is a supersaturated solution of lanreotide in water in dose strengths of 60, 90, and 120 mg for proposed for administration by deep subcutaneous injection in the superior external quadrant of the buttock _____ every 4 weeks. It is supplied ready for use in clear polypropylene pre-filled syringe with _____ needle.

2.2 General Clinical Pharmacology

The clinical pharmacology of lanreotide was characterized in studies using the IRF, MPF and Autogel formulations. For the peptide lanreotide the PK was characterized from studies conducted using the IRF formulation. The systemic distribution and elimination of lanreotide are independent of the formulation administered and will depend on the intrinsic PK of the molecule, while the apparent terminal half-life is dependent on the formulation due to different release rates. Under steady-state conditions, the PD profile of lanreotide is dependent on the serum concentration of lanreotide achieved rather than the formulation administered. The sponsor has conducted certain pivotal studies with the Autogel formulation and has also included supporting data obtained from studies involving the administration of lanreotide IRF and MPF formulations.

The PK profile of lanreotide Autogel has been evaluated in both healthy subjects and acromegalic patients. The primary PD parameters, GH and IGF-1 have been evaluated in patients in one of the pivotal efficacy studies (Study 717) and in two supportive efficacy studies conducted with the Autogel (Study 701 and 710).

Table 2: Pivotal lanreotide Autogel PK studies in healthy subjects

Study Number / Location within NDA 22-074	Study Design	Treatment	Population	Main Study Objective
A-93-52030-149 / Module 5, Vols 1-4	Single center, open label, randomized, parallel group	Lanreotide IRF 7 µg/kg i.v. then lanreotide Autogel 60 mg, 90 mg or 120 mg dose, deep s.c., superior-external quadrant of the buttock	50 healthy subjects received lanreotide IRF, 38 received lanreotide Autogel	To evaluate absolute bioavailability, dose proportionality and PK profile using three dose concentrations
B-55-52030-047 / Module 5, Vols 14-16	Single center, single dose, single-blind	Lanreotide Autogel 60 mg, 90 mg or 120 mg s.c. to arm, abdomen or buttock (as deep as possible)	27 healthy male subjects received lanreotide Autogel	To investigate tolerability at three different injection sites, PK profile, antibody concentrations and safety at three different dose levels
B-54-52030-038 / Module 5, Vols 5-8	Single center, randomized, double blind, parallel group with additional drug interaction study	Lanreotide IRF 1 mg/kg i.v. then either lanreotide Autogel 60 mg, 90 mg or 120 mg dose i.m., or 60 mg s.c., lanreotide Autogel (600 mg/mg) 60 mg dose i.m., lanreotide Autogel (600 mg/mg) 60 mg dose i.m. or s.c.	42 healthy subjects received lanreotide IRF and lanreotide Autogel (6 per treatment group)	To evaluate PK profile using various routes of administration and peptide concentrations of lanreotide Autogel; to determine absolute bioavailability and tolerability; interaction with vitamin K and cyclosporine

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Table 3: Pivotal lanreotide Autogel PK in acromegalic patients

Study Number / Location within NDA 22-074	Study Design	Treatment	Population	Main Study Objective
E-28-52030-076 / Module 5, Vols 28-32	Randomized, parallel group, double blind, 4 monthly treatments	Lanreotide Autogel 60 mg, 90 mg or 120 mg dose, deep s.c., upper quadrant of the buttock, 4 fixed doses at 28 day intervals	18 acromegalic patients received lanreotide Autogel	To evaluate PK profile, efficacy and safety
E-28-52030-717 / Module 5, Vols 53-73	Pivotal, multicenter randomized including washout phase, placebo controlled phase, fixed dose phase and open label titration phase	12 week washout phase then 4 week double blind placebo controlled phase (patients randomly assigned to lanreotide Autogel 60 mg, 90 mg, 120 mg dose or equivalent placebo), then 16 week single blind, fixed dose phase of treatment with lanreotide Autogel 60 mg, 90 mg or 120 mg dose and then 32 week open label dose titration phase when patients received 8 injections of lanreotide Autogel, dose based on dose titration schema, all deep s.c. into the buttock	108 acromegalic patients in ITT population that received at least one dose of lanreotide Autogel, 94 in PP population for double blind phase, 89 in PP population single-blind phase, 76 in PP population for open label dose titration phase	To investigate the PK, PD, efficacy and safety profile of lanreotide Autogel
E-28-52030-709 / Module 5, Vols 164-170	Open multicenter study in patients previously treated with lanreotide MPF	Lanreotide MPF 30 mg i.m. 5 dose at fixed dosing intervals (5 to 16 days) then lanreotide Autogel 60 mg, 90 mg or 120 mg 3 doses every 28 days, deep s.c.	144 acromegalic patients received at least one dose of lanreotide MPF, 133 received at least one dose of lanreotide Autogel, 107 in PP population	To demonstrate that lanreotide Autogel has equivalent efficacy to that of lanreotide MPF
E-28-52030-710 / Module 5, Vols 171-183	Open multicenter study in patients previously treated with lanreotide MPF and with lanreotide Autogel at fixed doses	Lanreotide Autogel 60 mg, 90 mg or 120 mg up to 12 doses every 28 days, titrated according to response, deep s.c.	130 acromegalic patients	To demonstrate efficacy of titrated dose of lanreotide Autogel
E-92-52030-180 / Module 5, Vol 10	Multicenter, open label, noncomparative	Lanreotide IRF 7 µg/kg i.v. then lanreotide IRF 7 µg/kg s.c. then lanreotide MPF 30 mg i.m. single dose, then repeated dosing every 14 days and every 10 days	14 acromegalic patients received lanreotide IRF and 13 received lanreotide MPF	To assess the PK profile in acromegalic patients

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Table 4: Pivotal population PD studies using lanreotide Autogel

Study Number (PK Analysis No.)	Study Design	Treatment	Population	Main Study Objective
E-28-52030-717 (01PKS011) / Module 5 Vol 68-69	E _{max} model	Lanreotide Autogel 60, 90, 120 mg/ 4 weeks; deep s.c.	108 acromegalic patients in ITT population that received at least one dose of lanreotide Autogel, 94 in PP population for double blind phase, 89 in PP population single-blind phase, 76 in PP population for open label dose titration phase	To calculate E _{max} , EC ₅₀ and dose of lanreotide required to reduce GH concentrations to 2.5 ng/mL
PK analysis 01/PKR/050 (data from Studies E-28-52030-709, E-28-52030-710) / Module 5 Vol 50	E _{max} model	Lanreotide Autogel 60, 90, 120 mg/ 4 weeks; deep s.c.	144 acromegalic patients received at least one dose of lanreotide MPF, 133 received at least one dose of lanreotide Autogel, 107 in PP population	To calculate E _{max} , EC ₅₀ and dose of lanreotide required to reduce GH concentrations to 2.5 ng/mL
PK analysis 01/PKR/025 (data from Studies A-47-52030-705, E-88-52030-044 and E-54-52030-065) / Module 5 Vol 51	E _{max} model	Lanreotide MPF 30 mg every 7, 10 or 14 days /; i.m.	128 acromegalic patients who responded to treatment with lanreotide MPF	To calculate E _{max} , EC ₅₀ and dose of lanreotide required to reduce GH concentrations to 2.5 ng/mL

Apart from the above studies, several other supportive studies have been included in this NDA including

- Studies of lanreotide IRF in special populations (elderly, hepatic impaired, and renal impaired patients).
- PK studies characterizing the lanreotide IRF and MPF formulations.
- *In vitro* studies
- Primary and secondary PD studies

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The main PD effect of lanreotide relevant to the proposed indication is the reduction in serum concentrations of GH and IGF-1. These also constitute the primary efficacy markers for lanreotide in the treatment of acromegaly and these were measured in the pivotal clinical studies conducted with lanreotide in acromegalic patients.

Secondary pharmacological effects have also been investigated in a number of PD studies in both healthy and patients using lanreotide IRF and MPF. These effects include effects

on glycoregulation, gastrointestinal physiology (gallbladder contractility, gastric acidity, gastrointestinal motility and exocrine secretions), gastrointestinal transit (effect on endocrine secretions), and splanchnic and renal circulation.

GH is known to be released intermittently and is very variable throughout the day. For the determination of GH levels, a series of 7 samples (first sample taken after an 8-h fast at 8:00 in the morning and last sample was obtained at 11:00 in the morning just prior to injection of lanreotide) were obtained at 30-minute intervals at screening and at specified time points in the clinical studies. A single sample (same time as GH, 8:00 in the morning) was obtained for the assessment of IGF-1 levels at day 0 and at specified time-points in the clinical studies.

GH Assay: This assay is a two-site chemiluminescence immunoassay.

The limit of detection was 0.01 ng/ml and the analysis established a limit of quantitation as 0.15 ng/ml. The intra assay variation for the quality control samples was between 2.6% - 7.9%, while the inter-assay variation ranged from 4.7% - 6.6%.

IGF-1 Assay: The IGF-1 assay is also a two-site chemiluminescence immunoassay.

The limit of detection was 0.2 ng/ml and the analysis established a limit of quantitation as 3.4 ng/ml. The intra assay variation for the quality control samples was between 6.0 - 9.4%, while the inter-assay variation ranged from 6.6 - 8.4%.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes.

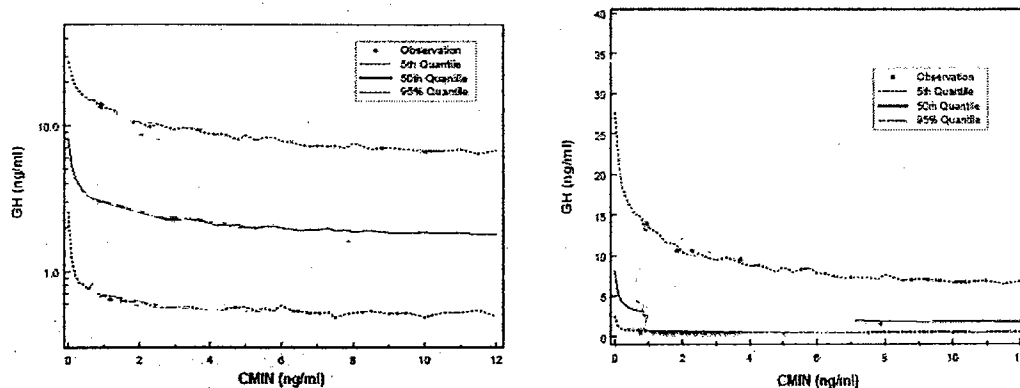
Lanreotide was assayed using a radioimmunoassay in the plasma, serum and urine (See Analytical Section).

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Population PD relationship was investigated based on the data obtained from Studies E28 52030 709, E28 52030 710 and E28 52030 717. Conclusions from the pharmacodynamic analyses based on data obtained from studies E28 52030 709 and E28 52030 710 were listed as following (Report 01/PKS/050, Vol 50, P36/409): A simple inhibitory Emax model allowing the possibility of an incomplete inhibition of GH, with inter-individual variability in EC50 (50% of Emax) and E0 (baseline value of GH) was selected as the best model. Emax was 0.821 (equivalent to 7.09 ng/ml) with a low relative standard error of 7.53%. The level of lanreotide needed to reduce the GH to EC50 was 0.206 ng/ml. The estimated E0 value was 8.63 ng/ml, reflecting the inclusion criterion for GH levels <10 ng/ml at study entry. The median lanreotide serum level needed to decrease the GH to 2.5 ng/ml (C25) was 1.127 ng/ml, and the mean remnant GH after Emax is achieved (GHR) was 1.733 ng/ml. No covariates were found to influence the PD relationship. The visual predictive check is shown in Figure 3.

Figure 3: Visual predictive check for the population pharmacodynamic model derived from studies E28 52030 709 and E28 52030 710 [Log (left) and linear (right) scale].



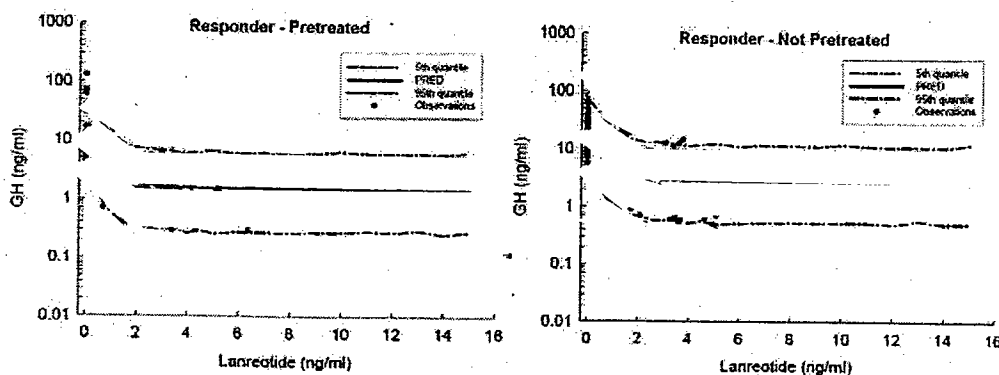
Conclusions from the pharmacodynamic analyses based on data obtained from Study E28 52030 717 were listed as following (Report 01/PKS/011, Vol 68, P66/67):

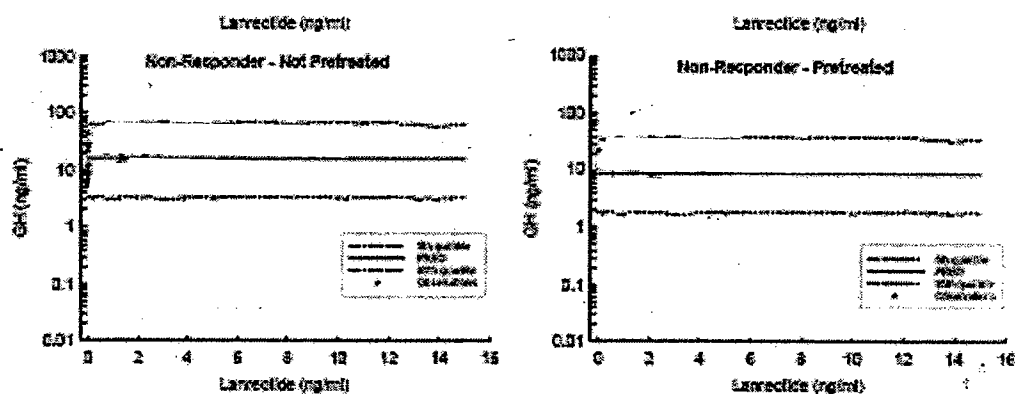
- Simple Sigmoidal Inhibitory EMAX model adequately described the relationship between lanreotide and GH concentrations.
- The population mean of EMAX was estimated to be around 82%, demonstrating the effectiveness of lanreotide.
- Baseline GH level (E_0) was significantly related to pre-treatment status within the last 3 months, estimating a lower value of E_0 for pre-treated patients (8.74 ng/ml) than for not pre-treated patients (15.9 ng/ml). The remaining covariates (age, weight, gender, Autogel dose level and visit) were not identified as significantly influencing on lanreotide pharmacodynamics.

- A mixture model on EC_{50} was included in the PK/PD model, assuming that the population consisted of two subpopulations: non-responders and responders to lanreotide treatment. The estimated percentage of non-responders (patients unaffected by the treatment) and responders were 13.7% and 86.3%, respectively. EC_{50} for non-responders was fixed to a high value of 100 ng/ml, and a value of 0.612 ng/ml was estimated in EC_{50} parameter for responder patients. The lower sensitivity obtained for non-responders indicates that these patients do not respond to lanreotide treatment even with high lanreotide concentrations.
- Interindividual variability (reported as CV%) was estimated in E_0 , $EMAX$ and EC_{50} , obtaining a high variability for E_0 (85%), moderate variability for EC_{50} (43%) and low variability for $EMAX$ (14%). Residual variability was well described by an additive-proportional error model, with standard deviation of the additive component of 0.116 ng·ml⁻¹ and coefficient of variation of 30% for the proportional component.
- A good precision in all population parameters was determined with low relative standard errors ranging from 2% to 41%.
- The median lanreotide serum level needed to decrease the GH to 2.5 ng/ml in lanreotide responder patients was 0.95 ng/ml, and the median GH concentration reached asymptotically when lanreotide concentration trends to infinity (GHR) was 1.71 ng/ml. The mean minimum steady state concentrations following 60 mg, 90 mg, and 120 mg dose are 1.8, 2.5, 3.8 ng/mL respectively from Study E-28-52030-076 (Table 7).
- 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.

The model predicted and observed GH concentrations versus lanreotide concentrations are shown in Figure 4 according to responder status of patients.

Figure 4: Observed GH concentration of all patients and population prediction (lines) vs. lanreotide concentration according to their responder status (Study E28 52030 717)





Secondary PD effects:

Effect on various hormones: Study E-54-52030-132 and E-54-52030-133 evaluated the effect of lanreotide on levels of GH, blood glucose, glucagon, motilin, pancreatic polypeptide, gastric inhibitory peptide (GIP), thyroid stimulating hormone (TSH), and secretin in healthy volunteers. The doses used were single s.c. injection of increasing doses (125, 250, 500 μ g) or continuous infusion of a 2000 μ g dose. Results indicated that there was a significant decrease in motilin, GIP, and pancreatic polypeptide secretion compared to placebo. During the placebo administration, increase over the baseline TSH levels was observed in 7/8 subjects. TSH is decreased during lanreotide administration, indicating a lack in increase observed during the nocturnal period. GH and IGF-1 levels also showed a statistical significant reduction.

Gastric acid output: Study E-47-52030-147 evaluated the effect of lanreotide on intragastric acidity and gallbladder contraction in healthy volunteers (N=6). Each subject received placebo and somatuline SR 30 mg in a single dose. Intramuscular injection of somatuline SR elevated the intragastric pH (median 24-h pH was increased from 1.57 to 3.30). However no significant difference was seen in gastric acid secretion on days 7 and 14. The postprandial gall bladder contraction was inhibited on Day 1. After placebo administration, the post prandial gall bladder volumes decreased from 15.5 ml to 8.4 ml, the volumes remained unchanged in somatuline SR group.

Exocrine pancreatic responses: In study E-47-52030-154 healthy subjects (n= 6) received either placebo or somatuline SR 30 mg i.m. as a single dose. A decreased volume of exogenously stimulated pancreatic secretion was seen only on Day 2. Similar effects were seen on pancreatic bicarbonate and amylase secretion. There was no difference between treatments for exogenously stimulated biliary secretion. Meal stimulated secretion of amylase and bilirubin were only inhibited by somatuline SR on Day 2. Similar effects as seen in other study were observed – inhibition in pancreatic polypeptide, cholecystokinin concentrations.

Renal plasma flow: In study E-92-52030-005, 12 healthy subjects received a single i.m. injection of somatuline PR 30 mg. Renal plasma flow and GFR was assessed by means of ^{131} I-hippuran, and ^{51} Cr-EDTA clearances respectively of Day -5, Day -1 and Day 0, Day 3 and Day 8 of drug administration. As related to baseline (Day -1), there were no

significant differences in renal plasma flow values. There was a significant decrease in GFR (15%) as compared to baseline on Day 0, the day of injection. This decrease was more in males as compared to women. In this study GH, IGF-1 levels were also measured to ensure that the subjects recruited had no pituitary disease. All subjects had GH below the limit of detection in majority of samples collected.

Meal stimulated splanchnic blood flow: E-47-52030-403 was a double-blind, randomized, placebo-controlled cross-over study in healthy male subjects (N=6). Each subject received one i.m. injection of either placebo or lanreotide at a dose of 30 mg with a washout of at least 14 days. Results indicated that there were no significant differences in baseline values of mesenteric arterial blood flow within each treatment and between the treatments for each of the observation days. After lanreotide, the values were significantly decreased as compared to placebo. Similarly the AUC of postprandial blood flow also decreased after lanreotide administration compared to placebo. Postprandial portal venous blood flow also showed similar behavior as the mesenteric arterial blood flow with lanreotide administration. However, there were no significant differences detected in renal arterial blood flow with lanreotide administration.

Parameters of glycoregulation: E-92-52030-174 was a single-center, double-blind controlled study in 8 healthy male volunteers. Biological tolerance on the basis of the principal parameters of glycoregulation (glucose, insulin, C-peptide and glucagon in the plasma) during the administration of treatment at various time points was evaluated. The administration of lanreotide by continuous pump caused a delay in the postprandial peak for glucose, insulin and C-peptide and a reduction in postprandial insulin and C-peptide peaks. There was an increase in the AUC for glucose with the high doses (2000 and 3000 µg/24h). A reduction in glucagon levels were noted with the high dose.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The dose - safety relationship for the major adverse events (diarrhea, bradycardia, diabetes, hypertension, and anemia) in the first treatment period of Somatuline Autogel in studies 52030 717, E28 52030 709/710, and E28-52030-076 was investigated. Since PK samples were not collected from every patient, the dose-safety relationship rather than the exposure-safety relationship was explored. Through the dose - safety analysis, it was found that:

- Diarrhea was the most common adverse reaction. By applying the logistic regression analysis, a significant dose-response relationship ($P = 0.0178$) was identified for the incidence of diarrhea (Figure 5). The results suggest that after initialization of Somatuline Autogel treatment, the probability of a patient to develop diarrhea is driven by dose. Higher dose yielded higher probability of diarrhea- 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.
- After initialization of Somatuline Autogel treatment (Figure 6)

- 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 ($P = 0.76$).
- 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.
- The other major adverse events (bradycardia, hypertension, diabetes, and anemia) were not dose related, based on the first treatment period of Studies E28-2030-717, E28-52030-709/710, and E28-52030-076. The incidences of adverse events are demonstrated in Figure 1. No obvious trend was identified across the dose range from 60 mg to 120 mg.

Figure 5: Dose-response relationship for the incidence of diarrhea after initialization of Somatuline Autogel treatment

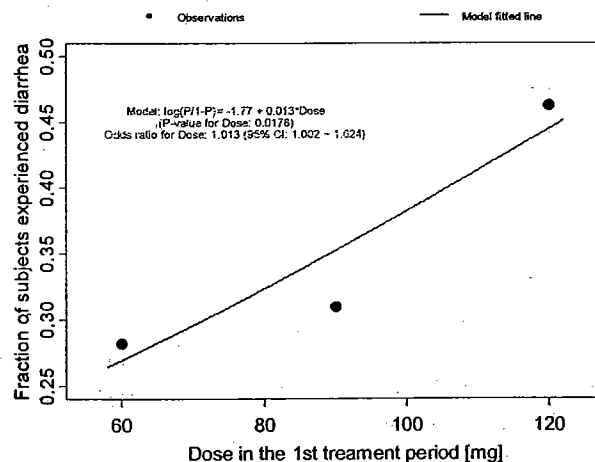
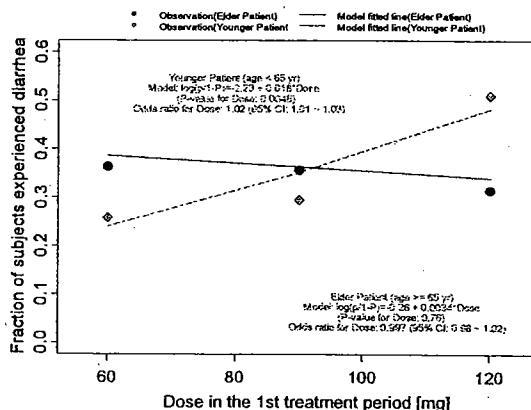


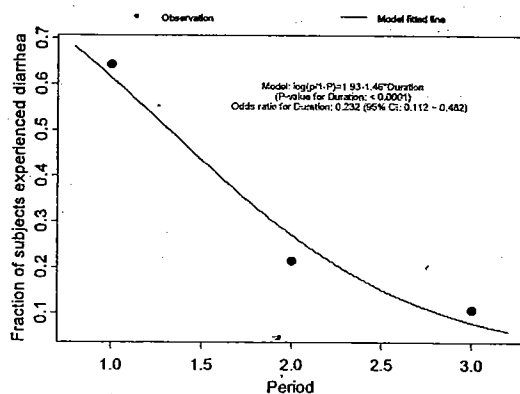
Figure 6: Dose-response relationship for the incidence of diarrhea in elder patient (age ≥ 65 yr) and in younger patient (age < 65 yr) after initialization of Somatuline Autogel treatment



The safety – duration relationship in a subgroup of patients being treated by 120 mg Somatuline Autogel for 3 consecutive periods was also investigated. Through incidence – treatment duration analysis, it was found that:

- By applying logistic regression analysis, a significant incidence – treatment duration relationship was identified for diarrhea ($P < 0.0001$) (Figure 7). The results suggest that 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.
- 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.

Figure 7: Incidence – treatment duration relationship for diarrhea in a subgroup of patients being treated by 120 mg in 3 consecutive periods



2.2.4.3 Does this drug prolong the QT or QTc interval?

Sponsor has not evaluated the effect of lanreotide on the QT interval in a thorough QT study. There is no literature data regarding lanreotide's effect on QT interval. Some reports have associated Octreotide, the approved somatostatin analog with possible risk of causing Torsades de Pointes and/or QT prolongation but at this time there is lack of substantial evidence (Website on QT drugs (www.qtdrugs.org) by Centers for Education and Research on Therapeutics, Arizona CERT).

Sponsor has conducted preclinical *in vitro* and *in vivo* assays to assess the potential of lanreotide to prolong QT interval. *In vitro* ionic current assay did not show HERG current inhibition and no significant effect on action potential in isolated canine Purkinje fibers was observed. The *in vivo* QT assessment in telemetry instrumented dogs infused with lanreotide doses of 1, 3, or 10 mg/kg/24h did not show any QT/QTc changes. The mean plasma concentration at the highest dose tested in dogs corresponded to approximately 330 ng/ml (mean steady state plasma concentration in humans after 120 mg Autogel was about 7.6 ng/ml).

Sponsor has monitored QT during the clinical trials of lanreotide. There was no evidence of an effect of lanreotide on QT interval. Lanreotide exerts similar effects as octreotide to lower the heart rate by approximately 4 b.p.m. leading to AEs of bradycardia in some patients.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

None.

2.2.5 Pharmacokinetic Characteristics

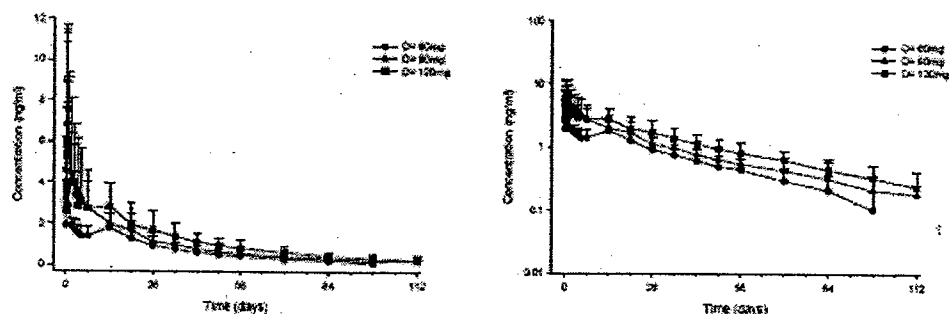
2.2.5.1 What are the PK characteristics of the drug and its major metabolite?

The PK and PD profile of lanreotide was established in healthy subjects and acromegalic patients using lanreotide immediate release formulation (IRF), and microparticle formulation (MPF), prior to development of lanreotide Autogel. The following sections describe the PK characteristics of lanreotide Autogel.

2.2.5.2 What are the single dose and multiple dose PK parameters?

Only single dose PK parameters of lanreotide Autogel were obtained in healthy volunteers. The following figure summarizes the serum lanreotide concentrations achieved following deep s.c administration at doses of lanreotide Autogel 60, 90, 120 mg.

Figure 8: Superimposed Mean $\pm$ SD lanreotide serum concentrations achieved in healthy volunteers following deep s.c. administration of lanreotide Autogel formulation at the doses of 60, 90, and 120 mg (linear and semilog plots)



The summary of PK parameters following the deep s.c dose is shown below in Table 5.

Table 5: Mean $\pm$ SD lanreotide pharmacokinetic parameters achieved in healthy volunteers after the deep s.c. administration of lanreotide Autogel at the doses of 60, 90, and 120 mg.

Parameter	D= 60 mg			D= 90 mg			D= 120 mg		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
T_{max} , day	0.33 $\pm$ (0.17-14.00)		13	0.50 $\pm$ (0.17 - 14.00)		13	0.29 $\pm$ (0.08 - 2.14)		12
C_{max} , ng·ml ⁻¹	4.25 $\pm$ 1.93		13	8.39 $\pm$ 4.91		13	6.79 $\pm$ 3.64		12
AUC _{0-28days} , ng·ml ⁻¹ ·day	42.0 $\pm$ 9.3		13	67.3 $\pm$ 25.4		13	73.3 $\pm$ 33.9		12
AUC ₀ , ng·ml ⁻¹ ·day	69.8 $\pm$ 19.2		13	107.3 $\pm$ 36.3		13	132.2 $\pm$ 42.0		12
AUC _∞ , ng·ml ⁻¹ ·day	78.2 $\pm$ 19.1		11	120.3 $\pm$ 34.1		12	150.8 $\pm$ 38.4		10
AUC/D, ng·ml ⁻¹ ·day·mg ⁻¹	1.30 $\pm$ 0.32		11	1.34 $\pm$ 0.38		12	1.26 $\pm$ 0.32		10
AUC extrapol., (%)	7.7 $\pm$ 5.2		11	6.6 $\pm$ 4.7		12	7.9 $\pm$ 5.5		10
$t_{1/2}$, day	23.3 $\pm$ 9.9		11	27.4 $\pm$ 9.4		12	30.1 $\pm$ 9.8		10
MRT _∞ , day	35.5 $\pm$ 12.0		11	36.8 $\pm$ 15.1		12	42.5 $\pm$ 13.2		10
F, (%)	73.4 $\pm$ 23.3		10	69.0 $\pm$ 17.1		11	78.4 $\pm$ 21.3		10

^a T_{max} is a median value

The mean C_{max} after the three doses were 4.25, 8.39, and 6.79 ng/ml while the half life was 23.3, 27.4, and 30.1 days respectively. Dose proportionality was assessed using the power model on parameters AUC_{0-28day}, AUC_{0-t}, AUC_∞ and C_{max} . All the 95% CI were wide indicating high variability but all included the value 1 indicating dose-proportionality.

Table 6: Statistics summary of the power model to assess dose-proportionality following single dose deep s.c. injection (Reviewer's analysis)

PK Parameter	Ratio	90% CI
AUC (ng/ml · day)	0.935	0.620 – 1.249
AUC _{0-28days} (ng/ml · day)	0.745	0.397 – 1.093
AUC _{0-t} (ng/ml · day)	1.29	0.91 – 1.68
C_{max} (ng/ml)	0.695	0.133 – 1.258

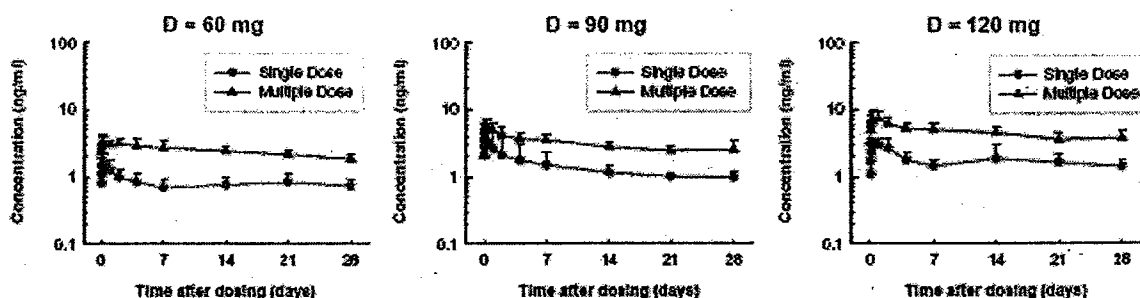
2.2.5.3 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

PK information in acromegaly patients was obtained from study E-28-52030-076 which was a phase 2 randomized, parallel group double-blind study to evaluate the PK profile of lanreotide Autogel (60, 90, and 120 mg). Patients received 4 deep S.C. doses at 28-day intervals (N=18; 6/group; 12 females: 6 males) Days 0, 28, 56, and 84.

Blood samples for determination of lanreotide Autogel were obtained prior to the first and fourth dose of drug and at 1, 2, 4, 6, and 8 h after each dose. In addition, samples were obtained 1, 2, 4, 7, 14, 21 days after the first dose and fourth dose. Trough levels were obtained prior to second (Day 28) and third (Day 56) doses.

After repeated dosing, lanreotide Autogel exhibited linear PK. The PK parameters increased in a dose-dependent manner (Table 7). Repeated administrations produce an accumulation in the body independent of dose level with a mean accumulation index of 2.7. The pattern of serum concentration-time profile curves did not differ to those obtained after single dose administration but concentrations were higher (Figure 9). The mean minimum serum levels of lanreotide after first, second, third and fourth Autogel administrations (Cmin1, Cmin2, Cmin3, Cmin4) were 0.725, 1.203, 1.546, and 1.822 ng/ml for 60 mg; 0.973, 1.655, 2.083, and 2.511 ng/ml for 90 mg; and 1.406, 2.162, 3.204 and 3.762 ng/ml for 120 mg. The Cmin increases with the number of consecutive administrations.

Figure 9: Comparative lanreotide serum level profiles in acromegalic patients following a single Autogel administration or four monthly Autogel administrations at dose 60, 90, 120 mg



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Table 7: Comparison of PK data (mean $\pm$ SD) for patients with acromegaly following a single dose and following four doses of lanreotide Autogel 60, 90, and 120 mg.

Parameter		Lanreotide Autogel Dose					
		60 mg	N	90 mg	N	120 mg	N
Cmin (ng/ml)	Dose 1	0.725 $\pm$ 0.191	6	0.973 $\pm$ 0.199	5	1.406 $\pm$ 0.306	5
	Dose 4	1.822 $\pm$ 0.304	4	2.511 $\pm$ 0.882	6	3.762 $\pm$ 1.012	6
Cmax (ng/ml)	Dose 1	1.650 $\pm$ 0.623	6	3.543 $\pm$ 2.546	5	3.053 $\pm$ 0.932	5
	Dose 4	3.821 $\pm$ 0.509	4	5.697 $\pm$ 1.672	6	7.685 $\pm$ 2.470	6
AUC τ (ng/ml-d)	Dose 1	22.27 $\pm$ 6.42	6	37.29 $\pm$ 14.23	5	48.49 $\pm$ 15.36	5
	Dose 4	68.79 $\pm$ 8.53	4	85.11 $\pm$ 17.10	6	126.66 $\pm$ 27.66	6

The following table shows the mean Cmin data after each of the four doses. Cmin values increased with each consecutive dose and appeared to be approaching steady-state after the 4th dose.

Table 8: Cmin data following administration of four deep s.c. doses of lanreotide Autogel 60, 90, 120 mg to acromegalic patients

Parameter	60 mg			90 mg			120 mg		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Cmin 1 (ng/ml)	0.725	0.191	6	0.973	0.199	5	1.406	0.306	6
Cmin 2 (ng/ml)	1.203	0.376	6	1.655	0.419	6	2.162	0.385	6
Cmin 3 (ng/ml)	1.546	0.418	5	2.083	0.534	6	3.204	0.532	6
Cmin 4 (ng/ml)	1.822	0.304	4	2.511	0.882	6	3.762	1.012	6

Steady state Cmin levels of lanreotide in acromegaly patients were assessed in pivotal clinical trials.

2.2.5.4 What are the characteristics of drug absorption?

The release profile of lanreotide Autogel is characterized by an initial burst release on the first day of administration that determines the Cmax followed by a sustained release to give a long apparent terminal half-life (23-30 days). The apparent terminal half-life of the lanreotide Autogel is limited by release from the depot and not by disposition half-life of the peptide (flip-flop). Following i.v. administration of lanreotide, elimination of lanreotide was very fast (1.14 h half life and 23.7 L/h clearance) and the volume of distribution at steady state was very low (16 L). The absolute bioavailability of the Autogel formulation was estimated using the exposure of lanreotide after a single intravenous dose (7 μ g/kg) of lanreotide and following a deep s.c administration of the Autogel in healthy volunteers. It was determined to be 73.4%, 69% and 78.4%

respectively for the 60, 90 and 120 mg doses.

Dose-dumping: The negligible initial burst release and overall control over entire releases after single doses at the three dose levels (60, 90, and 120 mg) demonstrates the robustness of the formulation drug release. The lanreotide AUC (0-2 days) was ~11% of the total AUC (0-28 days). Similar observations were made following multiple administrations of lanreotide Autogel.

Effect of application site: Study E-55-52030-047 was conducted to compare the local tolerability of single deep s.c. injection of lanreotide Autogel (60, 90, and 120 mg) at the following sites:

- Upper external quarter of the right buttock
- Right latero-umbilical abdominal wall
- Upper arm on the opposite side to the subject's dormant arm.

The study was performed in 27 healthy male subjects and each subject received only one injection at one site and one dose (N = 3 per dose and per site). Subjects fasted overnight before the morning administration. The injection sites were assessed for local tolerability, induration (hardening/redness of skin, itching and pain). The assessments were reported in a categorical scale (none 0, mild 1, moderate 2, and severe 3). The following table shows the summary of all the indurations reported in the study. Based on this, the buttock seems to be the preferred site of injections for lanreotide Autogel, where mild indurations appeared later (Day 42). Also with doses 90 mg and 120 mg the induration intensity was higher than with the 60 mg dose indicating some dose-related phenomena.

Table 9: Induration 24 hours and 42 days after injection, per severity, injection site and dose groups.

D0 - H24	Absent	Weak	Mild	Moderate	Severe
Right Buttock	8	0	1	0	0
Upper Arm	1	2	5	1	0
Abdominal Wall	1	3	3	2	0
D0 - H24	Absent	Weak	Mild	Moderate	Severe
60 mg	4	3	1	1	0
90 mg	3	2	2	2	0
120 mg	3	0	6	0	0

D42	Absent	Weak	Mild	Moderate	Severe
Right Buttock	5	0	3	1	0
Upper Arm	2	0	7	0	0
Abdominal Wall	0	0	6	3	0
D42	Absent	Weak	Mild	Moderate	Severe
60 mg	5	0	4	0	0
90 mg	0	0	7	2	0
120 mg	2	0	5	2	0

The C_{max} measured in this study varied greatly between subjects. Mean AUC₀₋₄₂ was similar across injection sites. Due to small number of subjects in each group and variability between subjects, reliable conclusions cannot be drawn regarding PK parameters. The sponsor has chosen the buttock to be the site of injection which is acceptable.

2.2.5.5 What are the characteristics of drug distribution?

The binding of radiolabeled lanreotide to human serum proteins was assessed in the concentration range of 5 to 370 nM. The overall binding for human serum was 78-83%. Human serum albumin (HSA) accounted for the largest fraction of bound lanreotide despite the low affinity of lanreotide to HSA. Lanreotide does not bind to erythrocytes. 25% of lanreotide serum binding is attributed to α -aminoacid glycoprotein (AAG) and lanreotide binds AAG with relatively high affinity. Changes in AAG concentration could result in changes to the lanreotide bound fraction and distribution between proteins.

2.2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance study has been not been conducted for lanreotide.

2.2.5.7 What are the characteristics of drug metabolism?

The metabolism of lanreotide has not been addressed. Lanreotide is a peptide and drug metabolizing enzymes (Phase 1 and Phase 2) are not expected to be involved in its metabolism.

2.2.5.8 What are the characteristics of drug excretion?

Following i.v. administration of lanreotide immediate release formulation, the elimination was very fast (1.14 h half life and 23.7 L/h clearance) (Study 149). Sponsor also conducted a PK study to characterize lanreotide elimination following continuous s.c. infusion for 5 days in healthy volunteers (Study E-54-52030-134). The PK study was conducted as an open-label and parallel study. 20 volunteers were divided into 2 groups: the first 10 were assigned to low dose group, lanreotide 0.75 mg per day for 5 days. The next ten volunteers were assigned to high dose group, lanreotide 3.0 mg per day escalated to 6.0 mg per day after 24 h and continuing for an additional 4 days. 24 h after beginning of the continuous infusion, a booster injection of 0.375 mg and 1.5 mg was administered

s.c. for both low and high dose groups respectively. Fecal and urinary excretion of lanreotide was assessed by measuring lanreotide immunoreactivity in urine and fecal 24 h samples on Days 3 and 4, when steady-state plasma concentrations were expected.

The excretion of lanreotide in urine and feces was low. At steady state, the fraction of the amount administered over 24 h that was excreted in urine was approximately 1-5% and 0.3-2.3% for the low and high dose groups respectively. Data on fecal excretion was collected from 4 subjects in the high dose group on Days 3 and 4 of the infusion period. The amount of drug recovered was less than 0.5% of the drug administered over a 24-h period. (This recovery of unchanged lanreotide in the feces is likely an indicative of biliary excretion of the peptide).

Another study (E-54-52030-67) in which 13 healthy male subjects received a single 3 mg s.c. dose of lanreotide IRF also showed that renal excretion of lanreotide represents a minor elimination route with less than 1% of the administered dose recovered in the urine.

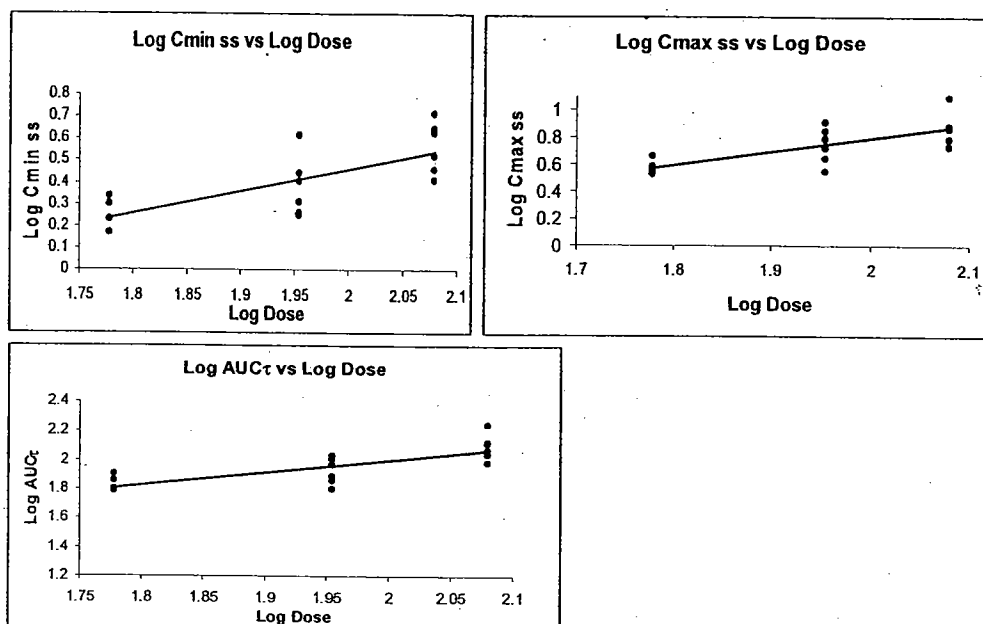
2.2.5.9 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

After repeated dosing, lanreotide Autogel exhibited linear PK in acromegaly patients. The PK parameters increased in a dose-dependent manner (As shown in section 2.2.5.1). Power model was used to assess dose-proportionality. The estimates of slope after single and multiple doses are shown in Table 10. As shown, the CI includes the value of 1, indicating dose-proportionality.

Table 10: Power model: Dose-proportionality analysis (Reviewer's analysis)

PK Parameter	Dose	Ratio	95% CI
Cmin1 (on Day 28)	1	0.96	0.56 – 1.37
AUC τ (ng/ml·day)	1	1.12	0.59 – 1.66
Cmax (ng/ml)	1	1.03	0.18 – 1.88
Cminss (on Day 112) (ng/ml)	4	1.02	0.48 – 1.56
AUC τ (ng/ml·day)	4	0.87	0.47 – 1.27
Cmaxss (ng/ml)	4	0.96	0.45 – 1.48

Figure 10: Dose proportionality of lanreotide Autogel at steady state. Plots of mean values for C_{min} ss, C_{max} ss and AUC_τ.



2.2.5.10 How do the PK parameters change with time following chronic dosing?

See above sections.

2.2.5.11 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

PK: Population PK analysis of lanreotide in healthy subjects (i.v bolus administration of lanreotide IRF) demonstrated that the inter-subject variability expressed as CV% was 19% for total plasma clearance. The time-course of lanreotide release after deep s.c. administration of lanreotide Autogel was described using an absorption rate that decreased exponentially as a function of logarithm of time. The population release parameter showed an inter-subject variability (CV%) for the first order rate constant of absorption at the time of administration as 44%.

PD: A simple inhibitory E_{max} model with inter-individual variability on EC₅₀ and E₀ adequately described the observed data in the pivotal clinical study. The population parameter estimates are presented in Table 11. Inter-individual variability (reported as CV%) was estimated in E₀, E_{MAX} and EC₅₀, obtaining a high variability for E₀ (85%), moderate variability for EC₅₀ (43%) and low variability for E_{MAX} (14%). Residual variability was well described by an additive-proportional error model, with standard deviation of the additive component of 0.116 ng·ml⁻¹ and coefficient of variation of 30% for the proportional component.

Table 11: Population pharmacodynamic model parameters of lanreotide derived from studies E28 52030 717

Parameter	Units	Estimate	IIV	P
EMAX	-	0.823	14%	NA
EC50 _{NR}	ng/ml	100 [#]	43%	13.7%
EC50 _R	ng/ml	0.612	43%	86.3%
E0 _{NFT}	ng/ml	15.9	85%	NA
E0 _{PT}	ng/ml	8.74	85%	NA
Gamma	-	2.63	NE	NA
Additive_Error	ng/ml	0.116	NA	NA
Proportional_Error	%	30%	NA	NA

IIV, inter-subject variability (CV); P, fraction of population belonging to one of the two subpopulations; EMAX, Maximum effect; EC50_{NR} and EC50_R, lanreotide level that decreases GH by 50% of EMAX in non-responder and responder patients, respectively; E0_{NFT} and E0_{PT}, baseline level of GH for patients not previously treated and previously treated; Gamma, Sigmoidicity parameter; NE, not estimated; NA, not applicable; #, fixed value.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

No dosage adjustment is proposed based on age, weight, gender, race, hepatic or renal disease. The reviewer recommends that the starting dose of lanreotide Autogel in patients with moderate and severe renal and hepatic impairment to be 60 mg.

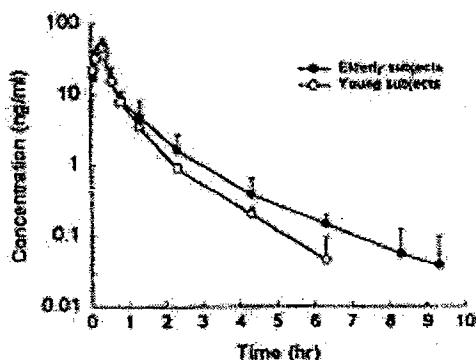
2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Sponsor conducted an open-label and parallel PK study (E-92-52030-012 reviewed under in elderly and healthy subjects following administration of one intravenous infusion (20 min) of 7 µg/kg lanreotide. 13 young healthy subjects (mean age 23.8 yrs; all male) and 12 elderly subjects (mean age 67.9 yrs; 6 male; 6 female) completed this study.

Conclusions: It was concluded that the intravenous infusion caused no statistically significant differences in mean C_{max} , AUC and CL values of the two groups. However, significant differences were found in $t_{1/2}$ and V_{ss} mean values between the two groups with the values being higher in elderly subjects compared to young. The sponsor concluded that the longer half-life obtained in elderly subjects could be attributed to the significant increase in V_{ss} in elderly compared to young and therefore related to distribution phase rather than the elimination phase. It was further indicated that the higher V_{ss} values observed in elderly could be related to their lower basal serum albumin levels as compared to young. There was higher inter-individual variability in elderly.

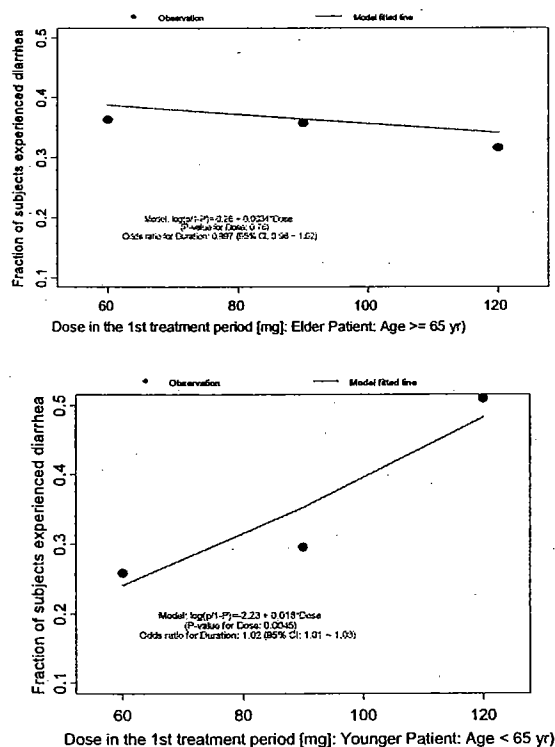
Figure 11: Time course of mean $\pm$ SD serum levels of lanreotide following one i.v. infusion (20 min) at 7 $\mu\text{g/kg}$ dose to young and elderly subjects.



Sponsor has not proposed any dosage reductions based on age since Somatuline Autogel dose selection will be based on therapeutic response. Sponsor has also stated that the expected serum lanreotide concentrations in the elderly are in the range of serum concentrations safely tolerated in healthy young subjects.

Comments: Although there were significant differences in $t_{1/2}$ and V_{ss} mean values between the young vs. elderly subjects with the values being higher in elderly subjects compared to young, there were no differences in exposure and C_{max} . There were about 24% elderly subjects (> 65 years) in the clinical trials and the adverse events were not significantly different as compared to young subjects. The pharmacometric reviewer further investigated the dose-diarrhea relationships within the elder patients (≥ 65 years) and the younger patients (< 65 years). The model fitted curve is illustrated in Figure 12. As the data demonstrated, elder patients did not have a higher incidence of diarrhea. Within the elder patients, diarrhea does not appear to be dose-dependant ($P = 0.76$). The data also showed that about 50% of younger patient suffered from diarrhea at the dose of 120 mg in the first treatment period. However, following current proposed initial dosing regimen (i.e. 90 mg for every 28 days), the incidence of diarrhea was about 30% in younger patients. Therefore there is no need to adjust dose of lanreotide in elderly subjects.

Figure 12: Logistic model fitting for diarrhea-dose relationship in elder patients (Top: age ≥ 65 yr) and in younger patients (Bottom: age < 65 yr)



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2.3.2.2 Pediatrics

Acromegaly is a disease of adults. The pathogenic features of the disease can only occur after epiphyseal closure. The effect of growth hormone on open epiphyses of children causes increased linear growth (gigantism). The conduct of clinical studies in acromegaly in the pediatric population is not feasible. Somatuline® Autogel® has not been evaluated in pediatric population.

2.3.2.3 Gender

No specific study has been conducted with lanreotide Autogel to address the effect of gender.

Study 149 showed that gender-difference may contribute to the high inter-subject variability in C_{max} observed after a single administration of lanreotide Autogel. The C_{max} was statistically higher in males than in females after administration of 60 mg Autogel deep s.c. (5.12 ng/ml compared to 3.22 ng/ml respectively). These suggest a

difference in the rate of absorption of lanreotide from the depot and may be slower in females due to gender differences in the distribution of fat at the injection site.

On the other hand, following repeated dosing (Study E28-52030-076) the exposure was similar in males and females following administration of 60, 90, and 120 mg: 79.4, 120.1 and 148.5 ng/ml in males compared to 75.9, 120.6 and 153.1 ng/ml in females.

The effect of gender on the PK parameters of the Autogel was also assessed by pooling the parameters for 27 subjects (13 males; 14 females) following i.m. administration and from 11 (5 males; 6 females) following s.c. administration in study E-54-52030-038 (Table 12). No significant differences were observed for PK parameters except $t_{1/2}$ between males and females after both routes of administration. The $t_{1/2}$ tended to be longer in females (28 days for females versus 19 days for males by i.m. route; 34 days for females versus 22 days for males by s.c. route) (Table 12). (The differences between males and females are similar to the differences observed in PK between the i.m. and s.c. routes. This may indicate that lanreotide administration in females was rather a deep-s.c. administration than a true i.m. due to the relatively short i.m. needle (32 mm) and the anatomical differences between genders).

Table 12: Effect of gender

Effect of gender on the pharmacokinetic parameters of the autogel formulation administered intramuscularly (n = 27, males = 13, females = 14)

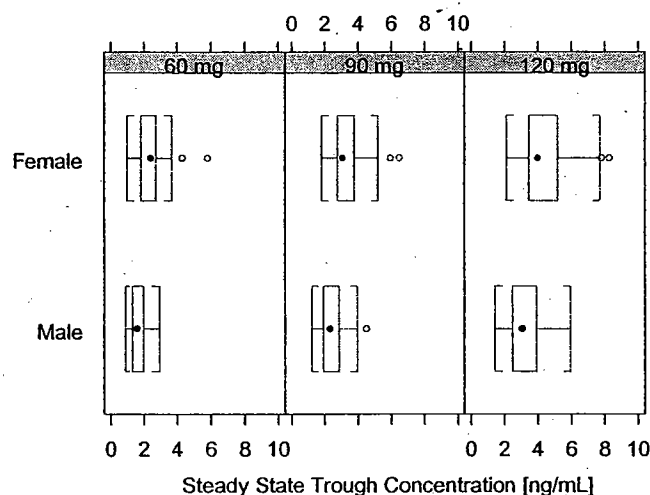
	Gender	F	Cl/F (L/h)	$t_{1/2}$ (days)
Mean	Male	0.71	29	19
SD		0.2	5	9
Median		0.70	29	16
Mean	Female	0.65	28	28
SD		0.1	6	13
Median		0.65	27	24
Kruskal-Wallis (p-value)		0.2	0.4	0.07

Effect of gender on the pharmacokinetic parameters of the autogel formulation administered subcutaneously (n = 11, male = 5, female = 6)

	Gender	F	Cl/F (L/h)	$t_{1/2}$ (days)
Mean	Males	0.58	35	22
SD		0.1	4	9
Median		0.60	34	23
Mean	Females	0.73	31	34
SD		0.2	4	12
Median		0.71	31	35
Kruskal-Wallis (p-value)		0.1	0.2	0.08

The plasma lanreotide C_{min} steady state levels were also measured in the clinical studies in acromegaly patients (Figure 13). As shown there appeared to be no differences in the median C_{min} steady state levels between males and females.

Figure 13: Effect of gender on Cmin-steady-state levels of lanreotide measured in patients (Study 717, 709/710)

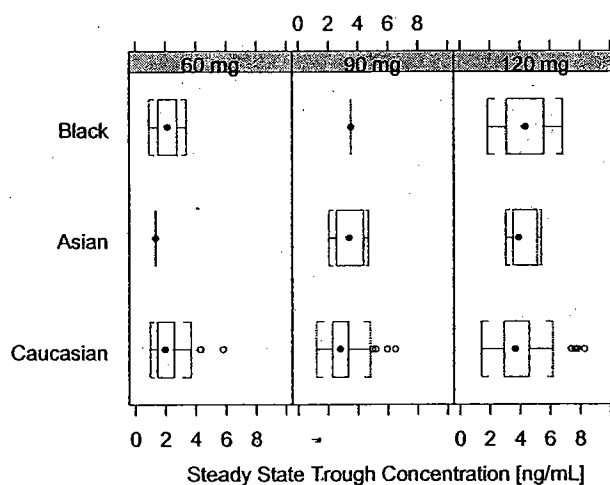


Comments: No dosage adjustments are proposed by the sponsor based on gender. This is acceptable.

2.3.2.4 Race and Body Weight

Formal PK studies to explore the effect of race and body weight on the PK of lanreotide Autogel have not been conducted. The pivotal clinical study E28-52030-717 as well as studies E28-52030-709/710 included PK data from subjects of different races and weight to allow the comparison.

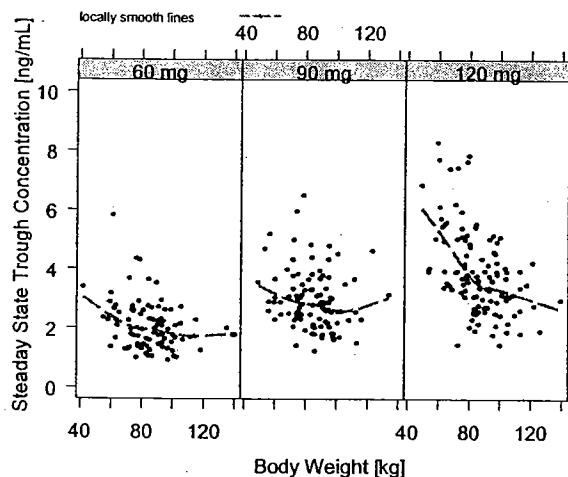
Figure 14: Effect of race on lanreotide Cmin-steady state levels



As shown in Figure 14, there were no differences in the lanreotide steady state trough levels in Asian (N = 13), Black (N = 5) and Caucasian (N = 284) patients.

The effect of body weight on the steady state lanreotide trough concentrations is shown in Figure 15. There appeared to be a trend towards lower concentrations with increasing body weight especially with highest dose level group (120 mg). However, since the dose will be titrated based on GH and IGF-1 levels, no dose adjustment is needed based on body weight.

Figure 15: Effect of body weight on lanreotide C_{min}-steady state levels



Comments: No dosage adjustments are proposed by the sponsor based on race and body weight. This is acceptable.

2.3.2.5 Renal Impairment

The sponsor conducted this study only in patients with severe renal insufficiency requiring dialysis (ESRD). The sponsor has stated that literature data indicate that the natural somatostatin and its analogues may induce a reduction in glomerular filtration rate and the effective renal plasma flow in normal population and in patients suffering from Type 1 diabetes mellitus. The sponsor therefore stated that ethical reasons did not allow for recruitment of mild and moderate renal impaired patients. This approach was followed by the approved somatostatin analogue, octreotide.

Study E-92-52030-011 was reviewed under This was an open-label, parallel study to compare the PK of lanreotide in patients with ESRD and healthy subjects. All subjects were administered with one intravenous bolus injection of 7 µg/kg lanreotide and the time-course of serum lanreotide was assessed. The plasma concentration time profile and the PK parameters in healthy and ESRD patients are as follows:

Figure 16: Time course of mean $\pm$ SD serum levels of lanreotide following i.v. bolus administration of 7 $\mu\text{g/kg}$ lanreotide to healthy volunteers and to patients suffering from severe chronic renal insufficiency.

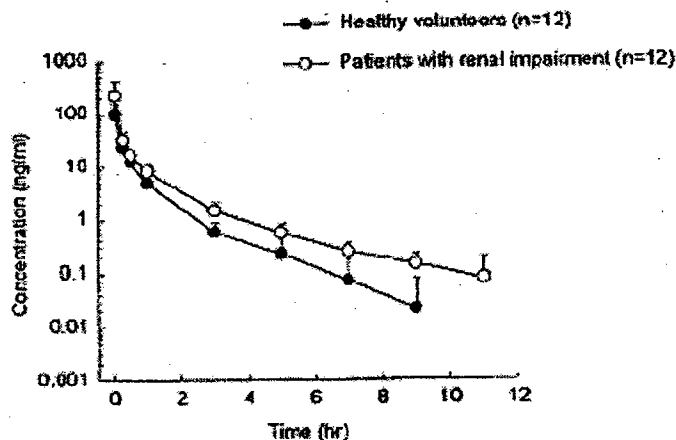


Table 13: Mean $\pm$ SD PK parameters of lanreotide following i.v. bolus administration of 7 $\mu\text{g/kg}$ lanreotide to healthy volunteers and to patients suffering from severe chronic renal insufficiency.

Parameter	Healthy volunteers (n=12)		Patients with severe renal insufficiency (n=12)		Statistics
	Mean	sd	Mean	sd	
C(0) ng.ml^{-1}	127.18	78.47	307.45	274.32	0.0195
$t_{1/2}$ hr	1.32	0.68	2.39	1.15	0.0015
AUC $\text{ng.ml}^{-1}.\text{hr}$	32.30	11.18	62.95	33.87	0.0020
MRT h	0.65	0.48	0.77	0.20	NS
CL $\text{L.hr}^{-1}.\text{kg}^{-1}$	0.244	0.092	0.138	0.060	0.0021
V_1 L.kg^{-1}	0.092	0.070	0.040	0.027	0.0203
V_{ss} L.kg^{-1}	0.172	0.160	0.110	0.062	NS
V_z L.kg^{-1}	0.456	0.289	0.442	0.205	NS

NS : no statistically significant differences ($p > 0.05$)

Conclusions: A reduction of total serum clearance and an increased half-life (approximately doubled) were observed in patients with ESRD when treated with a single intravenous dose of lanreotide 7 $\mu\text{g/kg}$. Similarly there was an increased exposure of lanreotide (2-4 times higher) in renal impaired patients. The initial serum concentrations were also high in renal impaired patients than in healthy subjects.

The reduction in total clearance observed with octreotide and lanreotide in renal patients treated with hemodialysis could be due to important renal metabolism of both analogues.

Comments: No dosage adjustments are proposed by the sponsor based on renal impairment status. This study was done only in end stage renal insufficiency patients and there is no exposure data 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

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impaired patients. Based on the results of this study, it is therefore recommended to reduce the starting dose of lanreotide Autogel in moderate and severe renal impaired patients to 60 mg.

2.3.2.6 Hepatic Impairment

The study submitted under [redacted] (Study E-92-52030-013) was conducted mostly in mild hepatically impaired patients and Child-Pugh classification was not used for classifying hepatic function. This study was not found acceptable in the review of [redacted]

[redacted] Sponsor has submitted an additional study conducted in hepatic impaired patients in this NDA (Study E-38-52030-701).

This was a parallel study in 12 healthy subjects and 12 patients with chronic hepatic impairment; all subjects (all Asian), received a single dose of 7 µg/kg of lanreotide i.v. over 20 min.

Inclusion criteria for patients: 12 Patients with hepatic pathology of B or C degree of the Child Pugh's classification. At the end of the study, the classification of patients was reassessed and 3 patients (17, 21, and 24) that were previously B or C had hepatic impairment scores of 6, 5, 6 respectively corresponding to Grade A on Child Pugh's scale. One of the patients had a score of 4 and did not enter the classification and all 4 patients were not used in sponsor's analysis.

Per-protocol patients (PK-PP) comprised of 8 patients (4 patients excluded # 16, 17, 21, 24) and 12 healthy subjects, while intent-to-treat patients (ITT) comprised of all subjects (12-healthy and 12 patients). The plasma concentration-time profiles and the PK parameters are shown in Figure 17 and Tables 14 and 15 below.

Figure 17: Lanreotide serum concentrations (mean ± SD) achieved in healthy volunteers and patients suffering from chronic impairment of hepatic function following an intravenous infusion for twenty minutes of lanreotide at the dose of 7 µg/kg (ITT and PK-PP population).

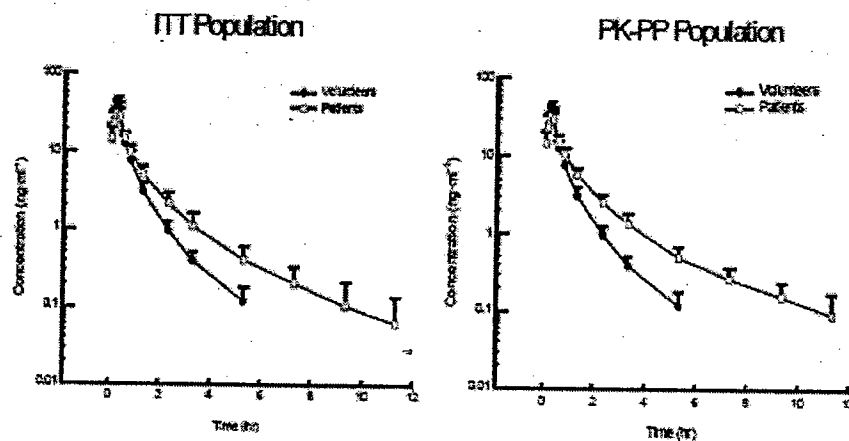


Table 14: Comparative pharmacokinetic parameters of lanreotide estimated in 12 healthy volunteers and in 12 hepatic impaired patients following an intravenous infusion for 20 min at the dose of 7 µg/kg (ITT population).

Parameter	Units	Healthy Volunteers		Patients		Statistics
		Mean	S.D.	Mean	S.D.	
T _{max}	hr	0.339	0.027	0.322	0.035	0.694976
C _{max}	ng·ml ⁻¹	37.345	13.883	33.169	8.239	0.453278
t _{1/2}	hr	1.015	0.194	2.473	1.143	0.000053
λ _z	hr ⁻¹	0.707	0.146	0.339	0.150	0.000053
AUC	ng·ml ⁻¹ ·hr	21.704	6.360	27.723	5.552	0.012439
AUC _t	ng·ml ⁻¹ ·hr	21.527	6.344	27.246	5.421	0.015176
V _{ss}	L·kg ⁻¹	0.205	0.060	0.319	0.123	0.005799
V _z	L·kg ⁻¹	0.489	0.095	0.907	0.414	0.000524
Cl	L·hr ⁻¹ ·kg ⁻¹	0.343	0.079	0.262	0.056	0.012418
MRT	hr	0.597	0.098	1.250	0.492	0.000048
MRT infusion	hr	0.764	0.098	1.417	0.492	0.000079

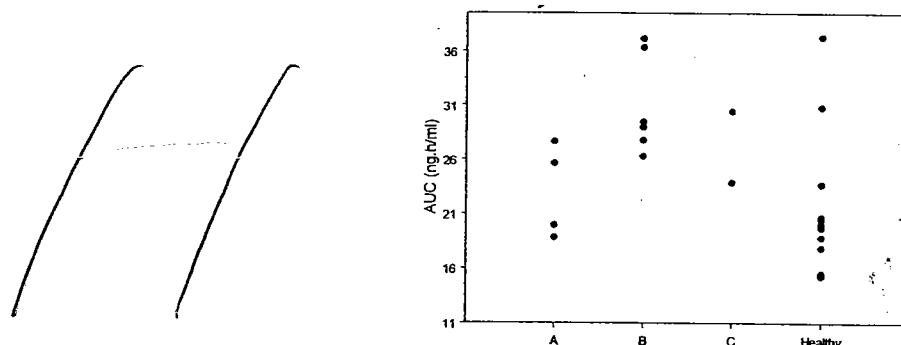
Table 15: Comparative pharmacokinetic parameters of lanreotide estimated in 12 healthy volunteers and in 8 hepatic impaired patients following an intravenous infusion for 20 min at the dose of 7 µg/kg (PK-PP population).

Parameter	Units	Healthy Volunteers N=12		Patients N=8		Statistics
		Mean	S.D.	Mean	S.D.	
T _{max}	hr	0.339	0.027	0.318	0.043	0.622972
C _{max}	ng·ml ⁻¹	37.345	13.883	34.394	8.514	0.695423
t _{1/2}	hr	1.015	0.194	2.998	1.041	0.000060
λ _z	hr ⁻¹	0.707	0.146	0.280	0.160	0.000000
AUC	ng·ml ⁻¹ ·hr	21.704	6.360	30.090	4.810	0.002873
AUC _t	ng·ml ⁻¹ ·hr	21.527	6.344	29.497	4.575	0.003853
V _{ss}	L·kg ⁻¹	0.205	0.060	0.349	0.135	0.004234
V _z	L·kg ⁻¹	0.489	0.095	1.036	0.442	0.000085
Cl	L·hr ⁻¹ ·kg ⁻¹	0.343	0.079	0.237	0.035	0.002856
MRT	hr	0.597	0.098	1.464	0.468	0.000069
MRT infusion	hr	0.764	0.098	1.630	0.468	0.000148

The differences in CL, V_{ss}, V_z, AUC, MRT and t_{1/2} were statistically significant between healthy and patients with hepatic impairment. Clearance was about 30% lower in hepatic impaired patients than in healthy (0.237 L/Kg.h versus 0.343 L/Kg.h). The half-life was about 3 h in the PK-PP population (Sponsor's analysis was between two groups: healthy and hepatic impaired (B& C combined)).

Individual AUC and C_{max} for all the subjects in the study are shown below. As seen the mean exposure in the hepatic impaired group patients is higher than the healthy subjects.

Figure 18: Plots of individual Cmax (Left panel) and AUC (right panel) of hepatic impaired patients and healthy control subjects



Comments: No dosage adjustments are proposed by the sponsor based on hepatic impairment status. According to the Medical Reviewer, in the pooled lanreotide Autogel studies there were 23 patients with impaired hepatic function and 393 subjects with no documented impaired hepatic function. There was a higher incidence of GI related adverse events in patients with impaired hepatic function as compared with patients with no impaired hepatic function. Renal and urinary disorders were also common in patients with hepatic impairment at 30.4% (7/23) compared to 6.6% (26/393) although these adverse events were of no major clinical concern. The PK study addressed the deficiency in the AE letter and classified patients based on CHILD-PUGH scale. There appears to be increased exposure in the moderate as compared to mild and severe categories. Also, there were only 2 patients with severe hepatic impairment. There are not enough patients with severe hepatic impairment to draw conclusions and guidance states that each group to have at least 6 subjects. It is recommended that the starting dose of lanreotide Autogel be reduced to 60 mg in moderate and severe hepatic impairment.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

Pharmacogenetics/pharmacogenomic information is not available in this submission.

2.3.2.8 What pregnancy and lactation use information is there in the application?

Based on the package insert, lanreotide is classified as a pregnancy — drug. There are no adequate well-controlled studies in pregnant women. According to sponsor, preclinical studies showed no evidence of teratogenic effects associated with lanreotide during organogenesis. At a dose of 4 mg/animal (4 times the maximum recommended human dose) impaired fertility due to inhibition of growth hormone secretion was observed in female rats.

It is not known whether this drug is excreted in human milk.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety.

None.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

The sponsor has conducted drug-drug interaction studies with cyclosporin and Vitamin K. Interaction with other drugs or other extrinsic factors (diet, smoking, alcohol, herbal products) have not been studied.

2.4.2 Drug-Drug Interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

No.

Sponsor conducted an *in vitro* protein binding interaction study of lanreotide and lidocaine since both have similar protein binding in humans (~80%). The results indicated that lidocaine (4-20 μ M) binding was unchanged in the presence of 400 μ M lanreotide.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

There is no information on whether lanreotide is a substrate of CYP enzymes and the influence of genetics is unknown. Since lanreotide is a peptide, involvement of CYP enzymes will be likely very minimal.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

This has not been addressed with lanreotide. However literature data discusses the possibility of somatostatin analogs modulation of CYP450 activity either directly or through modulation of growth hormone concentrations (*Clinical Pharmacology and Therapeutics*, 1998; 64:150-159). A secondary effect of this would be the potential for

decreased metabolic clearance of concomitant drugs known to be metabolized by CYP enzymes in patients treated with Lanreotide Autogel particularly if the therapeutic index of the drug is low. Since the severity of the interaction is not known, the patients may need to have dose levels adjusted for concomitant medications.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Not known.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Not known.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Combination therapy is not proposed in the label.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Sponsor pooled the Autogel studies in acromegalic patients and concomitant medications were reported by 91% of patients. The medications used by > 10% patients included: thyroid hormones (28%), acetylcholine esterase (ACE) inhibitors (20%), glucocorticoids (19%), anilides (15%), dihydropyridine derivatives (15%), 3-oxandrostren derivatives (15%), beta blocking agents (14%), benzodiazepine derivatives (13%), propionic acid derivatives (11%) and platelet aggregation inhibitors excluding heparin (10%). Other medications included analgesics (29%), anti-inflammatory products (23%), antidiabetic medication (17% including biguanides and sulfonylureas).

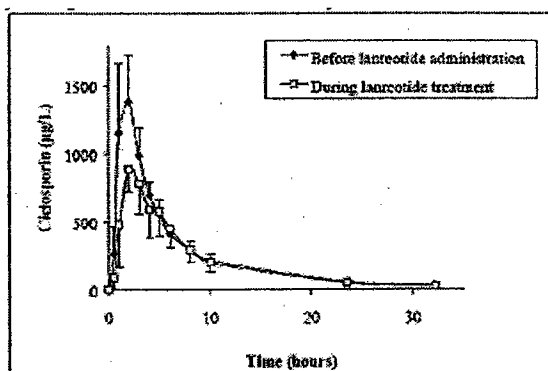
2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Clinical drug interaction studies with the following drugs: Cyclosporin and Vitamin K has been conducted.

Interaction with cyclosporin:

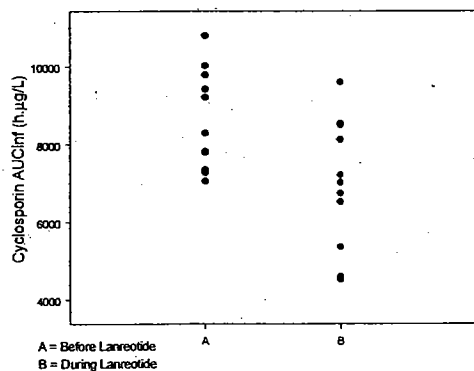
The sponsor conducted the drug interaction study since another analog of somatostatin, octreotide (Sandostatin) approved by the Agency in 1988 significantly decreases the bioavailability of cyclosporin A. The mechanism that most probably accounts for the interaction could be a reduction in the extent of cyclosporin absorption. This study was reviewed under (Study E33-52030-038). Briefly, 12 healthy subjects participated in the interaction study. They received 300 mg cyclosporin A capsules (Sandimmun Neoral, micro-emulsion formulation; 6 males; 6 females) po on two occasions: eleven days before (D-11) and fourteen days (D14) after the single lanreotide autogel (60, 90, or 120 mg) injection. Serial blood samples were taken during the 32 h following drug administration in order to determine cyclosporin PK. The results indicated that the mean AUC and C_{max} for cyclosporin were reduced by 19% and 36% respectively (Figure 19).

Figure 19: Mean $\pm$ SD concentration-time profiles of cyclosporin administered before and 14 days after the lanreotide Autogel administration (N =11).



Individual AUC and C_{max} are shown in the figure below.

Figure 20: Plots of individual cyclosporin AUC (Left panel) and C_{max} (right panel) given either before or during lanreotide treatment



B = During Lanreotide

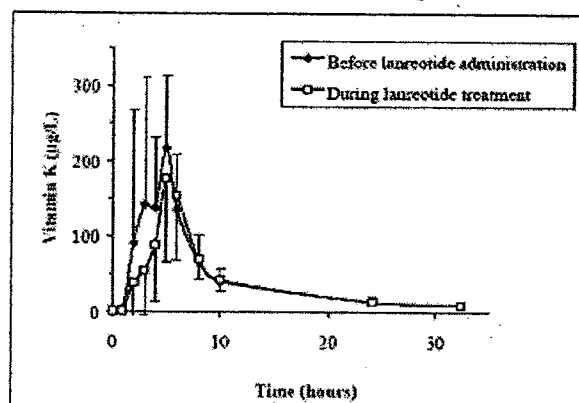
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Comment: Labeling indicates that lanreotide interaction with cyclosporin is clinically significant and attention should be paid to the blood levels of cyclosporin in patients concomitantly treated with lanreotide and dose adjustment may be warranted.

Interaction with Vitamin K:

This study was also reviewed under (Study E33-52030-038). Interactions with octreotide/lanreotide and lipophilic substances like fat soluble vitamins (A, D, E, K) are theoretically possible, even if vitamin D and K absorption were unaffected by octreotide. Therefore sponsor conducted this interaction study. Briefly, 12 healthy subjects participated in this study and Vitamin K levels PK analyzed before and after 14 days of treatment with lanreotide. The results indicated that there was no statistically significant change in Vitamin K PK parameters evaluated before or after lanreotide administration.

Figure 21: Mean SD concentration-time profiles of the vitamin K administered before and 14 days after the lanreotide Autogel administration (N=12).



Comment: The observed results could be due to large variability in the Vitamin K levels and relatively small N. Cmax did not meet the BE criteria, however AUC met the standards.

Other potential interactions: Sponsor has stated from limited published data that concomitant administration of a somatostatin analog and bromocriptine may increase the bioavailability of bromocriptine. Flogstad AK et. al., (*J Clin Endocrinol Metab*:79(2): 461-5, 1994) reported a study to compare octreotide, bromocriptine or a combination of both drugs in patients with acromegaly. The results showed that the PK parameters of octreotide were unchanged by the co-administration of bromocriptine. However the bioavailability of bromocriptine increased by approximately 40% when co-administered with octreotide compared with administration alone.

Also concomitant administration of bradycardia inducing drugs (e.g. beta blockers) may have an additive effect on the slight reduction of heart rate associated with lanreotide. The pharmacological GI effects of somatoline Autogel may reduce the intestinal absorption of co-administered drugs.

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2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Somatostatins have other effects including inhibition of glucagon and insulin release, which may result in hypoglycemia/hyperglycemia. Due to this class effect on glycoregulation, the blood glucose levels of acromegaly patients is monitored when the dose-strength of somatostatin analog is altered and anti-diabetic treatment is adjusted accordingly.

There is a potential of pharmacodynamic interaction between somatostatin analogs and orally administered drugs due to their effects on GIT. For example inhibitory actions on the neuropeptide release from the gut and pancreas; prolonging orocecal transit time and inhibits GIT secretion and contraction of biliary tract including gallbladder. Other actions include inhibition of the stimulatory effects of thyroid releasing hormone on release of thyroid-stimulation hormone.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Not known.

2.4.3 What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

Not known.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The proposed to-be-marketed formulation of lanreotide Autogel is the same as that used in the pivotal clinical trial (study 717, 81).

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

Not applicable.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

No studies have been carried out to investigate the effect of food on the PK profile of lanreotide Autogel, as this is not relevant for a prolonged release product that is administered by deep S.C. injection.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

///

2.5.6 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

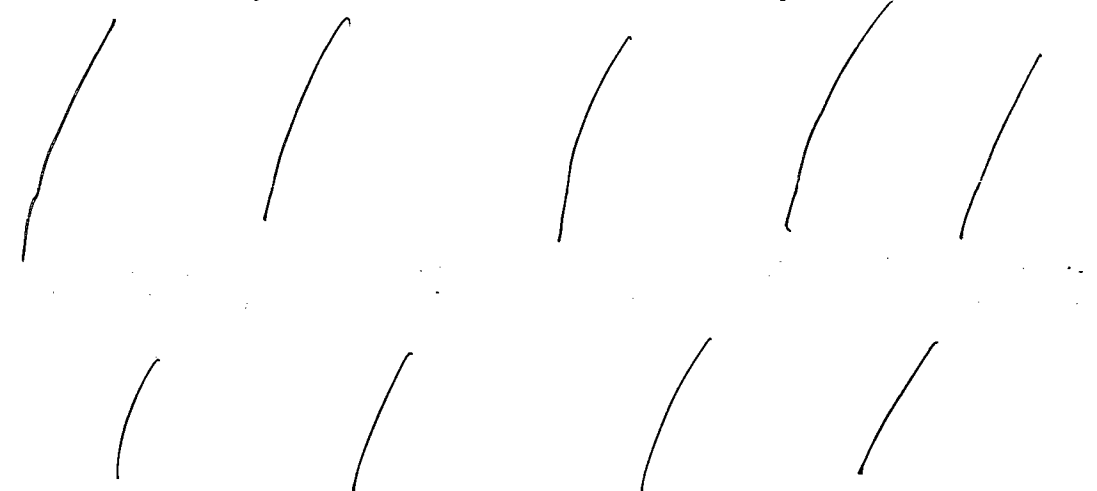
2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

Not applicable.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma/urine in the clinical pharmacology and biopharmaceutics studies?

A radioimmunoassay was used to detect lanreotide in human plasma, serum and urine.



Lanreotide in human serum, plasma and urine appeared to be stable for sufficient time to permit storage and manipulation of samples (freeze-thaw cycles, storage for up to 24 h at 4°C and 20°C for serum, and plasma samples and up to 24 h at 4°C for urine samples).

The results of long term stability showed that lanreotide is stable in human serum when stored up to 19 months at -20°C.

2.6.2 Which metabolites have been selected for analysis and why?

Only lanreotide was analyzed in all studies.

2.6.3 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

The following table summarizes the analytical method validation reports for lanreotide.

Table 16: *In vivo* analytical methods summary

Study #	Sample	✓	LOQ	Recovery (%)	Intra-assay Precision Repeatability	Inter-assay Precision Reproducibility
95/PKS/015	Human Serum	✓	LOQ = 0.078 ng/ml	102.4 – 106.9%	5.5 – 13.6%	6.2 – 13.25%
03/PKS/097	Human Serum	✓	LOQ = 0.078 ng/ml	94.2 – 102.1%	5.5 – 11.1%	6.3 – 12.8%
94/PKS/12	Human Serum	✓	LOQ = 0.039 ng/ml	93.96 – 105.6%	4.0 – 11.5%	5.5% – 15.76%
P98815	Human Serum	✓	LOQ = 0.078 ng/ml	93.6 – 110.14%	6.71 – 7.85%	10.6 – 13.26%
95/PKS/17	Human Urine	✓	LOQ = 0.078 ng/ml	92.3 – 107.2%	7.37 – 11.24%	10.68 – 13.26%
02/PKS/23	Human Urine	✓	LOQ = 0.2 ng/ml	86.7 – 95.6%	3.2 – 7.4%	5.8 – 10.8%
95/PKS/39	Human Plasma	✓	LOQ = 0.078 ng/ml	99.4 – 102.3%	6.3 – 10.2%	7.4 – 12.6%

Comments:

✓

Immunogenicity: The presence of antibodies to lanreotide can lead to interference in the assay by increasing radioimmunoprecipitation. In the absence of antibodies the background interference is < 10%. The presence of antibodies to lanreotide was analyzed in 9 studies with lanreotide Autogel where serum samples had been collected to measure serum lanreotide concentrations using RIA. The number and percentages of patients with 10-30% nonspecific binding (NSB) and > 30% NSB in these studies are summarized in the following table. As shown, the percentage of patients or subjects exposed to lanreotide Autogel with NSB < 10% ranged from 82-100%. The percentage of patients/subjects exposed to lanreotide Autogel with NSB 10-30% ranged from 0-14%, while the percentage of patients/subjects with NSB > 30% ranged from 0-4%. Based on this, sponsor concluded that long term treatment with lanreotide Autogel does not lead to an increase in antibodies to lanreotide. This result was similar in naïve and lanreotide pretreated patients.

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Table 17: Summary of % NSB in the lanreotide assay observed in studies with lanreotide Autogel at any timepoint

Study	Treatment Duration (Weeks)	N	< 10% NSB N (%)	10-30% NSB N (%)	> 30% NSB N (%)
Patient Studies					
E-28-52030-717	54	107	101 (94)	5 (5)	1 (<1)
E-28-52030-076	12	18	15 (83)	2 (11)	1 (6)
A-93-52030-077	46 to 48	63	52 (83)	8 (13)	2 (3)
E-28-52030-709	12	133	109 (82)	19 (14)	5 (4)
E-28-52030-710	48	130	109 (84)	15 (12)	4 (3)
A-92-52030-046	30	97	82 (85)	12 (12)	3 (3)
Healthy Subject Studies					
A-93-52030-149	Single injection	38	37 (97)	1 (3)	0
E-55-52030-047	Single injection	27	27 (100)	0	0

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 ✓ Draft Labeling

 Deliberative Process

4.2 Pharmacometric Review

PHARMACOMETRIC REVIEW

NDA:	22074
Drug name:	Somatuline Autogel (Lanreotide acetate)
Indication:	Treatment of acromegaly
Proposed Regimen (Sponsor):	60, 90, 120 mg SC q4w
Sponsor:	Beaufour Ipsen Pharma
OCP Reviewer	Jayabharathi Vaidyanathan, Ph.D.
PM Reviewer:	Hao Zhu, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	NDA
Submission Date:	October 30, 2006
PDUFA Date:	August 30, 2007

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Executive Summary

This review highlights the pharmacometric findings for Somatuline Autogel dose-safety relationship. These findings provide supportive evidence when the review division considering the appropriate label.

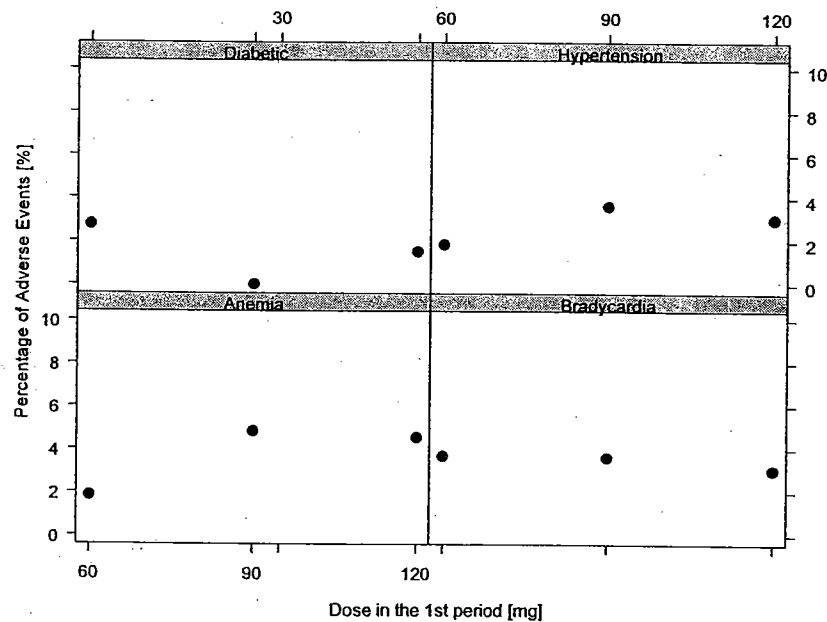
The major pharmacometric findings are:

- 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.
- 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 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, 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. The incidences of adverse events are demonstrated in Figure 1. 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, diabetes, and anemia) is identified over time.

Please note:

No predefined and standardized criteria were used by the sponsor to define the occurrence of adverse events (AEs) of hypertension, bradycardia, diabetes mellitus, diarrhea, or anemia across the seven clinical studies (717, 721, 709, 710, 087, 081, and 076). AEs were determined case by case by the clinical investigators.

Figure 1 Incidence of major adverse events (bradycardia, hypertension, diabetics and anemia) in different dose groups during the first treatment period of Studies E28 52030 717, E28 52030 709/710, and E28-52030-076



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Question Based Review

Is there a dose/exposure-safety relationship?

We investigated the dose - safety relationship for the major adverse events (diarrhea, bradycardia, diabetic, hypertension, and anemia) in the first treatment period of Somatuline Autogel in studies 52030 717, E28 52030 709/710, and E28-52030-076. Since PK samples were not collected from every patient, the dose-safety relationship rather than the exposure-safety relationship was explored. Through the dose – safety analysis, we found that:

- Diarrhea is the most common adverse reaction. By applying the logistic regression analysis, a significant dose-response relationship ($P = 0.0178$) was identified for the incidence of diarrhea (Figure). The results suggest that after initialization of Somatuline Autogel treatment, the probability of a patient to develop diarrhea is driven by dose. Higher dose yields higher probability of diarrhea- 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.
- After initialization of Somatuline Autogel treatment (Figure 3),
 - 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 ($P = 0.76$).
 - 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.
- The other major adverse events (bradycardia, hypertension, diabetics, and anemia) are not dose related, based on the first treatment period of Studies E28 52030 717, E28 52030 709/710, and E28-52030-076. The incidences of adverse events are demonstrated in Figure 1. No obvious trend is identified cross the dose range from 60 mg to 120 mg.

We also investigated the safety – duration relationship in a subgroup of patients being treated by 120 mg Somatuline Autogel for 3 consecutive periods. Through incidence – treatment duration analysis, we found that:

- By applying logistic regression analysis, a significant incidence – treatment duration relationship was identified for diarrhea ($P < 0.0001$) (
- Figure). The results suggest that 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
- 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

Figure 2 Dose-response relationship for the incidence of diarrhea after initialization of Somatuline Autogel treatment

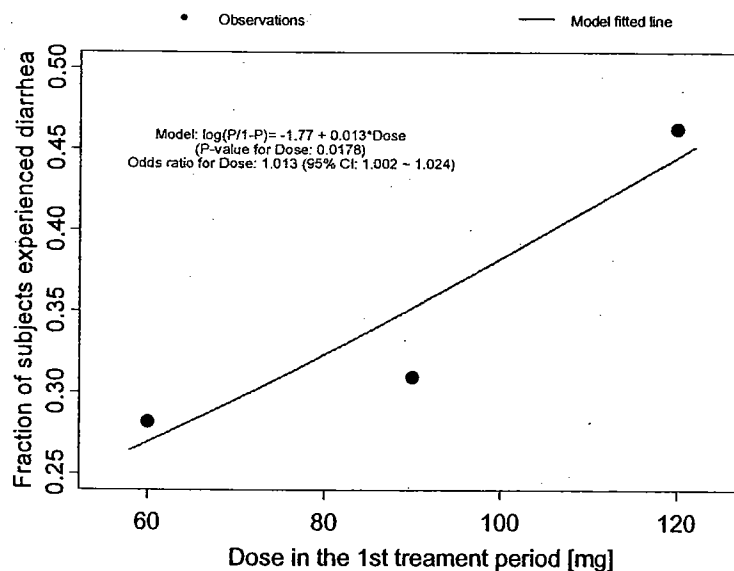


Figure 3 Dose-response relationship for the incidence of diarrhea in elder patient (age ≥ 65 yr) and in younger patient (age < 65 yr) after initialization of Somatuline Autogel treatment

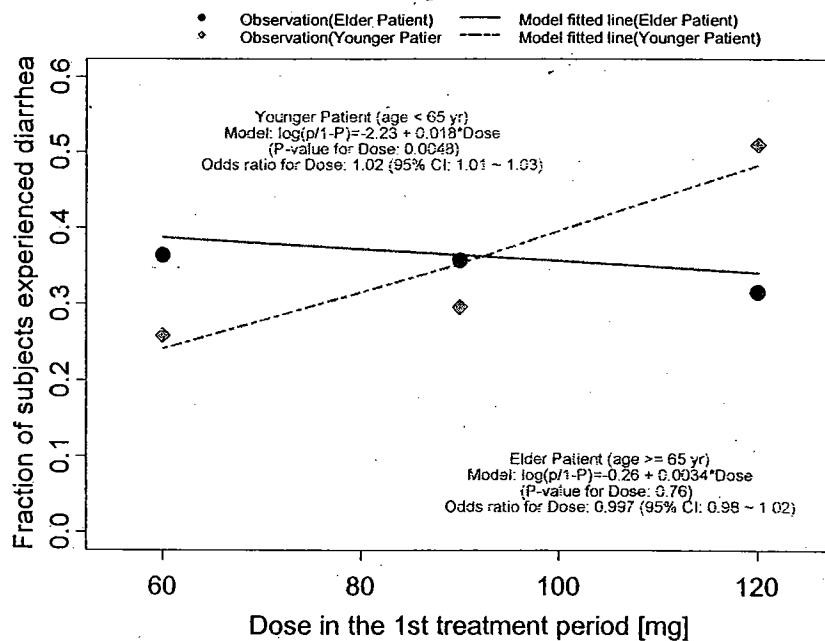
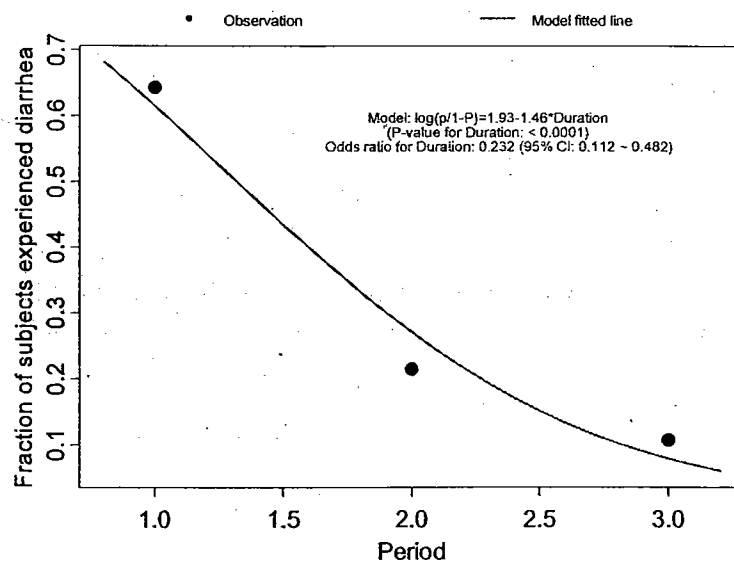


Figure 4 Incidence – treatment duration relationship for diarrhea in a subgroup of patients being treated by 120 mg in 3 consecutive periods



Recommendations

The Office of Clinical Pharmacology finds that this NDA submission is acceptable.

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Introduction

Background

Acromegaly is an uncommon hormonal disorder that develops when the pituitary gland produces too much growth hormone during adulthood which causes the bones (hands, feet, and face) to increase in size. Acromegaly usually affects middle-aged adults. In children who are still growing, too much growth hormone can cause a condition called gigantism. These children have exaggerated bone growth and an abnormal increase in height. If not treated promptly, acromegaly can lead to serious illness and even become life-threatening. Treatment of acromegaly involves approaches to lower the production of growth hormone.

Conventional first-line treatment for acromegaly is surgical excision of the tumour, sometimes accompanied by pituitary radiotherapy. However, over 50% of treated patients remain symptomatic. Analogues of somatostatin, a naturally occurring inhibitor of GH secretion, provide one of the few non-surgical treatments for acromegaly and have been shown to improve clinical symptoms in these patients.

Lanreotide is a synthetic octapeptide analogue of somatostatin, which binds preferentially to pituitary somatostatin receptors to inhibit growth hormone (GH) secretion. It is more stable than natural somatostatin, with an elimination half-life ($t_{1/2\alpha}$) of approximately 2 hours in healthy subjects. Lanreotide has an inhibitory effect on GH release, and therefore reduces insulin-like growth factor-1 levels.

With the objective of extending the duration of lanreotide release and obtaining a 28-day dosing interval, a new formulation named as Somatuline Autogel that has been developed. This formulation is a supersaturated solution for injection that contains only lanreotide and water, and requires a single deep subcutaneous (s.c.) injection every 28 days. It is supplied in a prefilled, ready-to-use polypropylene syringe.

This NDA submission is to obtaining marketing approval of Somatuline Autogel for the indication for:

- The long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy
-

Sponsor's Analysis

aim of analysis

The objective of the sponsor's PK/PD analysis is:

- To determine pharmacokinetic parameters of lanreotide after repeated dose administration.
- To perform a population pharmacokinetic and pharmacodynamic (PK/PD) analysis of lanreotide and growth hormone (GH) levels.

Studies

A 93 52030 149 (Phase I): This was an open, randomized, pharmacokinetic (PK) study in three parallel groups of healthy subjects. The objective of the study was to evaluate the absolute bioavailability and dose-proportionality of single dose lanreotide Autogel 60, 90, and 120 mg after deep subcutaneous injection. Totally 54 subjects were enrolled and 37 finished the study. Subjects received a single intravenous (i.v.) administration, followed by a single deep s.c. administration.

- Day -3: single i.v. dose of 7 µg/kg lanreotide immediate release formulation (IRF). Blood samples for lanreotide analysis were taken 0, 5, 15, 30 min, 1, 1.5, 2, 4, 6, 8, and 12 hours after dosing.
- Day 0: single deep s.c. dose of lanreotide Autogel 60, 90 or 120 mg. Blood samples for lanreotide analysis were taken 0, 1, 2, 4, 6, 8, 12, and 24 hours after dosing, and in the mornings on Days 2, 3, 4, 5, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98, and 112.
- Subsequent blood samples were taken until serum concentrations of lanreotide fell below the limit of quantification of the analytical method.
- Blood samples for lanreotide antibody analysis (non-specific binding, NSB) were taken on Days -3, 28, 56, 84, 98 and 112, and at later visits in subjects who returned to the clinic after Day 112.
- Clinical laboratory tests were carried out at screening and on Days 28, 84, and 112.
- When subjects visited the clinic to have their last blood sample taken, post-study evaluations were also carried out.

Adverse events were monitored throughout the study. Vital signs, ECG, and physical examination data were collected at various times during the study.

E-28-52030-076 (Phase II): Phase II, randomized, parallel groups, double-blind pharmacokinetic study of lanreotide autogel (60, 90, or 120 mg) after 4 deep subcutaneous injections (administered every 28 days) in acromegalic patients. The primary objective of this study was to characterize the pharmacokinetic profile of lanreotide autogel in acromegalic patients following multiple deep subcutaneous (s.c.) injections. The secondary objectives included the evaluation of the effectiveness of lanreotide autogel [based on mean growth hormone (GH) levels, insulin-like growth

factor-1 (IGF-1) levels and clinical symptoms] and the evaluation of the treatment tolerability. A total of 20 patients were screened and 18 patients were randomized and received at least one dose of study treatment including 6 patients each who received 60, 90 and 120 mg lanreotide autogel. Patients received up to 4 deep subcutaneous injections of lanreotide autogel at 28-day intervals at fixed doses of 60, 90 or 120 mg based on random assignment. Each enrolled patient participated in the study for 18 to 27 weeks depending on the duration of the screening period required to meet the entry criteria

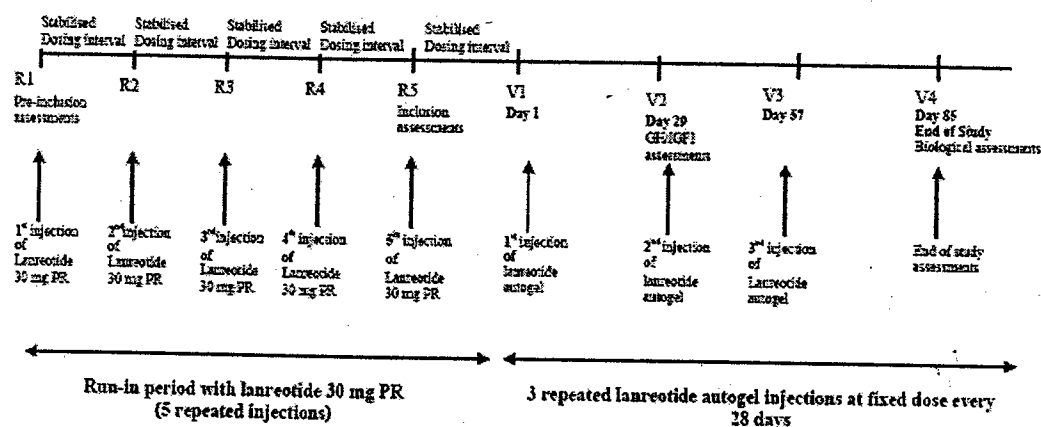
E28 52030 709 (Phase III): Open, comparative multi-centre Phase III study evaluating the efficacy of three repeated deep subcutaneous administrations of lanreotide Autogel (60, 90 or 120 mg) at fixed doses in acromegalic patients previously treated with lanreotide 30 mg PR for a minimum of three months. The objective for study E28 52030 709 was to show that the effect on GH levels of three identical injections of 60, 90, 120 mg lanreotide autogel at 28-days intervals is no less than the effect on GH levels of five injections of 30 mg PR lanreotide i.m. at a fixed interval. 133 patients received at least one dose of lanreotide Autogel and 131 completed the treatment with lanreotide Autogel.

At entry, patients were to have a documented diagnosis of active acromegaly within the previous five years .basal GH > 5 ng/ml or elevated IGF-1 (age and sex adjusted) .or GH level > 2 ng/ml after an oral glucose tolerance test measured after the most recent surgical or radiation treatment. After entry into the study, treatment with lanreotide 30 mg PR was to be continued during a run-in period. Patients were to receive **five injections of lanreotide 30 mg PR** at the same dosing interval as the last dosing interval before entering the study. (Visits R1 to R5).

At the end of the run-in period, patients were to fulfill the following inclusion criteria to receive lanreotide Autogel: GH level $\leq$ 10 ng/ml at the end of the dosing interval of the fourth injection of lanreotide 30 mg PR, just before the fifth injection.

The day of the first lanreotide Autogel injection was also the final day of the last dosing interval of the run-in period. Patients were to receive **three identical s.c. injections of lanreotide Autogel every 28 days**, for a total duration of 12 weeks. (Visits V1 to V4). The dose of Autogel injections was based on the dosing interval of lanreotide 30 mg PR as follows:

- Dosing interval of lanreotide 30 mg PR between 12 and 16 days at the end of the run-in period: patients to switch to lanreotide Autogel 60 mg,
- Dosing interval of lanreotide 30 mg PR between 8 and 11 days at the end of the run-in period: patients to switch to lanreotide Autogel 90 mg,
- Dosing interval of lanreotide 30 mg PR between 5 and 7 days at the end of the run-in period: patients to switch to lanreotide Autogel 120 mg.



E28 52030 710 (Phase III): Open, comparative multi-centre 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 PR and with lanreotide Autogel at fixed doses in study E28 52030 709. A total of 130 patients were recruited from the 131 patients who completed the previous study, one patient did not enter the study for personal reasons. All 130 patients received at least one dose of lanreotide Autogel. The objective of the study was to investigate whether treatment with lanreotide autogel titrated according to patient GH and IGF1 levels improved efficacy compared to treatment with fixed dose lanreotide autogel or lanreotide 30 mg PR in the preceding phase III study (E28 52030 709).

On the final day of this study and first day of the study E28 52030 710 (Visit V4), eligible patients, received an injection of lanreotide Autogel every 28 days, over the course of 48 weeks of the same dose as the preceding study (12 injections).

The study was designed in 3 blocks of 4 administrations of lanreotide Autogel at titrated doses, adjusted according to biochemical efficacy. The study design was such that after titration, (done at V4, V8 and V12 or weeks 0, 16 and 32 respectively) patients received 4 deep s.c. injections of lanreotide Autogel, allowing steady state levels to be reached.

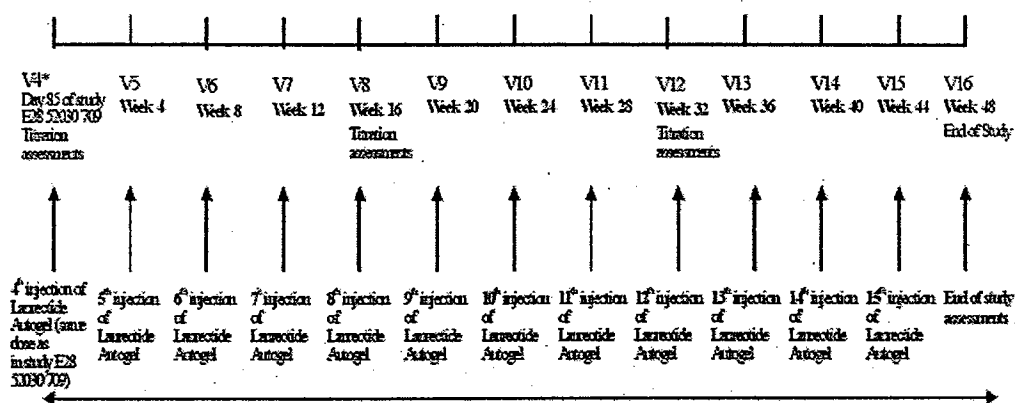
- The dose of lanreotide Autogel administered at V4 in week 0 was the same as the last dose received by the patient in the preceding study.
- The doses at weeks 4, 8, 12 and 16 were adapted according to the biochemical response of the patient assessed at week 0.
- The doses at weeks 20, 24, 28 and 32 were adapted according to the biochemical response of the patient assessed at week 16.
- The doses at weeks 36, 40 and 44 were adapted according to the biochemical response of the patient assessed at week 32.

The titration criteria were the following:

- Patients with mean GH > 2.5 ng/ml:

- Patients receiving lanreotide Autogel 60 mg were uptitrated to lanreotide Autogel 90 mg every 28 days
- Patients receiving lanreotide Autogel 90 mg were uptitrated to lanreotide Autogel 120 mg every 28 days
- Patients receiving lanreotide Autogel 120 mg remained on lanreotide Autogel 120 mg every 28 days
- Patients with mean GH ≥ 1 ng/mL and ≤ 2.5 ng/mL:
 - No change
- Patients with mean GH < 1 ng/mL and IGF-1 normalised:
 - Patients receiving lanreotide Autogel 60 mg remained on lanreotide Autogel 60 mg every 28 days
 - Patients receiving lanreotide Autogel 90 mg were down-titrated to lanreotide Autogel 60 mg every 28 days
 - Patients receiving lanreotide Autogel 120 mg were down-titrated to lanreotide Autogel 90 mg every 28 days
- Patients with mean GH < 1 ng/mL and IGF-1 not normalised:
 - No change

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

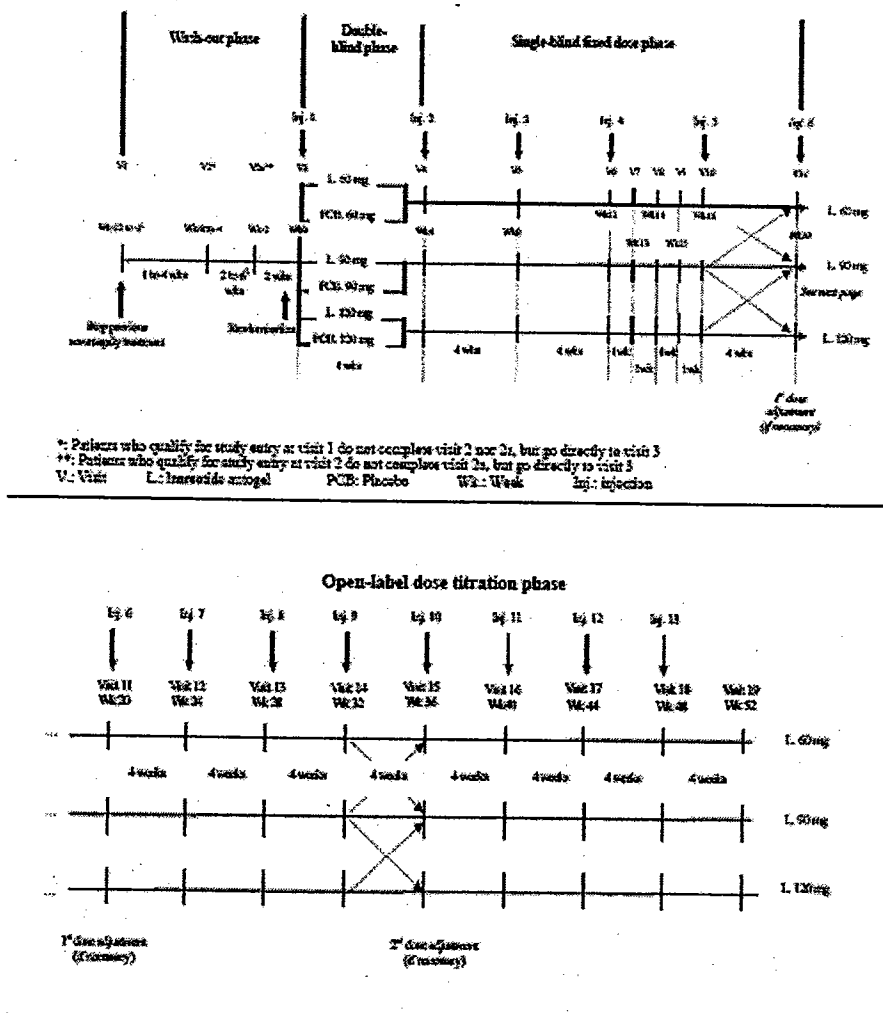


Repeated Injections of Titrated Doses of Lanreotide Autogel Every 28 days

E28 52030 717 (Phase III):

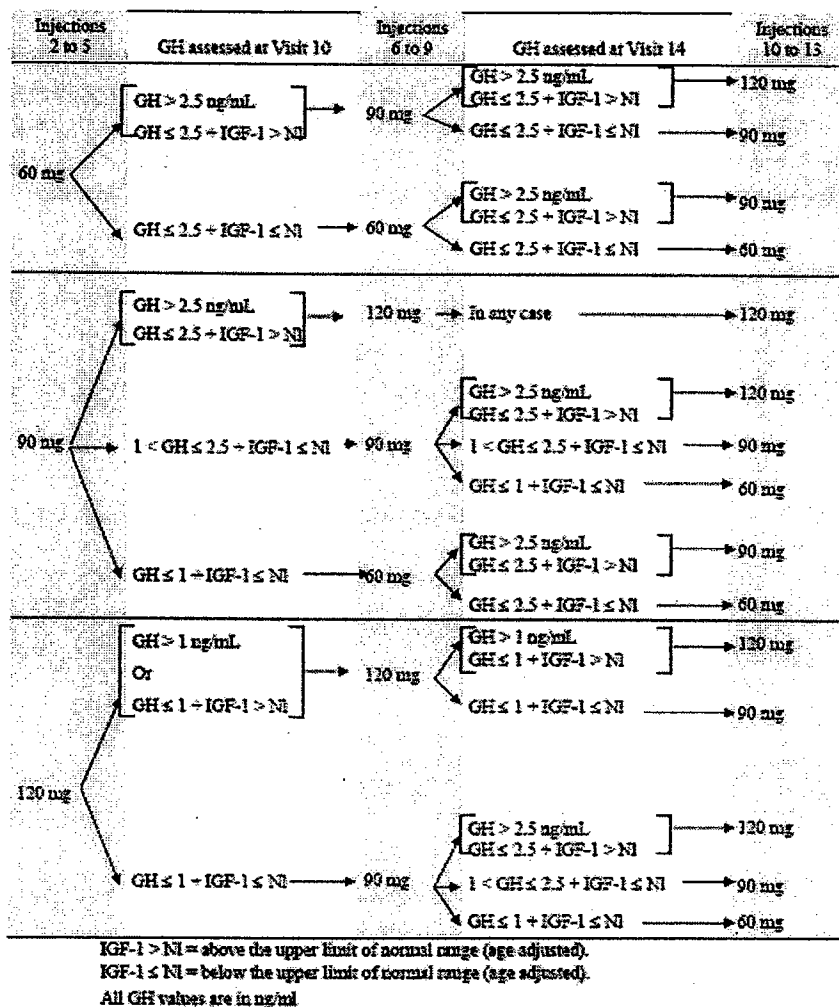
This was a phase II, multi-centre, randomized study conducted in acromegalic patients previously treated or not by surgery, radiotherapy, somatostatin analogs or dopamine agonists. The study consisted of 4 distinct phases. The first phase was a wash-out phase (week -12 to week 0). This phase was required only for patients who were previously treated with a somatostatin analog or a dopaminergic agonist. The objective was to obtain the baseline GH and IGF-1 values. The second phase was a double-blind, placebo-controlled phase (week 0 to week 4). Patients were randomized into one of 6 treatment groups: lanreotide autogel 60 mg, lanreotide autogel 90 mg, lanreotide autogel 120 mg,

placebo 60 mg, placebo 90 mg, or placebo 120 mg based on random assignment. The objective for the 2nd phase was to demonstrate activity of lanreotide autogel versus placebo. The third phase was a single-blind, fixed-dose phase (week 4 to week 20); 4 injections of lanreotide autogel 60, 90 or 120 mg based on dose group as assigned during double-blind phase. The objective was to evaluate the efficacy, safety, pharmacokinetic and pharmacodynamic profile of the 3 doses of lanreotide autogel. Finally, the fourth phase was an open-label dose titration phase (week 20 to week 52); 8 injections of lanreotide autogel at a dose based on dose titration schema. Two dose adjustments could be made. The objective for the last phase was to evaluate the efficacy and safety of titrated doses of lanreotide autogel. The study schema was listed as following:



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Dose was adjusted using the following schema in the last phase of the study.



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Data

The clinical PK/PD data after 4 injections every 28 days of the same dose was used for the analysis assuming that the terminal half-life of the Autogel formulations ranges between 23 and 31 days. Data from 129 out of 144 patients were used for the PK/PD analysis.

Blood samples for analysis of lanreotide serum levels were to be taken at every visit before lanreotide administration.

Blood samples for assessment of GH were to be taken every 4 weeks. As GH secretion has peaks and troughs over a 24 hour period, an average of 9 measurements taken at 30

minutes intervals (over a 4 hour period) was used to evaluate the mean GH concentration for each patient.

Table 1 Sampling schedule in studies E28 52030 709 and E28 52030 710.

VISIT		Administration		Assesments	
Ident.	Week [†]	Formulation	N° Injection	Lanreotide	GH
R1	-	30 mg PR	1 st	x	-
R2	-	30 mg PR	2 nd	x	-
R3	-	30 mg PR	3 rd	x	-
R4	-	30 mg PR	4 th	x	-
R5	-	30 mg PR	5 th	x	x
V1	1	Autogel	1 st	x	-
V2	4	Autogel	2 nd	x	x
V3	8	Autogel	3 rd	x	-
V4 [‡]	12	Autogel	4 th	x	x
V5	16	Autogel	5 th	x	-
V6	20	Autogel	6 th	x	-
V7	24	Autogel	7 th	x	-
V8	28	Autogel	8 th	x	x
V9	32	Autogel	9 th	x	-
V10	36	Autogel	10 th	x	-
V11	40	Autogel	11 th	x	-
V12	44	Autogel	12 th	x	x
V13	48	Autogel	13 th	x	-
V14	52	Autogel	14 th	x	-
V15	56	Autogel	15 th	x	-
V16	60	End	End	x	x

x: Sample extraction

‡: Time measured from the 1st Autogel injection in study E28 52030 709

&: Visit 4 corresponds to the last day of the study E28 52030 709 and to the first day of the study E28 52030 710

Methods

Population PK analysis

Population PK analysis (Report 05/PKR/107) for lanreotide data obtained from Study A 93 52030 149 was performed using the First Order Conditional Estimation (FOCE) method with INTERACTION implemented in the software NONMEM V. For basic population model selection, firstly, the disposition of lanreotide in serum was characterized with compartmental model using the data obtained from i.v. bolus injection, and secondly, the absorption profile of lanreotide autogel was determined using serum concentration values corresponding to deep s.c. administrations and fixing the individual Bayes posterior estimated of the disposition parameters. For covariate model selection, a graphical screening of the relative importance of several covariates and their relationships with parameters was examined using Xpose. The covariate relationship was further

selected by means of Generalized Additive Models (GAM) and tested in NONMEM using the forward and backward selection approach. Final model was determined by choosing appropriate residual error model and different variance-covariance structure. Once the final model was determined, different techniques such as, cross-validation, visual predictive check, local minimum were used to conduct the final model validation.

Population PD analysis

Population PD models with data obtained from Study E28 52030 709 and Study E28 52030 710 (Report 01/PKR/050) were built using the NONMEM software (Version V, Level 1.0) with user-supplied routine \$PRED. The observed GH values were modeled together with minimum concentration at steady state. Different basic population models such as simple inhibitory Emax model, sigmoidal inhibitory Emax model were tested. Generalized additive models (GAM) in Xpose were used to initially select the potential significant covariates and covariates models. The covariates that were selected using GAM were then evaluated in NONMEM. The effect of each of the selected covariates was tested individually. Continuous covariates were centered about the mean value. Covariates that showed significance were then incorporated one at a time until the full covariate model was obtained (forward inclusion). Following the forward inclusion, a backward elimination was then performed. If a covariate was not found to be significant it was dropped in favor of the simpler model. The final model was evaluated using simulation, cross-validation and checking the attainment of local minimum.

Population PD models with data obtained from Study E28 52030 717 (Report 01/PKS/011) were built using NONMEM software (Version V, Level 1.0) in order to determine the relationship between GH concentrations and lanreotide concentrations. Basic model was explored between simple inhibitory Emax model and sigmoidal inhibitory Emax model. Then covariates were selected by using GAM approach and using NONMEM. Then mixture model was applied by using \$MIX in NONMEM. The final model was selected based on simulation, cross-validation method and the attainment of local minimum was checked.

Results

Population PK Analysis

The population PK analysis was firstly conducted based on the PK samples obtained from healthy subjects in Study A93 52030 149. (Report 05/PKR/107, Vol 2, P-45).

Population analysis of Lanreotide after i.v. bolus administration of Lanreotide IRF (D= 7 µg/kg) involved fitting a three open compartment model to the serum concentration-time data. No clinically relevant relationship with any of the covariates tested (age, height, weight and gender) was found. Using the i.v. bolus injection data, the drug disposition parameters were obtained (Table 2) and the diagnostic plots were presented in Figure 5.

Table 2 Lanreotide disposition parameters in healthy subjects.

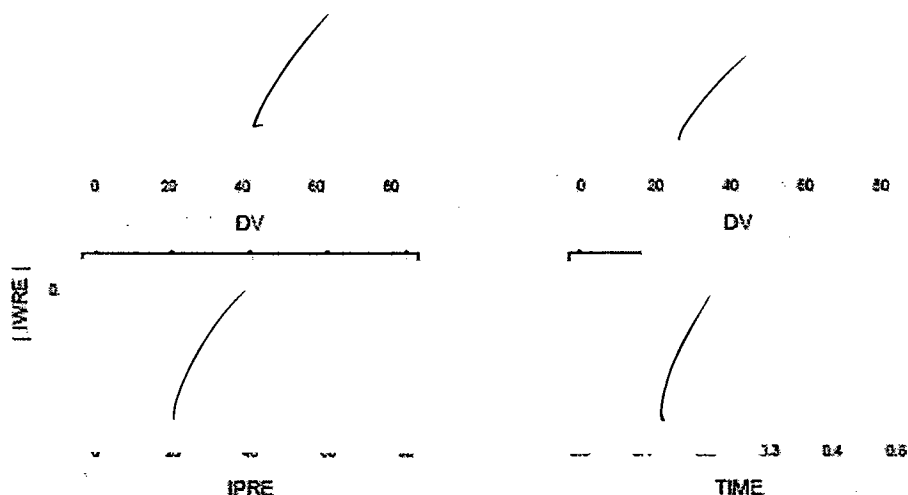
Parameter	Units	Estimate	IIV (%)
CL	l/h	22.0	19
V _c	l	5.08	NE
CL _{D1}	l/h	12.1	NE
V _{P1}	l	4.18	NE
CL _{D2}	l/h	2.20	NE
V _{P2}	l	5.61	23
V _{ss}	l	14.9	NA
Proportional Error	%	20	NA

IIV(%), inter-subject variability expressed as coefficient of variation (CV%); V_c, V_{P1}, and V_{P2}, apparent volumes of distribution of the central, shallow and deep compartments, respectively; V_{ss}, volume of distribution at steady state that corresponds to the sum of the three volumes of distribution; CL, total plasma clearance; CL_{D1}, and CL_{D2}, distribution clearance between the central and shallow and deep peripheral compartments, respectively; NE, not estimated; NA,

Figure 5 Diagnostic plots for the population PK model using i.v. bolus data in healthy subjects.

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Time-course of Lanreotide release after deep s.c. Lanreotide Autogel administration was adequately described using an absorption rate that decreased exponentially as a function of logarithm of time, resembling the solid depot formation at the injection site. The population absorption parameters were listed in Table 3.

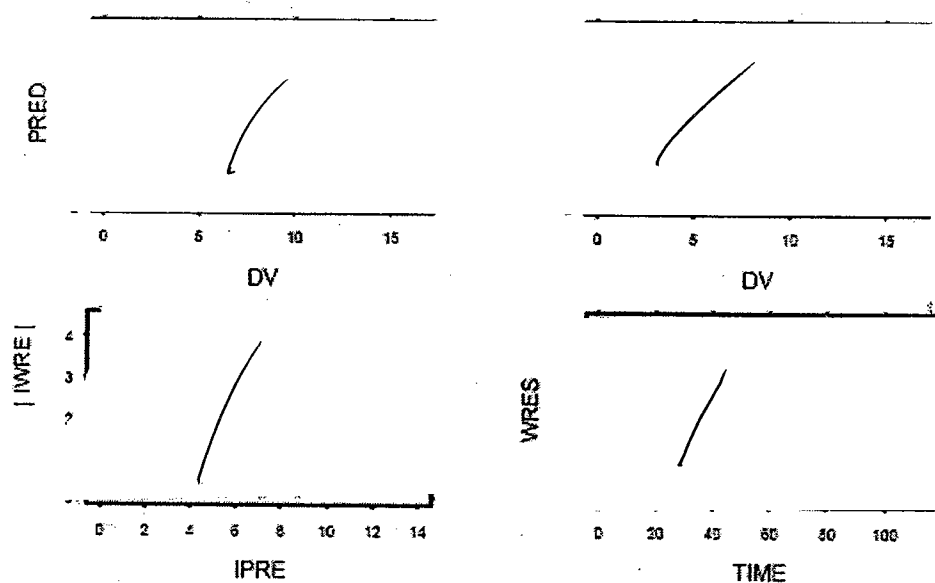
Table 3 Lanreotide population release parameters

Parameter	Units	Estimate	IIV (%)
$K_a = K_b \cdot e^{(-K_{cc} \cdot \ln(\text{Time}))}$			
K_b	day ⁻¹	0.0354	44
K_{cc}	day ⁻¹	0.076	122
t_{lag}	day	0.036	NE
F	-	69.7	19
Additive_Error	ng/ml	0.0383	NA
Proportional_Error	%	27	NA

IIV (%), inter-subject variability expressed as coefficient of variation (CV%); K_a , absorption constant; K_b , 1st order rate constant of absorption at the time of administration; K_{cc} , 1st order rate constant governing the exponential decrease in K_a as function of $\ln(\text{time})$; t_{lag} , lag time; F, bioavailability; NE, not estimated; NA, not applicable.

The diagnostic plots for the final model were presented in the Figure 6.

Figure 6 Diagnostic plots for the final model using s.c. data from healthy subjects.



PD Analysis

Population PD relationship was investigated based on the data obtained from Studies E28 52030 709, E28 52030 710 and E28 52030 717. The outcomes were reported in two study reports 01/PKS/050 (for Study E28 52030 709 and Study E28 52030 710) and 01/PKS/011 (for Study E28 52030 717).

In study report 01/PKS/050, the PD analysis was conducted based on the data obtained from Studies E28 52030 709 and E28 52030 710. The population of the study was 129 acromegalic patients, 62 males and 67 females with age ranging from 24 to 77 years that supplied 497 observations. A simple inhibitory Emax model with interindividual variability on EC_{50} and E_0 adequately describes the observed data. The population parameter estimators were presented in Table 4. The visual predictive check and the goodness-of-fit plots were demonstrated in Figure 7 and Figure 8 respectively. No covariates were found to influence the PD relationship.

Table 4 Population pharmacodynamic model parameters of lanreotide derived from studies E28 52030 709, E28 52030 710

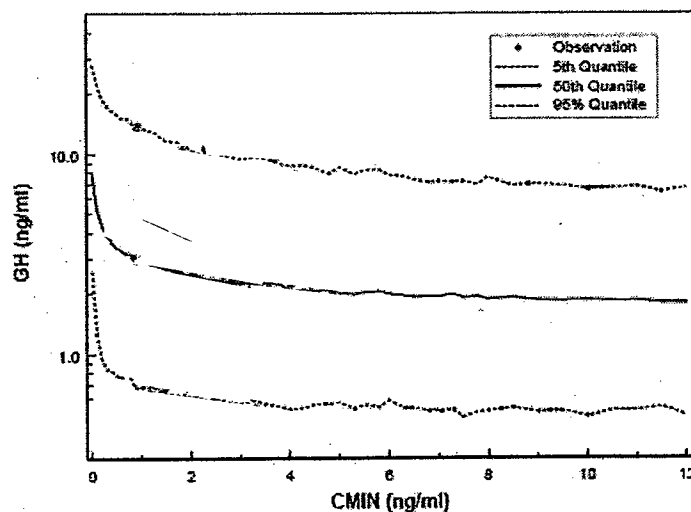
Population parameters		Estimate	±	RSE (%)
<i>Pharmacodynamic parameters</i>				
E_{max}	Maximum effect (constrained between 0 and 1)	0.821	±	7.53
EC_{50}	Lanreotide level that decreases GH by 50% of E_{max} (ng/ml)	0.206	±	50.00
E_0	Estimated basal value of GH (ng/ml)	8.63	±	31.17
<i>Interindividual variability</i>				
σ_{EC50}	Interindividual variability of EC_{50} (CV %)	200.75	±	36.48
σ_{E0}	Interindividual variability of E_0 (CV %)	67.82	±	13.41
<i>Residual variability</i>				
σ_{Prop}	Proportional error model of residual variability (CV %)	26.89	±	10.89

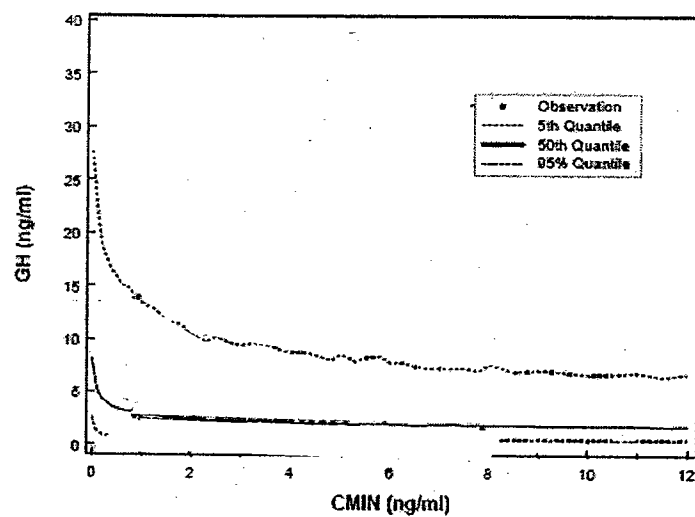
RSE (%): relative standard error expressed in percentage calculated by (Standard Error / Mean)*100

CV %: coefficient of variation expressed in percentage

(Source: Table 7 in volume50 on page 32)

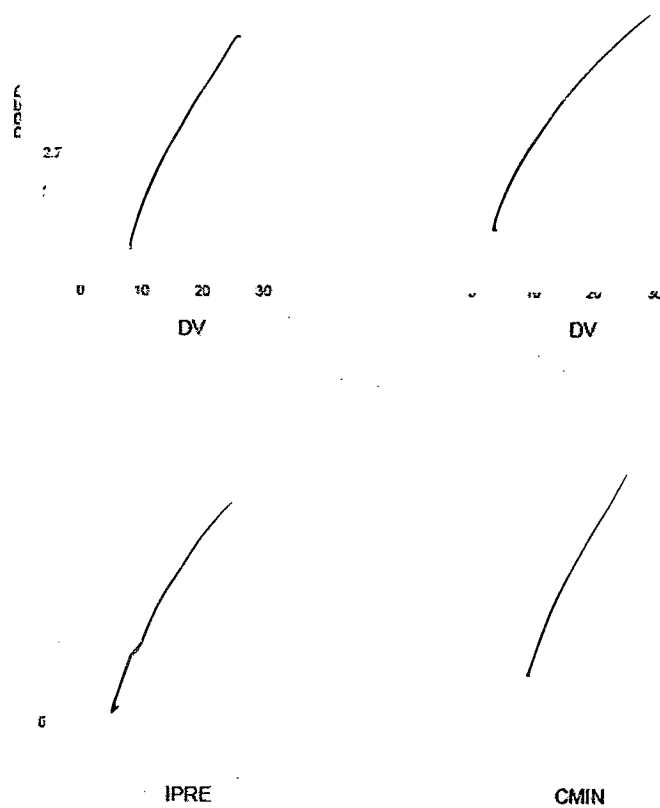
Figure 7 Visual predictive check for the population pharmacodynamic model derived from studies E28 52030 709 and E28 52030 710





(Source: Figure 177, Vol 50)

Figure 8 Diagnostic plots for the population pharmacodynamic model derived from studies E28 52030 709 and E28 52030 710



(Source: Figure 165, Vol 50).

The study report 01/PKS/011 was based on the data obtained from study E28 52030 717. Totally 107 patients were included in the pharmacodynamic analysis. Simple sigmoidal inhibitory Emax model adequately described the relationship between lanreotide and GH concentrations. The model includes the pre-treatment status (pre-treated or not) within the previous 3 months to the first administration as a covariate on E_0 . Also a mixture model on EC_{50} was included in the model, assuming that the population consists of two subpopulations: non-responders and responders to lanreotide treatment. The population PD parameters were the following: non-responders and responders to lanreotide treatment. The population pharmacodynamic parameters were listed in the Table 5.

Table 6 displays the variability of the random effects shown as the coefficients of variation in percentages (diagonal terms). The off-diagonal terms in this table are the coefficient of correlation between two given parameters, estimated from the variances and covariances between these two parameters.

Table 5 Model parameter estimates for final pharmacodynamic model derived from data obtained from study E28 52030 717.

Parameter	Units	Estimate	IIV	P
EMAX	-	0.823	14%	NA
$EC_{50_{NR}}$	ng/ml	100 [#]	43%	13.7%
EC_{50_R}	ng/ml	0.612	43%	86.3%
$E_{0_{NPT}}$	ng/ml	15.9	85%	NA
$E_{0_{PT}}$	ng/ml	8.74	85%	NA
Gamma	-	2.63	NE	NA
Additive_Error	ng/ml	0.116	NA	NA
Proportional_Error	%	30%	NA	NA

IIV, inter-subject variability (CV); P, fraction of population belonging to one of the two subpopulations; EMAX, Maximum effect; $EC_{50_{NR}}$ and EC_{50_R} , lanreotide level that decreases GH by 50% of EMAX in non-responder and responder patients, respectively; $E_{0_{NPT}}$ and $E_{0_{PT}}$, baseline level of GH for patients not previously treated and previously treated; Gamma, Sigmoidicity parameter; NE, not estimated; NA, not applicable; #, fixed value.

Table 6 Estimates of variance components in the final model derived from study E28 52030 717.

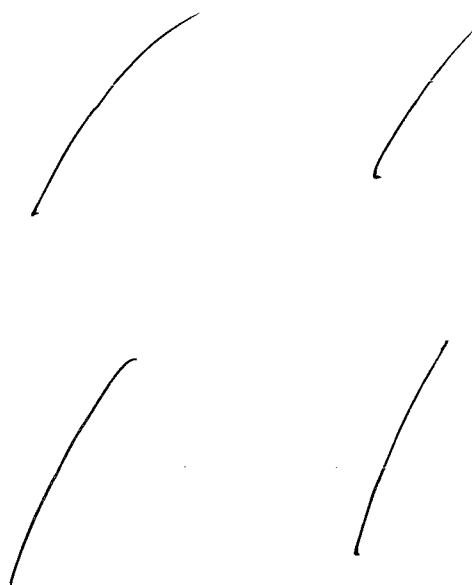
Parameter	Parameter		
	EMAX	EC50	E0
EMAX	14%	-	-
EC50	-0.66	43%	-
E0	0.39	-0.22	65%

Diagonal elements in table represent coefficient of variation for corresponding random effect. Off-diagonal elements represent coefficient of correlation between the two corresponding parameters. Because the matrix is symmetric, only the lower triangular matrix is shown.

(Source: Volume 68 (53 main report) Table 10 and Table 11)

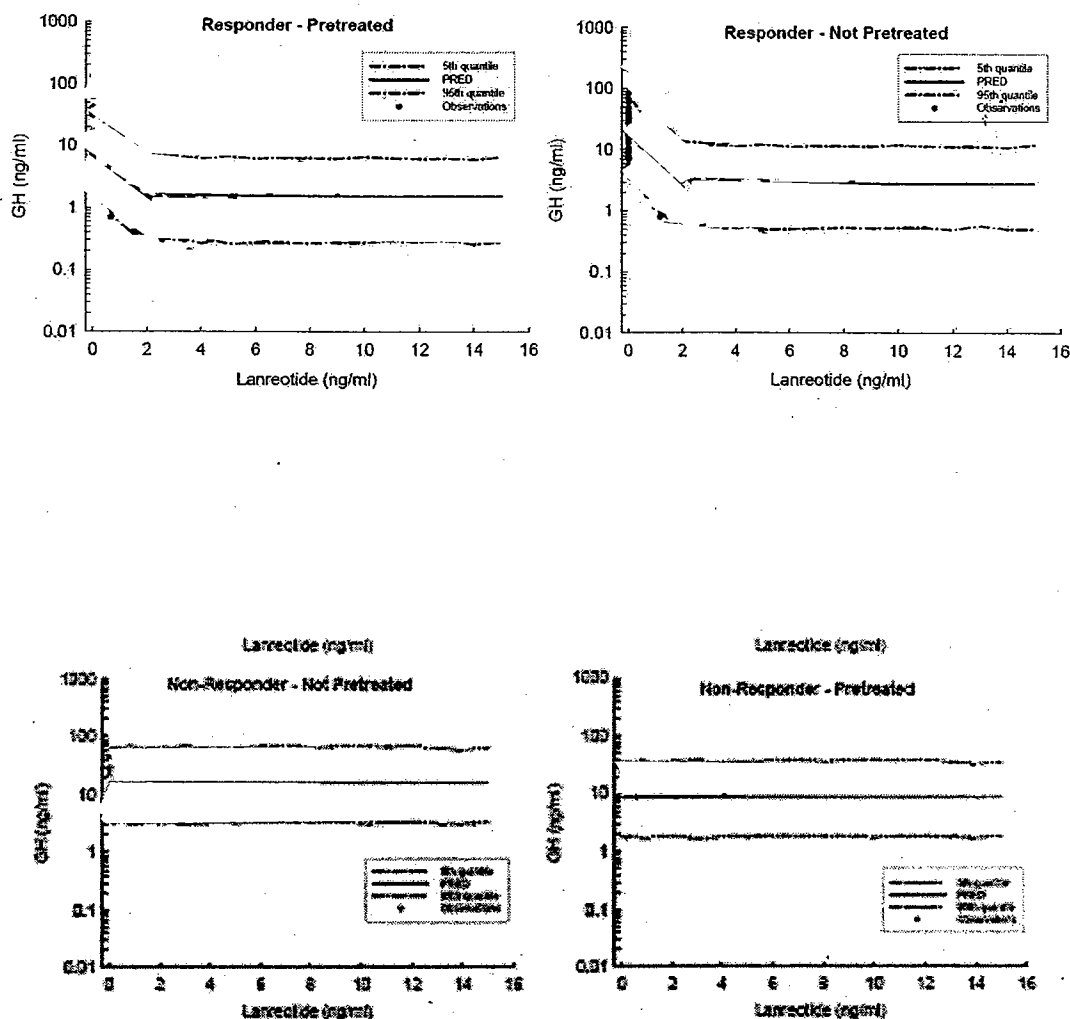
The diagnostic plots were presented in the Figure 9. The model predicted and observed GH concentrations versus lanreotide concentration were plotted in Figure 10, according to the responder status of patients.

Figure 9 Basic goodness-of-fit plots for the final PD model derived from study E28 52030 717



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Figure 10 Observed GH concentration of all patients and population prediction (lines) vs. lanreotide concentration according to their responder status (Study E28 52030 717)



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Sponsor's Conclusions

Conclusions from the population pharmacokinetic analyses based on data obtained from Study A93 52030 149 were listed as following (Report 05/PKR/107, Vol2, P51/52):

- The pharmacokinetics of Lanreotide after i.v. bolus injection of Lanreotide IRF ($D=7\mu\text{g/kg}$) revealed that the serum concentration-time curves were best described by an open three-compartment model with first-order elimination. Values of drug clearance (CL) and volume of distribution at steady state (V_{ss})

were 22 l/h and 14.9 l, respectively, with a low degree of interindividual variability on CL (19%). The half-life associated to the terminal disposition phase ($t_{1/2\gamma}$) was relatively short (approximately 2 h).

- The use of mixed effects modelling allowed to properly describe the pharmacokinetics of Lanreotide Autogel after deep s.c. administration to healthy volunteers. Absorption rate decreased exponentially as a function of logarithm of time, resembling the changes occurring within Lanreotide Autogel once it has been subcutaneously injected.
- Negligible initial burst release and overall control over entire releases after single dose at the three dose levels (60, 90 and 120 mg) demonstrated the robustness of formulation drug release.
- A dose proportional behaviour of Lanreotide Autogel was shown over the investigated dose range (60 mg to 120 mg), with an incomplete absolute bioavailability of 69.7%.
- No clinically relevant relationship with any of the demographic covariates tested (age, weight and gender) was found. The lack of involvement of weight and gender in the interindividual variability of population PK parameters of this model supports the use of fixed dosing and confirms the appropriateness of this route of administration (deep s.c.) for both genders, respectively. It should be taken into account that mean individual predicted C_{max} values were higher in males than in females ($p < 0.05$) and that difference contributed to increase the interindividual variability on C_{max} . However, there was insufficient PK data to support the inclusion of this covariate in the final model.
- Population results of this study were in good agreement with those obtained using the non-compartmental approach.

Conclusions from the pharmacodynamic analyses based on data obtained from Studies E28 52030 709 and E28 52030 710 were listed as following (Report 01/PKS/050, Vol 50, P36/409):

- A simple inhibitory Emax model allowing the possibility of an incomplete inhibition of GH, with interindividual variability in EC_{50} and E_0 was selected as the best model. Emax was 0.821 (equivalent to 7.09 ng/ml) with a low relative standard error of 7.53%. The level of lanreotide needed to reduce the GH to 50% of Emax (EC_{50}) was 0.206 ng/ml. The estimated E_0 value (baseline value of GH) was 8.63 ng/ml, reflecting the inclusion criterion for GH levels < 10 ng/ml at study entry. The median lanreotide serum level needed to decrease the GH to 2.5 ng/ml (C_{25}) is 1.127 ng/ml, and the mean remnant GH after Emax is achieved (GHR) is 1.733 ng/ml.

Conclusions from the pharmacodynamic analyses based on data obtained from Study E28 52030 717 were listed as following (Report 01/PKS/011, Vol 68, P66/67):

- Simple Sigmoidal Inhibitory EMAX model adequately described the relationship between lanreotide and GH concentrations.

- The population mean of EMAX was estimated to be around 82%, demonstrating the effectiveness of lanreotide.
- Baseline GH level (E_0) was significantly related to pre-treatment status within the last 3 months, estimating a lower value of E_0 for pre-treated patients ($8.74 \text{ ng}\cdot\text{ml}^{-1}$) than for not pre-treated patients ($15.9 \text{ ng}\cdot\text{ml}^{-1}$). The remaining covariates (age, weight, gender, autogel dose level and visit) were not identified as significantly influencing on lanreotide pharmacodynamics.
- A mixture model on EC_{50} was included in the PK/PD model, assuming that the population consists of two subpopulations: non-responders and responders to lanreotide treatment. The estimated percentage of non-responders (patients unaffected by the treatment) and responders were 13.7% and 86.3%, respectively. EC_{50} for non-responders was fixed to a high value of $100 \text{ ng}\cdot\text{ml}^{-1}$, and a value of $0.612 \text{ ng}\cdot\text{ml}^{-1}$ was estimated in EC_{50} parameter for responder patients. The lower sensitivity obtained for non-responders indicates that these patients do not respond to lanreotide treatment even with high lanreotide concentrations.
- Interindividual variability (reported as CV%) was estimated in E_0 , EMAX and EC_{50} , obtaining a high variability for E_0 (85%), moderate variability for EC_{50} (43%) and low variability for EMAX (14%). Residual variability was well described by an additive-proportional error model, with standard deviation of the additive component of $0.116 \text{ ng}\cdot\text{ml}^{-1}$ and coefficient of variation of 30% for the proportional component.
- A good precision in all population parameters was determined with low relative standard errors ranging from 2% to 41%.
- The median lanreotide serum level needed to decrease the GH to $2.5 \text{ ng}\cdot\text{ml}^{-1}$ (C25) in lanreotide responder patients was $0.95 \text{ ng}\cdot\text{ml}^{-1}$, and the median GH concentration reached asymptotically when lanreotide concentration trends to infinity (GHR) was $1.71 \text{ ng}\cdot\text{ml}^{-1}$.

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Reviewer's Comments on Sponsor Analysis

- The population pharmacokinetic analysis based on Study A93 52030 149 in healthy volunteer was adequately preformed using non-linear mixed effect model.
- The population pharmacodynamic model based on Studies E28 52030 709 and E28 52030 710 sufficiently describes the growth hormone change over time following Somatuline autogel administration.
- The population pharmacodynamic model based on data obtained from Study E28 52030 717 is acceptable to describe the growth hormone change over time following Somatuline antogel administration. However, we suggest that the sponsor fix the interindividual variability of Emax to zero, and then estimate different EC₅₀ values for the responders and non-responders.
- The mean minimum steady state concentrations following 60 mg, 90 mg, and 120 mg dose are 1.8, 2.5, 3.8 ng/mL respectively from Study E-28-52030-076_ (Table 7 from Office of Clinical Pharmacology Review),
- 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 Emax of growth hormone reduction in the responder population.
- Based on the modeling outcome, the proposed dosing appears to be acceptable.

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Reviewer's dose/exposure response ANALYSIS

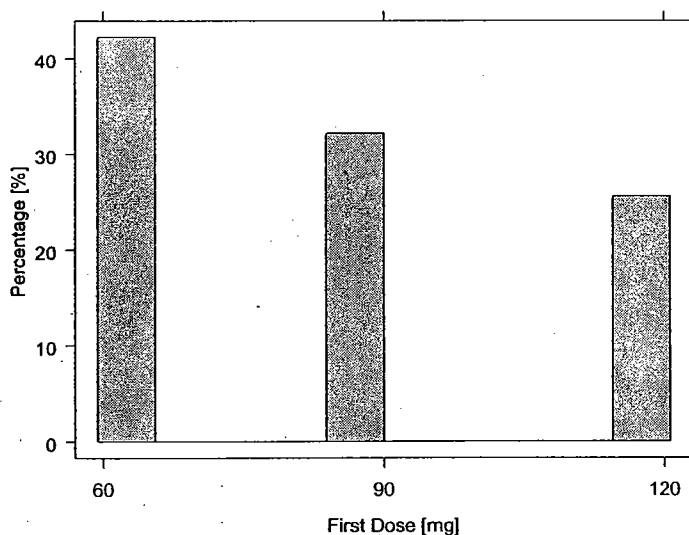
The FDA analyses were focused on the dose/exposure-safety relationship.

data

The original dataset was obtained from the sponsor through the 74 day filling communication. The original dataset (named as longitudinal PK safety dataset) contains safety information from 3 major clinical trials- Study E28 52030 717, Study E28 52030 709/710, and Study E28-52030-076. The data includes 270 subjects with 1017 observations at different dosing period.

Analyses datasets from subgroups of patients were created in order to avoid factors (such as treatment period or time, number of subjects in the treatment group) confounded with dose. The first dataset contains the safety information in the first treatment period of Somatuline Autogel. Totally 258 subjects with 258 observations from Studies E28 52030 717, E28 52030 709/710, and E28-52030-076 were included. Percentage of subjects exposed in the 3 different dose levels (60 mg, 90 mg, and 120 mg) was presented in Figure 11. The second dataset contains the safety information for the patients treated with 120 mg for 3 consecutive periods (dosing sequence is: 120-120-120). Totally 28 subjects with 84 observations from Study E28 52030 717 were included.

Figure 11 Percentage of subjects exposed in 3 different dose levels
(Pooled data from Studies E28 52030 717, E28 52030 709/710, and E28-52030-076)



Methods and results

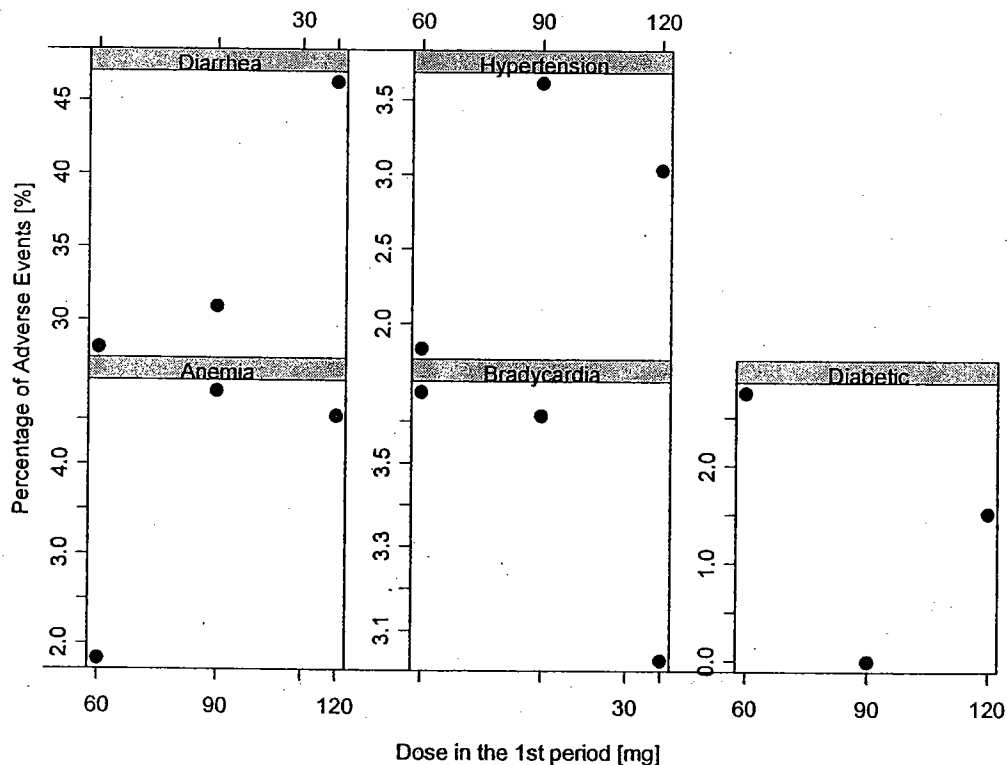
Dose-safety relationship was explored in the data obtained from the first treatment period as well as from the patients treated with 120 mg for 3-consecutive periods (dosing sequence is: 120-120-120).

Dose-safety relationship in the first treatment period

We investigated the dose - safety relationship in the first treatment period of Somatuline Autogel in the clinical studies. Since PK samples were not collected from every patient, the dose-safety relationship rather than the exposure-safety relationship was explored. The incidence of the major safety events were plotted against different doses that patients received in the first treatment period (Figure 12).

Figure 12 Incidence of the major safety events were plotted against different doses that patients received in the first treatment period

(Pooled data from Studies E28 52030 717, E28 52030 709/710, and E28-52030-76)



Note: Blue cycles represent the observed values.

A logistic regression analysis was conducted to explore the dose-safety relationship in the first treatment period following Somatuline Autogel administration. The logistic regression can be expressed by the following equation:

$$\log \frac{P_i}{1-P_i} = \alpha + \beta \cdot \text{Dose}$$

where P_i is the probability that an adverse event occur for subject i , and Dose represents the Somatuline Autogel dose that the i th subject received in the first treatment period. The logistic regression analysis was performed in SAS 9.1 using PROC LOGISTIC procedure.

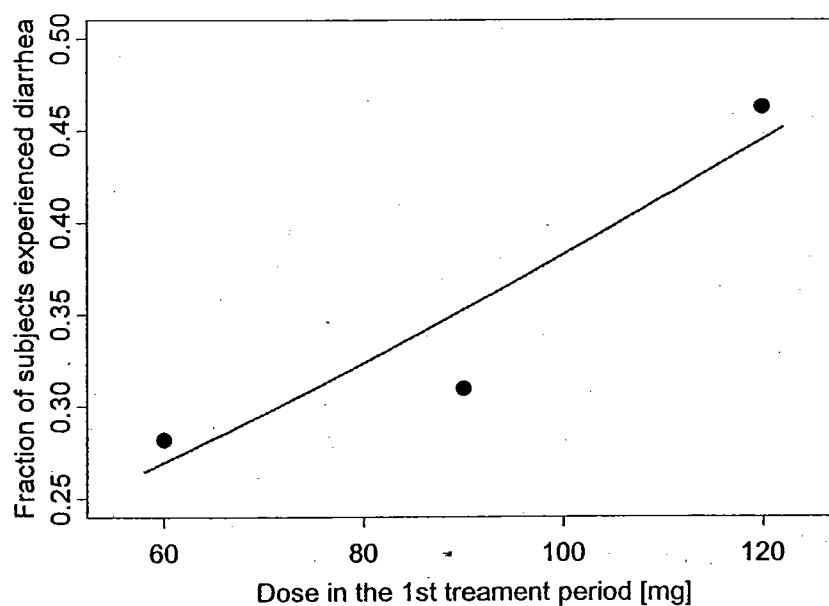
By applying the logistic regression analysis, a significant dose-response relationship was identified for the incidence of diarrhea. The parameters were presented in Table 7. The model fitted curve was demonstrated in Figure 13.

Table 7 Parameter estimates (Model: diarrhea ~ Dose)

Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-1.77	0.0003	-	-
Dose	0.0129	0.0178 (*)	1.013	1.002 ~ 1.024

*: Statistically significant.

Figure 13 Logistic model fitting for dose-diarrhea relationship



Note: Red line represents the model fitted curve and the blue cycles represent the observed values from pooled datasets including Studies E28 52030 717, E28 52030 709/710, and E28-52030-76.

We further investigated the dose-diarrhea relationships within the elder patients (≥ 65 years) and the younger patients (< 65 years). The parameter estimates from elder patient subgroup and the younger patient subgroup were illustrated in Table 8. The model fitted curve was illustrated in Figure 14. As the data demonstrated, elder patients do not have a higher incidence of diarrhea. Within the elder patients, diarrhea does not appear to be dose-dependant ($P = 0.76$). The data also showed that about 50% of younger patient suffer from diarrhea at the dose of 120 mg in the first treatment period. However, following current proposed initial dosing regimen (i.e. 90 mg for every 28 days), the incidence of diarrhea is about 30% in younger patients.

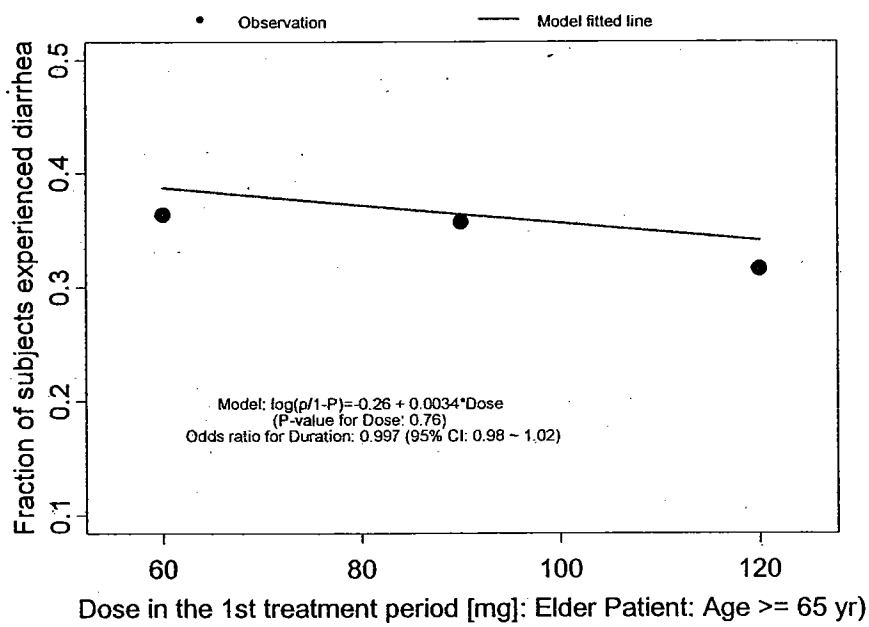
Table 8 Parameter estimates in elder patients and younger patients.

Model in elder patients (≥ 65 year) : (Diarrhea ~ dose)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	- 0.26	0.80	-	-
Dose	-0.0034	0.76	0.997	0.98 ~ 1.02
Model in younger patients (< 65 year): (Diarrhea ~ dose)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-2.23	< 0.0001	-	-
Dose	0.018	0.0045 (**)	1.02	1.01 ~ 1.03

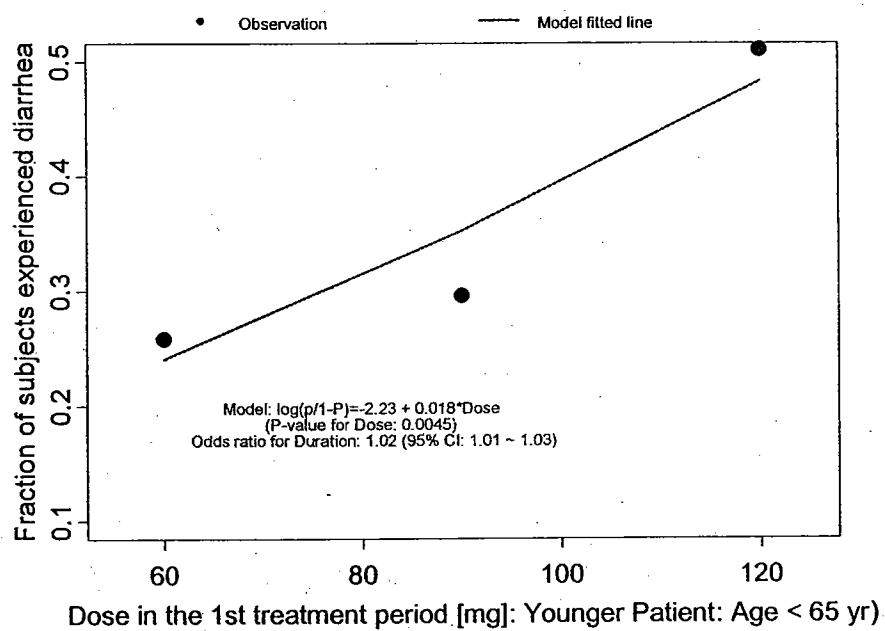
**: Statistically significant

Figure 14 Logistic model fitting for diarrhea-dose relationship in elder patients (age ≥ 65 yr) and in younger patients (age < 65 yr)

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(A)



(B)

Note:

(A) is for elder patient (Age ≥ 65 yr)

(B) is for younger patient (Age < 65 yr)

Dose response relationships for other adverse events including bradycardia, anemia, diabetic, and hypertension were also explored. The percentages of adverse events at different dose levels were summarized in Table 9, and no other significant dose - adverse events relationship was identified (Table 10).

Table 9 Percentages of adverse events at different dose levels in the first treatment period

Adverse Events	60 mg	90 mg	120 mg
Bradycardia	3.67	3.61	3.03
Anemia	1.83	4.82	4.54
Diabetic	2.75	0	1.52
Hypertension	1.83	3.61	3.03

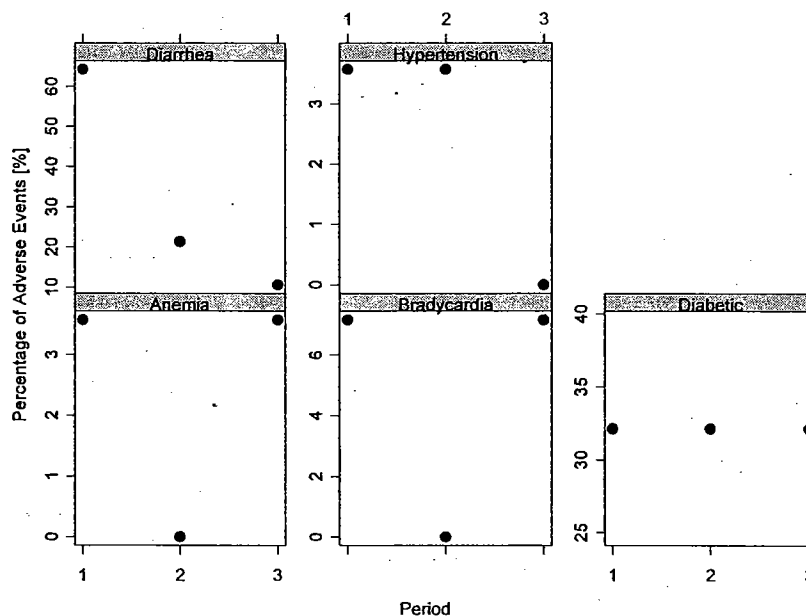
Table 10 Logistic regression results for major adverse events – dose relationship

Model: (Bradycardia ~ dose)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	- 3.07	0.013	-	-
Dose	-0.003	0.834	0.997	0.97 ~ 1.03
Model: (Anemia ~ dose)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	- 4. 60	0.0006	-	-
Dose	0.014	0.30	1.015	0.99 ~ 1.04
Model: (Diabetic ~ dose)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	- 0.784	0.103	-	-
Dose	0.001	0.786	1.001	0.991 ~ 1.012
Model: (Hypertension ~ dose)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	- 4.332	0.003	-	-
Dose	0.009	0.581	1.009	0.978 ~ 1.04

Safety- treatment duration relationship in patients treated by 120 mg in 3 consecutive periods

We investigated the safety – duration relationship in a subgroup of patients being treated by 120 mg Somatuline Autogel for 3 consecutive periods. The incidences of the major adverse events following 3 treatment periods were plotted in Figure 15.

Figure 15 Percentage of events for patients treated by 120 mg Somatuline Autogel in the three consecutive periods



Note: Blue cycles represent the observed values. Period is a surrogate for treatment duration.

A logistic regression analysis was conducted to explore the safety-treatment duration relationship in the subgroup of patients being treated by 120 mg in 3 consecutive periods. Period is a surrogate for the treatment duration time. The logistic regression can be expressed by the following equation:

$$\log \frac{P_i}{1-P_i} = \alpha + \beta \cdot \text{Duration}$$

where P_i is the probability that an adverse event occur for subject i , and Duration represents treatment duration time. The logistic regression analysis was performed in SAS 9.1 using PROC LOGISTIC procedure.

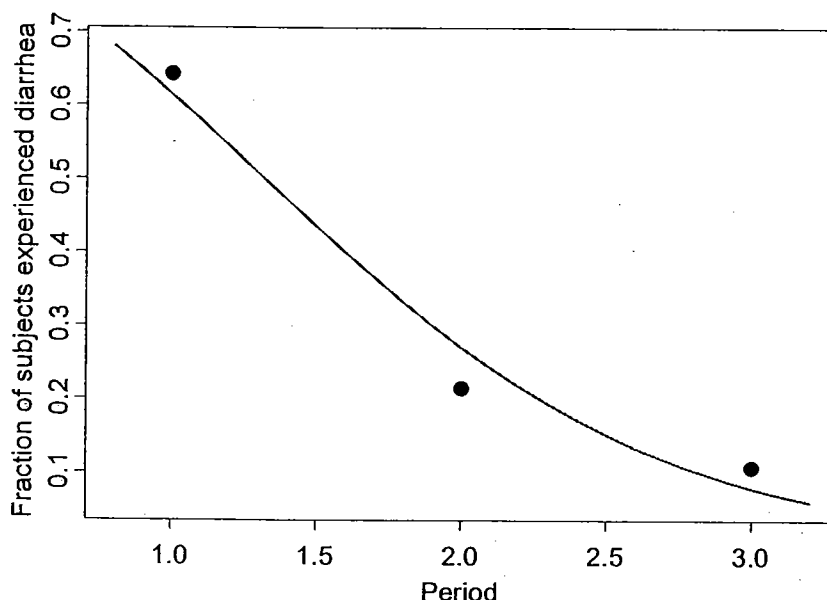
By applying the logistic regression analysis, a significant incidence-duration relationship was identified for the incidence of diarrhea. The parameters were presented in Table 11. The model fitted curve was demonstrated in Figure 16. Lower incidence of diarrhea was observed following longer treatment duration at 120 mg dose level.

Table 11 Parameter estimates (Model: diarrhea ~ duration)

Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	1.93	0.0045	-	-
Dose	-1.46	<0.0001 (***)	0.232	0.112 ~ 0.482

****: Statistically significant.

Figure 16 Logistic regression model fitting for the incidence of diarrhea – period (treatment duration) relationship



Note: red line represents the model fitted curve. Blue cycle represents the observed data.

Incidence and treatment duration response relationships for other adverse events including bradycardia, anemia, diabetic, and hypertension were also explored. No other significant treatment duration and adverse events relationship was identified (Table 12).

Table 12 Logistic regression results for major adverse events – dose relationship

Model: (Bradycardia ~ duration)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-3.00	0.03	-	-
Dose	0	0.63	1	0.29 ~ 3.42
Model: (Anemia ~ duration)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-3.71	0.05	-	-
Dose	0	1	1	0.18 ~ 5.57
Model: (Diabetic ~ duration)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-0.747	0.23	-	-
Dose	0	1	1	0.57 ~ 1.75
Model: (Hypertension ~ duration)				
Parameter	Estimate	P value	Odds ratio	95% CI

Intercept	-2.22	0.19	-	-
Dose	-0.85	0.41	0.43	0.06 ~ 3.21

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Pharmacometric Review Conclusions

The overall conclusions for the Pharmacometric review are:

- Significant dose response relationship was identified for diarrhea in the first treatment period following the Somatuline Autogel administration. Higher dose yields higher incidence of diarrhea in the first treatment period- 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.
- 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 ($P = 0.76$).
 - Within the younger patients, 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.
- 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. The incidences of adverse events are demonstrated in Figure 1. No obvious trend is identified across the dose range from 60 mg to 120 mg.
- Significant treatment duration and diarrhea relationship was identified in the patients treated with 120 mg Somatuline Autogel in 3 consecutive periods. Longer treatment duration time yields lower incidence of diarrhea-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.
- 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) is identified over time.

4.2. Individual Study Synopsis

Study # A-93-52030-149

Name of Sponsor/Company: IPSEN S.p.A.	Individual Study Table Referring to Part of the Dossier	(For national authority use only)
Name of Finished Product:		
Name of Active Ingredient(s): lanreotide		
Title of study: Pharmacokinetic study of lanreotide Autogel (60, 90 and 120 mg) administered to healthy subjects via deep subcutaneous route Study Number: LANREOTIDE-335-01 (IPSEN PROTOCOL A 93 52030 149)		
Investigators: / / / /		
Study centre(s): / / / /		
Publication (reference): Boscani P F et al. The bioavailability and dose-proportionality of lanreotide Autogel 60, 90 and 120 mg after deep subcutaneous injection: an open-label, parallel-group, randomized study in healthy volunteers; 12 th International Congress of Endocrinology, Lisbon, Portugal; 31 August – 4 September 2004 (Poster Presentation)		
Studied period: 2002 to 2003 Date of first enrolment: 28 February 2002 Date of last completed: 28 March 2003		Phase of development: I
Objectives: To evaluate the absolute bioavailability and dose proportionality of lanreotide Autogel® after deep subcutaneous (s.c.) administration at single doses of 60, 90, and 120 mg in healthy subjects.		
Methodology: This was an open, randomized, pharmacokinetic (PK) study in three parallel groups of healthy subjects. Subjects received a single intravenous (i.v.) administration, followed by a single deep s.c. administration. - Day -3: single i.v. dose of 7 µg/kg lanreotide immediate release formulation (IRF). Blood samples for lanreotide analysis were taken 0, 5, 15, 30 min, 1, 1.5, 2, 4, 6, 8, and 12 hours after dosing. - Day 0: single deep s.c. dose of lanreotide Autogel 60, 90 or 120 mg. Blood samples for lanreotide analysis were taken 0, 1, 2, 4, 6, 8, 12, and 24 hours after dosing, and in the mornings on Days 2, 3, 4, 5, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98, and 112. - Subsequent blood samples were taken until serum concentrations of lanreotide fell below the limit of quantification of the analytical method. - Blood samples for lanreotide antibody analysis (non-specific binding, NSB) were taken on Days -3, 28, 56, 84, 98 and 112, and at later visits in subjects who returned to the clinic after Day 112. - Clinical laboratory tests were carried out at screening and on Days 28, 84, and 112.		

Name of Sponsor/Company: IPSEN S.p.A.	Individual Study Table Referring to Part of the Dossier	(For national authority use only)
Name of Finished Product:		
Name of Active Ingredient(s): lanreotide		
- When subjects visited the clinic to have their last blood sample taken, post-study evaluations were also carried out. Adverse events were monitored throughout the study. Vital signs, ECG, and physical examination data were collected at various times during the study.		
Number of subjects: - Subjects planned: 54 - Subjects randomized: 54 - Subjects administered i.v. lanreotide IRF: 50 - Subjects administered deep s.c. lanreotide Autogel: 38 - Subjects completed the study: 37		
Diagnosis and criteria for inclusion: Healthy Caucasian males and females aged between 18 and 45 years, body weight within 10% of the ideal height/frame size as reported in the Height and Weight tables from Metropolitan Life Insurance, normal physical examination and laboratory test results, no history of allergic response to lanreotide or somatostatin analogues, no previous history of cholelithiasis, signed written informed consent, negative pregnancy test, no breast feeding women.		
Test products, dose and mode of administration, batch number: - Lanreotide IRF 1 mg vials for i.v. administration, 7 µg/kg, batch: LBCK (JBMJ and JBPN) - Lanreotide Autogel 60 mg pre-filled syringes for deep s.c. injection, batch: LBCL (KBB8) - Lanreotide Autogel 90 mg pre-filled syringes for deep s.c. injection, batch: LBCM (KBB3) - Lanreotide Autogel 120 mg pre-filled syringes for deep s.c. injection, batch: LBCN (LBBD)		
Duration of treatment: Single i.v. dose of lanreotide IRF and, after a three-day washout period, a single deep s.c. dose of lanreotide Autogel 60, 90, or 120 mg.		
Reference therapy, dose and mode of administration, batch number: Not applicable		
Criteria for evaluation: <u>Pharmacokinetics</u> The following PK parameters were calculated: <u>i.v.</u>: area under the serum concentration-time curve until the last quantifiable value (AUC_t), area under the serum concentration-time curve extrapolated to infinity (AUC_∞), elimination half-life ($t_{1/2\lambda_z}$), volume of distribution in the terminal phase (V_z), volume of distribution at steady state (V_{ss}), systemic clearance (CL), and mean residence time (MRT). <u>Deep s.c.</u>: empirical time to peak serum concentration (t_{max}), empirical peak serum concentration (C_{max}), AUC from time zero to Day 28 ($AUC_{0-28days}$), AUC_t, AUC extrapolated		

Name of Sponsor/Company: IPSEN S.p.A.	Individual-Study Table Referring to Part of the Dossier	(For national authority use only)
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to infinity (AUC), AUC normalized by dose (AUC/D), percentage of the AUC extrapolated (AUC_{extrap}), apparent elimination half-life ($t_{1/2\alpha}$), mean residence time (MRT_{LC}), absolute bioavailability (F).

Efficacy: not applicable.

Safety:

- Adverse event reporting;
- Laboratory tests (hematology, standard biochemistry, and urinalysis);
- General physical examination;
- Vital signs and ECG;
- Lanreotide antibodies (NSB).

Statistical methods:

Non-Compartmental Pharmacokinetic Analysis:

- Descriptive statistics were used to present lanreotide PK parameters.
- Two tests of dose proportionality were carried out:
 One-way analysis of variance (ANOVA): log-transformed $t_{1/2\alpha}$ and F and log-transformed, dose-normalized AUC, AUC_t, AUC_{0-28days} and C_{max} values (AUC/D, AUC_t/D, AUC_{0-28days}/D and C_{max}/D) were compared as a function of dose.
 Nonlinear power model: The parameters of interest were total AUC, AUC_t, AUC_{0-28days}, and C_{max}.
- Pre- and post-study vital signs were analyzed using the nonparametric Friedman test.

Population Pharmacokinetic Analysis:

- Disposition of lanreotide in serum was characterized with compartmental models using data obtained after i.v. bolus injection, and then the absorption profile of lanreotide Autogel was determined using serum concentration values corresponding to deep s.c. administrations and fixing the individual Bayesian posterior estimates of the disposition parameters. The individual apparent terminal $t_{1/2\gamma}$ and AUC of lanreotide were calculated from clearances and volumes of distribution using standard PK formulas.
- For lanreotide Autogel treatment, several different models with different numbers of input functions (zero-order and/or first-order absorption models, with or without lag-time, with or without an estimate of F different from one, etc.) were tested, and individual PK parameters after lanreotide Autogel administration were estimated.

Deconvolution Pharmacokinetic Analysis:

- The lanreotide *in vivo* absorption profile was estimated by deconvolution, and lanreotide concentration-time data were obtained from i.v. and deep s.c. administrations of lanreotide to each subject.

Two- and three-compartment open models were fitted to the i.v. lanreotide serum concentrations. Macroconstants obtained from the best fit were normalized by individual actual doses and then used for deconvolution analysis. The maximum dose of lanreotide

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absorbed from Autogel was then calculated from deconvolution results, and the cumulative percentage of the dose absorbed during various time periods after dosing was estimated.

Summary - Conclusions:

Pharmacokinetics

The PK parameters calculated following i.v. administration of 7 µg/kg lanreotide IRF are summarized in the table below.

Pharmacokinetics of Lanreotide in Serum After a 7 µg/kg i.v. Bolus Dose of Lanreotide IRF

Parameter	Mean (N=48)	SD	CV%
AUC _t (ng.h/mL)	21.1	7.9	37.4
AUC (ng.h/mL)	21.3	7.9	37.0
t _{1/2α} (h)	1.14	0.42	37.0
V _z (L)	37.8	14.9	39.4
V _{ss} (L)	16.1	9.6	59.9
CL (L/h)	23.7	6.6	27.8
MRT (h)	0.68	0.28	41.7

The PK parameters calculated following deep s.c. dosing with lanreotide Autogel 60, 90 or 120 mg are summarized in the table below.

Pharmacokinetics of Lanreotide in Serum After Deep s.c. Dosing with Lanreotide Autogel

Parameter	60 mg ^a			90 mg ^b			120 mg ^c		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
C _{max} (ng/mL)	13	4.25	1.93	13	8.39	4.91	12	6.79	3.64
t _{max} (day) ^d	13	0.33	(0.17-14.00)	13	0.50	(0.17-14.00)	12	0.29	(0.08-2.14)
AUC _{0-28days} (ng.day/mL)	13	42.0	9.3	13	67.3	25.4	12	73.3	33.9
AUC _t (ng.day/mL)	13	69.8	19.2	13	107.3	36.3	12	132.2	42.0
AUC (ng.day/mL)	11	78.2	19.1	12	120.3	34.1	10	150.8	38.4
AUC/D (ng.day/mL/mg)	11	1.30	0.32	12	1.34	0.38	10	1.26	0.32
AUC _{extrap} (%)	11	7.7	5.2	12	6.6	4.7	10	7.9	5.5
t _{1/2α} (day)	11	23.3	9.9	12	27.4	9.4	10	30.1	9.8
MRT _{1c} (day)	11	35.5	12.0	12	36.8	15.1	10	42.5	13.2
F (%)	10	73.4	23.3	11	69.0	17.1	10	78.4	21.3
F (%) ^e	12	67.3	21.1	12	61.6	17.9	12	66.6	22.9

^a AUC, AUC/D, AUC_{extrap}, t_{1/2α}, MRT_{1c} and F from Subjects 13 and 32 were not included due to inaccurate estimation of t_{1/2α}. F from Subject 38 was not calculated due to the inaccurate estimation of AUC i.v.

^b AUC, AUC/D, AUC_{extrap}, t_{1/2α}, MRT_{1c} and F from Subject 11 were not included due to inaccurate estimation of t_{1/2α}. F values from Subject 05 were not calculated due to the inaccurate estimation of AUC i.v.

^c AUC, AUC/D, AUC_{extrap}, t_{1/2α}, MRT_{1c} and F from Subjects 16 and 37 were not included due to inaccurate estimation of t_{1/2α} and a high AUC_{extrap} value (> 20%), respectively.

^d Median (min-max) values for t_{max} are presented.

^e F calculated by means of AUC_t (deep s.c. route).

Name of Sponsor/Company: IPSEN S.p.A.	Individual Study Table Referring to Part of the Dossier	(For national authority use only)
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The non-compartmental PK analysis indicated that lanreotide Autogel has a mean bioavailability of 73.4% for the 60 mg dose, 69.0% for the 90 mg dose, and 78.4% for the 120 mg dose.

A one-way ANOVA showed no statistically significant differences for AUC/D , AUC_t/D , $AUC_{0-28days}/D$, C_{max}/D , $t_{1/2LZ}$, or F at the three deep s.c. doses administered, indicating that dose proportionality could be concluded. Dose proportionality was confirmed by means of a non-linear power model for AUC , AUC_t , $AUC_{0-28days}$, and C_{max} .

In the population PK analysis, the time-course of lanreotide release after deep s.c. administration of lanreotide Autogel was adequately described using an absorption rate that decreased exponentially as a function of the logarithm of time, reflecting the solid depot formation at the injection site and the slow drug release from this depot. Limited initial burst release and controlled releases over a period of several weeks after single-dose administration of lanreotide at the doses of 60, 90, and 120 mg demonstrated the feasibility of the Autogel formulation for longer-term treatment. A dose proportional behavior of Lanreotide Autogel was shown over the dose range investigated (60 to 120 mg), with an absolute bioavailability of 69.7%. Overall, the results of the population PK analysis concurred with the results of the non-compartmental PK analysis. No clinically relevant relationship was found to any of the demographic variables tested (age, weight, and gender).

In the deconvolution PK analysis, the mean cumulative absorption percentages of lanreotide were 69.1%, 62.9%, and 66.7% for the 60, 90, and 120 mg doses, respectively. The mean percentages of lanreotide absorbed in the first 24 hours, relative to the administered dose, were 3.3%, 3.6%, and 2.8% for increasing doses, respectively. The maximum daily dose of lanreotide after the deep s.c. injection of lanreotide Autogel was less than 8% of the total dose administered.

Safety

The frequency of subjects with TEAEs was higher in the Autogel (deep s.c.) groups than in the IRF (i.v.) group, but there were no specific dose related trends across the Autogel groups. Gastrointestinal events were the most frequent TEAEs in all treatment groups (IRF and Autogel), in particular nausea in the IRF group, and diarrhoea, abdominal pain, abdominal distension, and vomiting in the Autogel groups.

Injection site induration occurred in 19 subjects, all in the Autogel (deep s.c.) groups, which the investigator considered to be due to the nature of the drug and the modality of injection. The reabsorption of these cutaneous indurations generally took a long time, ranging from one to ten months.

The one serious adverse event reported during this study was a case of biliary colic that occurred approximately three months after the subject had received a single i.v. dose of lanreotide IRF followed by a single deep s.c. dose of 60 mg lanreotide Autogel, and which

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resolved after cholecystectomy. Treatment with analogues of somatostatin is known to increase the risk of asymptomatic and symptomatic gallbladder lithiasis. However, the occurrence of biliary colic in a subject who had received only two single doses of lanreotide suggests either that the problem was pre-existing or that lanreotide caused the onset of biliary colic in this predisposed subject. There were no clinically relevant findings in the clinical laboratory data, or in the vital signs, ECG, or physical examination evaluations. <u>Conclusions</u> Lanreotide Autogel had a mean bioavailability of 73.4% for the 60 mg dose, 69.0% for the 90 mg dose, and 78.4% for the 120 mg dose. The rate and extent of absorption were dose proportional across this dose range. Limited initial burst release and controlled releases over a period of several weeks after single-dose administration demonstrated the feasibility of the Autogel formulation for longer-term treatment, with administration every four weeks. Lanreotide Autogel was safe and well tolerated, and the safety profile that was not affected by the dose administered. <u>Date of the report:</u> 27 June 2006		

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Study # EE-55-52030-047

Name of Sponsor/Company: IPSEN-BIOTECH	Individual Study Table Referring to Part of the Dossier	(For national authority use only)
Name of Finished Product: LANREOTIDE AUTOGEL		
Name of Active Ingredient(s): LANREOTIDE (INN)		
Volume:		
Page:		
Title of study: Phase I, single-blind, local tolerability study of lanreotide autogel (BIM 23014) after single 60, 90 and 120 mg subcutaneous injections at three different sites in healthy male volunteers. Study Number: E-55-52030-047		
Investigator: _____		
Study center: _____		
Publication (reference): Not Applicable		
Studied period (years):		Phase of development: I
Date of first enrolment: 17 th September 1998		
Date of the last visit for the follow-up: 28 th February 2001		
Study objectives: - The primary objective was to determine and to compare the local tolerability of single deep subcutaneous injections of lanreotide autogel (0.246 mg lanreotide per mg of autogel) administered at three different dosages (60, 90, 120 mg) and injected at three different sites (upper arm, abdominal wall, right buttock). - The secondary objectives were to evaluate the general safety, to perform a pharmacokinetic study, and to detect lanreotide antibodies.		
Methodology: This was a phase I, single-centre, single-blind study of three dose levels at the injection site. Blood sampling: Blood samples were taken on D0 at T0 (pre-dose), T8 and T24 and on D3, D5 and D7 and then at each weekly visit up to D42. If induration was present after D42, samples were taken every month for the first three months and then every three months for the following nine months.		
Number of subjects (planned and analyzed): Planned: 27 Screened: 35 Enrolled: 27 In tolerability analysis: 27 In pharmacokinetic analysis: 27		
Diagnosis and criteria for inclusion: The study was carried out in healthy male Caucasian volunteers (3 volunteers per dose and per site), aged 18 to 40 years.		
Test product, dose and mode of administration, batch number: Test product: Lanreotide acetate autogel (BIM 23014) presented under the following forms: Treatment A: Syringe of lanreotide autogel allowing the injection of 60 mg lanreotide Treatment B: Syringe of lanreotide autogel allowing the injection of 90 mg lanreotide Treatment C: Syringe of lanreotide autogel allowing the injection of 120 mg lanreotide Mode of administration: Subcutaneous injections, into the arm or the abdomen as deeply as permitted at the site and into the right buttock at a depth of 20 mm (total length of the needle). Batch number: <u>Treatment A:</u> GBNF (GBGY) <u>Treatment B:</u> GBNG (GBGZ) <u>Treatment C:</u> GBNH (GBG7)		
Expiry date: April, 30 th 1999		
Study duration:		

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Name of Sponsor/Company: IPSEN-BIOTECH	Individual Study Table Referring to Part	(For national authority use only)
Name of Finished Product: LANREOTIDE AUTOGEL	of the Dossier	
Name of Active Ingredient(s): LANREOTIDE (INN)	Volume: Page:	
42 days at least. If induration was present after D42, the subjects were followed every month for the first 3 months, every 3 months for 9 months and every 6 months until disappearance or stabilisation of the induration, the stabilisation being confirmed after 2 consecutive clinical examinations.		
Reference therapy: Not applicable		
Evaluation criteria: <u>Local tolerance</u> Local tolerance was assessed by examination of the injection site at each visit and evaluation of general safety including volunteer's subjective comments. Subjects made regular visits to —. They were hospitalised from T0 to T24 hours. They returned to — on the mornings of Days 3, 5 and 7 and then every 7 days for the following 5 weeks. If induration persisted at D42, subjects were followed up each month for the first three months, every three months for nine months, and then every six months until disappearance or stabilisation of the induration. An ultrasound study at the injection sites was scheduled at D42. If induration was present a further ultrasound study was scheduled around 18 months after D42. <u>Pharmacokinetics</u> Serum samples for lanreotide concentration determination were taken at T0, T8 and T24 hours, on D3, D5 and D7 and then at each weekly visit up to D42. If induration persisted after D42, further samples have been taken every month for the first three months and then every three months for the following nine months. Serum samples for lanreotide antibody determinations were taken on D0, D21 and D42. If induration persisted after D42, additional samples were taken every month for the first three months and then every three months for the following nine months. <u>Safety</u> A physical examination was performed prior to study start and at each visit after drug administration. Study events were recorded when reported spontaneously by the subject or observed by the investigator. Laboratory tests and ECG were performed prior to study start and on D42. Blood pressure and pulse rate measurements were performed at each visit. Statistical methods: <u>Pharmacokinetics:</u> Pharmacokinetic analysis of the data was performed by a non-compartmental approach using the WinNonlin pharmacokinetic program. Serum concentrations over time were analysed using descriptive statistics: mean, standard deviation (SD), coefficient of variation, median, minimum and maximum. The main pharmacokinetic parameters derived from the serum levels were: time to peak serum concentration (t_{max}), peak serum concentration (C_{max}) and area under the serum concentration time curve from time 0 to D42 (AUC_{0-42}). Descriptive statistics: mean, standard deviation (SD), median, minimum and maximum values of these derived parameters were calculated. <u>Lanreotide antibodies:</u> Serum antibodies were measured by radioimmunoassay in order to determine the non-specific binding.		

Name of Sponsor/Company: IPSEN-BIOTECH	Individual Study Table Referring to Part	(For national authority use only)
Name of Finished Product: LANREOTIDE AUTOGEL	of the Dossier	
Name of Active Ingredient(s): LANREOTIDE (INN)	Volume: Page:	
Safety: Descriptive statistics: mean, standard deviation (SD), standard error of mean, minimum and maximum values of the main parameters were calculated. Data from all subjects who received study medication were analysed to determine the local tolerability. Summary – conclusions: <u>The pharmacokinetic conclusions are as follows:</u> After subcutaneous administration, lanreotide C_{max} and AUC_{0-42} were highly variable whatever the dose and administration site, probably due to the small number of samples. Based on the pooled site results, C_{max} and AUC_{0-42} of lanreotide did not increase proportionally for subcutaneous injections ranging from 60 to 120 mg. Sustained serum concentrations of lanreotide were obtained for 42 days following a single subcutaneous injection of doses ranging from 60 to 120 mg. Residual concentrations were observed for some volunteers. After D42 + 2 or 3 months, lanreotide serum levels were lower than 0.3 ng/ml in 5 out of the 14 subjects presenting indurations. The other 9 subjects had no detectable lanreotide serum level. All samples analysed after D 42 + 3 months showed levels lower than the limit of quantitation (LOQ) (0.078 ng/ml). Lanreotide antibody levels were determined in all volunteers and no antibodies were detected in any subject. All NSB% values were lower than or equal to 6.8 %. <u>Safety results:</u> Up to D42, local symptoms at injection site (pain, redness and itching) were reported. Pain was reported by three out of 27 subjects (11%): it was of mild intensity in all cases and resolved spontaneously. Redness was reported by three out of 27 subjects (11%). It was mild except for one subject, in whom it appeared to be moderate, and resolved spontaneously in all subjects. Itching was reported in three out of 27 subjects (11%). This was of mild intensity and resolved spontaneously. After D42, no pain and no itching were observed, however one subject reported redness of moderate intensity on D42 + 24 months. As expected induration was reported in most subjects: 17 (63%) subjects at D0 (H24) and 20 (74%) subjects at D42. Within 24 months after D42, when looking at the subjects' changes in surface of induration, the indurations disappeared or decreased in 68% of the subjects, were stable in 23% of the subjects and increased in 9% of the subjects. However they were less frequent when lanreotide autogel was injected in the right buttock as compared to other injection sites. According to these results, the buttock appears to be the most appropriate site for lanreotide autogel deep s.c. administration. During the course of the study, there were no dropouts for serious adverse events, but one serious adverse event (cholecystic syndrome) occurred at D42 + 1 month. From D0 up to D42 + 24 months, 69 adverse events were reported by 89% of the subjects. Most of the AEs reported were diarrhoea, abdominal pain or headaches (respectively reported by 67%, 44% and 22% of subjects). These events are those already expected following the use of somatostatin analogues. Some pharyngitis and tooth disorders were also reported. Date of the report: Amended version: February 18th, 2004		

Study E-28-52030-076

Name of Sponsor/Company: Beaufour Ipsen Pharma	Individual Study Table Referring to Part of the Dossier	<i>(For national authority use only)</i>
Name of Finished Product: LANREOTIDE AUTOGEL	Volume:	
Name of Active Ingredient(s): LANREOTIDE (I.N.N.) ACETATE	Page:	
Title of study: Phase II, randomized, parallel groups, double-blind pharmacokinetic study of lanreotide autogel (60, 90, or 120 mg) after 4 deep subcutaneous injections (administered every 28 days) in acromegalic patients		
Study number: E-28-52030-076		
Investigators: The study was conducted by ' _____ '		
Study centre(s): The study was conducted at _____		
Publication (reference): None		
Studied period (years): Date of first enrollment: 29 October 2001 Date of last completed: 29 July 2002		Phase of development: II
Objectives: The primary objective of this study was to characterize the pharmacokinetic profile of lanreotide autogel in acromegalic patients following multiple deep subcutaneous (s.c.) injections. The secondary objectives included the evaluation of the effectiveness of lanreotide autogel [based on mean growth hormone (GH) levels, insulin-like growth factor-1 (IGF-1) levels and clinical symptoms] and the evaluation of the treatment tolerability.		
Methodology: This was a phase II, randomized, parallel group, double-blind study designed to evaluate the pharmacokinetic profile of lanreotide autogel (60, 90, and 120 mg) in patients with active acromegaly. Patients were randomized on a 1:1:1 basis to receive 4 deep subcutaneous injections of fixed doses of 60, 90 or 120 mg lanreotide autogel at 28-day intervals.		
Number of patients (planned and analyzed): <u>Planned:</u> Approximately 18 acromegalic patients, 6 per treatment group. <u>Analyzed:</u> A total of 20 patients were screened and 18 patients were randomized and received at least one dose of study treatment including 6 patients each who received 60, 90 and 120 mg lanreotide autogel.		
Diagnosis and criteria for inclusion: Patients 18 years of age or older with active acromegaly, defined by a mean GH serum level > 5 ng/mL (mean GH value was calculated from blood samples collected at 0, 30, 60, 90, 120, 150 and 180 minutes). Main exclusion criteria included receipt of radiotherapy for acromegaly within 3 years or pituitary surgery within 3 months prior to visit V1; anticipated need for pituitary surgery		

Name of Sponsor/Company: Beaufour Ipsen Pharma	Individual Study Table Referring to Part of the Dossier	(For national authority use only)
Name of Finished Product: LANREOTIDE AUTOGEL		
Name of Active Ingredient(s): LANREOTIDE (LNN) ACETATE	Volume: Page:	

(adenomectomy) or radiotherapy during the study period; any prior receipt of lanreotide autogel, lanreotide 30 mg, GH antagonist, or octreotide long-acting formulation; short-acting formulation of octreotide within 5 days prior to visit V2a; short-acting formulation or long acting formulation of a dopaminergic agonist within 7 or 14 days, respectively, prior to visit V2a; known hypersensitivity to any of the test materials or related compounds; and clinically significant renal, cardiac or hepatic abnormalities.

Test product, dose and mode of administration, batch number:
 Patients received up to 4 deep subcutaneous injections of lanreotide autogel at 28-day intervals at fixed doses of 60, 90 or 120 mg based on random assignment.
 The batch numbers of lanreotide autogel 60 mg, 90 mg and 120 mg used in this study were KBHV, KBH9 and KBH8, respectively.

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

Reference therapy, dose and mode of administration, batch number:
 Not applicable.

Criteria for evaluation:
Pharmacokinetics:
 Blood samples for determination of lanreotide serum levels were obtained prior to and at 1, 2, 4, 6, and 8 hours and 1, 2, 4, 7, 14 and 21 days after the first and fourth doses of study medication and prior to the second and third doses; samples were analyzed using radioimmunoassay.
 The mean minimum serum levels of lanreotide at visit 10, 11, 12 and 19, corresponding to C_{min1} , C_{min2} , C_{min3} and C_{min4} (minimum serum concentrations after the first, second, third and fourth lanreotide administrations, respectively) were obtained.
 Pharmacokinetic parameters time to maximum concentration (T_{max}), maximum serum concentration (C_{max}), area under the concentration-time curve from 0 to the last experimental point before the second administration (AUC_0), area under the concentration-time curve during a dosing interval (AUC_τ), mean residence time from 0 to the last experimental point before the second administration (MRT_0), T_{max} at steady state ($T_{max,ss}$), C_{min} at steady state ($C_{min,ss}$), C_{max} at steady state ($C_{max,ss}$), average concentration (C_{avg}), accumulation indices and peak-trough fluctuation (PTF) were calculated using WinNonlin software.
Efficacy:

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

Name of Sponsor/Company: Beaufour Ipsen Pharma	Individual Study Table Referring to Part of the Dossier	(For national authority use only)
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V19. <u>Safety:</u> The following safety assessments were conducted: monitoring for adverse events, clinical laboratory tests, physical examinations, vital signs (blood pressure and heart rate), electrocardiogram (ECG), echocardiography, ultrasound of gall bladder and concomitant medications.		

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between the two dose groups. Abnormal fibrinogen levels post-infusion, were reported in 10 volunteers: 5 from each dose group. Four volunteers in the low dose group had fibrinogen levels below normal range and 1 had a fibrinogen level above normal range. In the high dose group, 3 had fibrinogen levels below the normal range and 2 experienced high fibrinogen levels compared to normal range. These changes were not statistically or clinically significant.

1.3.1.3 Liver Function

A transient elevation of serum aminotransferases including SGPT/AST and SGOT/ALT was observed in 9 of 20 volunteers, including 5 in the low dose group and 4 in the high dose group. Simultaneous elevation of both aminotransferases was observed in all of the volunteers except for 1 who had only elevated SGPT. The highest enzymes levels were observed in 2 volunteers in the low dose group. All elevations appeared during the post-infusion period and returned to baseline values at Day 11. Concomitant elevations of γ -glutamyl transferase were also observed in 4 volunteers. There were no elevations in alkaline phosphatase or total bilirubin.

1.3.1.4 Kidney Function

Lanreotide did not modify serum creatinine or creatinine clearance. The renal response to 12-hour water deprivation or water load prior to lanreotide infusion, during the infusion and post-infusion periods was the same with regard urinary flow rate, excretion of water load, Na^+ , K^+ and osmolality for the two dose groups.

1.3.1.5 Biochemistry

Total cholesterol levels above 200 mg/dl were found in 9 volunteers from the low dose group and 7 from the high dose group. No significant changes in total cholesterol levels were observed after the treatment with lanreotide. LDL and HDL cholesterol was measured but was not used in the analysis. Abnormally high triglyceride levels compared to normal range were found in 12 volunteers: 5 from the low dose group and 7 from the high dose group. Most of these abnormalities were observed prior to the infusion or were isolated single values. Random abnormalities were also found in calcium and potassium plasma concentrations, $[\text{Ca}^{2+}]_p$ and $[\text{K}^+]_p$, serum proteins, albumin, BUN and uric acid. None of these changes were statistically or clinically significant nor were related to lanreotide treatment.

1.3.2 Lanreotide Pharmacological Efficacy

Serum glucose levels were transiently increased by lanreotide in 5 volunteers: 1 from the low dose group and 4 from the high dose group. Individual plasma

glucagon levels fluctuated above or below baseline within the normal range. The hormones responsible for the regulation of glycemia were found elevated in 2 volunteers, one with elevated glucagon and 1 with elevated insulin levels.

Serum IGF-I levels fluctuated within normal ranges during the trial. However, a decreasing trend in serum IGF-I levels was evident in both dose groups. In the high dose group the difference between baseline and the maximum change post treatment was statistically significant ($p = 0.0001$). No changes in testosterone levels compared to normal range were found in this trial. However, a decreasing trend in plasma testosterone levels on Day 1 was observed in 7 male volunteers from the high dose group. In this group, the difference between baseline and the maximum change post treatment was statistically significant ($p = 0.0016$). Serum luteinizing hormone (LH) levels paralleled plasma testosterone levels. A decreasing trend in LH levels was observed in the high dose group. The difference between baseline and the maximum change post treatment was statistically significant ($p = 0.0018$).

1.3.3 Pharmacokinetics

Details of pharmacokinetic methods, procedures and results will be submitted in an amendment to this NDA.

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4.4 OCP Filing Form

Office of Clinical Pharmacology				
New Drug Application Filing and Review Form				
General Information About the Submission				
NDA Number	22-074	Brand Name	Somatuline Autogel	
OCP Division	2	Generic Name	Lanreotide acetate	
Medical Division	DMEP	Drug Class	Somatostatin analog	
OCP Reviewer	Jayabharathi Vaidyanathan, Ph.D.	Indication(s)	Treatment of Acromegaly	
OCP Team Leader (Acting)	Jim Wei, Ph.D.	Dosage Form	60/90/120 mg Subcutaneous injection	
		Dosing Regimen	QD	
Date of Submission	10/30/06	Route of Administration	Subcutaneous injection	
Estimated Due Date of OCP Review	7/16/07	Sponsor	Beaufour Ipsen Pharma	
PDUFA Due Date	8/30/07	Priority Classification	Standard	
Division Due Date	7/26/07			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:		4		
multiple dose:		2		
Patients-				
single dose:				
multiple dose:		1		
Dose proportionality -				
fasting / non-fasting single dose:		1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:		1		
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:		1		
renal impairment:		1		
hepatic impairment:		2		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:		11		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:		1		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		37		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable)		
Comments sent to firm ?		Yes.		
QBR questions (key issues to be considered)	1) What are the PK characteristics of lanreotide from the Autogel fomulation? 2) Is the dose and dosing regimen appropriate? 3) What are the PD properties of lanreotide Autogel?			
Other comments or information not included above				
Primary reviewer Signature and Date	Jaya bharathi Vaidyanathan, Ph.D.			
Secondary reviewer Signature and Date	Jim Wei, Ph.D.			

Background:

Somatuline Autogel (lanreotide acetate) injection is a synthetic octapeptide and an analogue of somatostatin. This is a prolonged release formulation of lanreotide intended for deep subcutaneous injection as a treatment for patients with acromegaly. It is proposed to be supplied in three strengths (60, 90, 120 mg) ready to use prefilled syringes. Lanreotide was designated as an orphan drug by the Agency for the treatment of acromegaly on September 11, 2000.

Lanreotide was first developed as an immediate release formulation (IRF). The IRF was not developed for commercial use. Lanreotide was then developed for commercial use as a micro-particle formulation (MRF) administered every 7, 10 or 14 days. Since 1994, the MRF has been approved in over 50 countries.

Subsequently Autogel formulation was developed to further extend the duration of lanreotide release, allowing for administration once every 4 weeks. Lanreotide Autogel is registered in over 40 countries for treatment of acromegaly and carcinoid syndrome since 2001. This NDA contains studies conducted with IRF, MRF as well as Autogel formulations. The NDA is mostly paper submission & certain portion is electronic (CRF, labeling, few data sets). The proposed commercial formulation has been used in pivotal efficacy studies (E28-52030-717) and E-54-52030-81).

The starting dose strength of lanreotide Autogel 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.

Data from 5 different studies were used to evaluate the bioavailability of lanreotide Autogel. The critical study with the intended market formulation is A-93-5200-149. No change in formulation was made from Phases 2 to 3. Several PK and PD studies are included in the submission. Radioimmunoprecipitation assays (RIA) methodologies for determination of lanreotide in human biomaterial has been developed and validated.

Conclusions: The Clinical Pharmacology section of this application is filable.

Comments to sponsor:

- Please submit the pivotal PK and PD study reports electronically.
- Population PK/PD Analysis: Submit data sets as follows:
Please submit the following datasets to support the population PK/PD analysis of studies A 47 52030 705, E88 52030 044, and 52030 ST8065.

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets, i.e. PK/PD data from the non-responders should also be included in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Please submit longitudinal PK, efficacy, and safety data from all available studies in order for us to perform exposure-response modeling.

Longitudinal data

The longitudinal data (at all available time points) from should be submitted in the following format:

Efficacy data format

Study number (integer), Patient number (integer), dose group (dose received in mg or mg/kg), Treatment group, Visit number (including dropout visit) (integer), elapsed time since first dose (hr), plasma concentration (CP), AUC_{ss}, C_{ss}, GH, IGF-1, responder status(0=non responder, 1=responder), and covariates

Sample of efficacy data structure

PATNO	STUDY	DOSE	GROUP	VISIT	TIME	CP	AUC _{ss}	C _{ss}	GH	IGF-1	Responder
1	1	X	1	0	0	0	45	4.5	9.1	2.3	0
1	1	X	1	1	2	15	45	4.5	2.1	1.2	1
2	2	Y	2	0	0	0	76	3	7.6	1.0	0
2	2	Y	2	2	3	30	76	3	7.6	4.2	0
3	3	Z	1	0	0	0	23	7	10.0	5.3	0
4	4	X	2	0	0	0	33	8	2.0	3.4	1
...											

Adverse event data format

Study number (integer), Patient number (integer), dose group (dose received in mg or mg/kg), Treatment group, Visit number (including dropout visit) (integer), elapsed time since first dose (hr), AUC_{ss} , C_{ss} , Adverse events (0=no, 1=yes), diarrhea, abdominal pain, and covariates.

Sample of adverse event data structure

PATNO	STUDY	DOSE	GROUP	AUC_{ss}	C_{ss}	AE	Diarrhea	Abdominal pain			
1	1	X	1	45	4.5	0	0	0			
2	1	X	1	76	4	1	0	1			
3	2	Y	2	23	5	1	1	1			
4	2	Y	2	33	4	0	0	0			
5	3	Z	1	42	7	1	1	0			
6	4	X	2	11	8	1	0	1			
...											

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

/s/

Jayabharathi Vaidyanathan
7/13/2007 04:33:23 PM
BIOPHARMACEUTICS

Hao Zhu
7/13/2007 04:35:17 PM
BIOPHARMACEUTICS

Sally Choe
7/13/2007 05:33:08 PM
BIOPHARMACEUTICS

Jogarao Gobburu
7/13/2007 06:09:35 PM
BIOPHARMACEUTICS

12/22/06

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-074	Brand Name	Somatuline Autogel
OCP Division	2	Generic Name	Lanreotide acetate
Medical Division	DMEP	Drug Class	Somatostatin analog
OCP Reviewer	Jayabharathi Vaidyanathan, Ph.D.	Indication(s)	Treatment of Acromegaly
OCP Team Leader (Acting)	Jim Wei, Ph.D.	Dosage Form	60/90/120 mg Subcutaneous injection
		Dosing Regimen	QD
Date of Submission	10/30/06	Route of Administration	Subcutaneous injection
Estimated Due Date of OCP Review	7/16/07	Sponsor	Beaufour Ipsen Pharma
PDUFA Due Date	8/30/07	Priority Classification	Standard
Division Due Date	7/26/07		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	10		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:		4		
multiple dose:		2		
Patients-				
single dose:				
multiple dose:		1		
Dose proportionality -				
fasting / non-fasting single dose:		1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:		1		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:							
geriatrics:		1					
renal impairment:		1					
hepatic impairment:		2					
PD:							
Phase 2:							
Phase 3:							
PK/PD:							
Phase 1 and/or 2, proof of concept:		11					
Phase 3 clinical trial:							
Population Analyses -							
Data rich:							
Data sparse:							
II. Biopharmaceutics							
Absolute bioavailability:		1					
Relative bioavailability -							
solution as reference:							
alternate formulation as reference:							
Bioequivalence studies -							
traditional design; single / multi dose:							
replicate design; single / multi dose:							
Food-drug interaction studies:							
Dissolution:							
(IVIVC):							
Bio-wavier request based on BCS							
BCS class							
III. Other CPB Studies							
Genotype/phenotype studies:							
Chronopharmacokinetics							
Pediatric development plan							
Literature References							
Total Number of Studies		37					
Filability and QBR comments							
	"X" if yes	Comments					
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable)					
Comments sent to firm ?		Yes.					
QBR questions (key issues to be considered)	1) What are the PK characteristics of lanreotide from the Autogel formulation? 2) Is the dose and dosing regimen appropriate? 3) What are the PD properties of lanreotide Autogel?						
Other comments or information not included above							
Primary reviewer Signature and Date	Jaya bharathi Vaidyanathan, Ph.D.						
Secondary reviewer Signature and Date	Jim Wei, Ph.D.						

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Sample of efficacy data structure

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1	1	X	1	0	0	0	45	4.5	9.1	2.3	0
1	1	X	1	1	2	15	45	4.5	2.1	1.2	1
2	2	Y	2	0	0	0	76	3	7.6	1.0	0
2	2	Y	2	2	3	30	76	3	7.6	4.2	0
3	3	Z	1	0	0	0	23	7	10.0	5.3	0
4	4	X	2	0	0	0	33	8	2.0	3.4	1
...											

Adverse event data format

Study number (integer), Patient number (integer), dose group (dose received in mg or mg/kg), Treatment group, Visit number (including dropout visit) (integer), elapsed time since first dose (hr), AUC_{ss}, C_{ss}, Adverse events (0=no, 1=yes), diarrhea, abdominal pain, and covariates.

Sample of adverse event data structure

PATNO	STUDY	DOSE	GROUP	AUC _{ss}	C _{ss}	AE	Diarrhea	Abdominal pain			
1	1	X	1	45	4.5	0	0	0			

2	1	X	1	76	4	1	0	1			
3	2	Y	2	23	5	1	1	1			
4	2	Y	2	33	4	0	0	0			
5	3	Z	1	42	7	1	1	0			
6	4	X	2	11	8	1	0	1			
...											

Attachments (List of studies):

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MODULE 5 CLINICAL STUDY REPORTS***

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
5	Module 5 Note to Reviewer	1	99 of 330	
5.1	TABLE OF CONTENTS OF MODULE 5	1	99 of 330	
5.2	TABULAR LISTINGS OF ALL CLINICAL STUDIES	1	99 of 330	
5.3	CLINICAL STUDY REPORTS	1	99 of 330	
5.3.1	Reports of Biopharmaceutic studies	1	99 of 330	
5.3.1.1	Bioavailability study reports	1	99 of 330	
	A-93-52030-149 Pharmacokinetic study of lanreotide Autogel (60, 90 and 120 mg) administered to healthy subjects via deep subcutaneous route	1	99 of 330	Case Report Forms Datasets
5.3.1.2	Comparative Bioavailability and Bioequivalence Study Reports	5	103 of 330	
	E-54-52030-038 Randomised, parallel, and double-blind phase I study in healthy volunteers, testing slow-release Autogel formulations of the somatostatin analogue lanreotide	5	103 of 330	Datasets
	00/PKR/75 Lanreotide serum levels prediction after repeated administration of lanreotide Autogel at doses of 60, 90 and 120 mg.	9	107 of 330	
	E-33-52030-032 Randomised, parallel, controlled, double-blind phase I study of the pharmacokinetics, the pharmacodynamics, and the safety profile of the new slow release "Autogel" formulation of the somatostatin analogue lanreotide, compared with the reference "LP" formulation, in healthy volunteers.	10	108 of 330	Case Report Forms
	E-92-52030-175 Part A: Tolerance, PK, linearity & absolute bioavailability study of lanreotide after 3 single s.c. administrations and 1 single i.v. administration Part B: Lanreotide P.R. tolerance and PK study after a single i.m. administration	10	108 of 330	
	E-92-52030-180 Pharmacokinetic profile of the somatostatin analogue BIM-23014 in acromegalic patients: absolute bioavailability and multiple dose administration of the slow-release formulation	10	108 of 330	Case Report Forms

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	E-92-52030-001 A pharmacokinetic study in healthy volunteers with two semisolid formulations of the somatostatin analogue lanreotide	10	108 of 330	
5.3.1.3		11	109 of 330	
	/ / /	11	109 of 330	
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies	11	109 of 330	
	95/PKS/015 Validation of radioimmunoassay lanreotide in human serum	11	109 of 330	
	03/PKS/097 Validation of lanreotide radioimmunoassay in human serum from Japanese population	11	109 of 330	
	94/PKS/12 Validation of RIA Somatoline in human serum not diluted with rat serum	11	109 of 330	
	P98815 Validation of a radioimmunoassay for the determination of lanreotide in human serum	12	110 of 330	
	95/PKS/017 Validation of RIA lanreotide in human urine	12	110 of 330	
	02/PKS/023 Validation of lanreotide radioimmunoassay in human urine	12	110 of 330	
	95/PKS/39 Validation of RIA of lanreotide in human plasma	13	111 of 330	
	GUMC 0001 Validation of — radioimmunoassay for human plasma samples	13	111 of 330	
	GUMC 0002 Validation of antibody stock MD-1 used in the angiopeptin radioimmunoassay for human plasma samples	13	111 of 330	
	Development and validation of a radioimmunoassay for a somatostatin analogue, lanreotide	13	111 of 330	

*** Elements of this Module are provided in electronic format in the 'mS' folder of the electronic portion of the Application. Electronic elements can be accessed through the series of hyperlinks in the file *ndatoc.pdf*.

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
5.3.2	<i>Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials</i>	14	112 of 330	
5.3.2.1	<i>Plasma Protein Binding Study Reports</i>	14	112 of 330	
	23014 Ph 136 Study of plasma binding of lanreotide	14	112 of 330	
5.3.2.2	<i>Reports of Hepatic Metabolism and Drug Interaction Studies</i>	14	112 of 330	
5.3.2.3	<i>Reports of Studies Using Other Human Biomaterials</i>	14	112 of 330	
	RO-10 Comparative in vitro somatostatin receptor subtype binding profiles	14	112 of 330	
	23014 Ph 135 Effect of BIM 23014C on platelet aggregation and release of beta-thromboglobulin	14	112 of 330	
5.3.3	<i>Reports of Human Pharmacokinetic (PK) Studies</i>	14	112 of 330	
5.3.3.1	<i>Healthy Subject PK and Initial Tolerability Study Reports</i>	14	112 of 330	
	E-55-52030-047 Phase I, single-blind, local tolerability of lanreotide Autogel (BIM 23014) after single 60, 90 and 120 mg subcutaneous injections at three different sites in healthy male volunteers	14	112 of 330	Case Report Forms Datasets
	E-92-52030-010 Study on the pharmacokinetic linearity of the somatostatin analogue BIM-23014 in healthy volunteers	17	115 of 330	
	E-92-52030-014 Multiple dose administration study of the somatostatin analogue lanreotide acetate (BIM-23014C) in healthy volunteers	17	115 of 330	
	E-54-52030-134 Lanreotide pharmacokinetics and elimination following continuous s.c. infusion for 5 days in healthy volunteers	17	115 of 330	
	E-54-52030-067 Part A: Tolerance and pharmacokinetic study of lanreotide (BIM 23014) after one single 3mg subcutaneous administration. Part B: Lanreotide slow release formulation pharmacokinetic study after single 30 mg intramuscular administration in twelve normal healthy volunteers	18	116 of 330	

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	E-54-52030-093 Pilot study of the kinetics of lanreotide acetate (40 mg) in autogel form after a single intramuscular injection in healthy volunteers	18	116 of 330	
	E-92-52030-035 A pharmacokinetic study in healthy volunteers following a single subcutaneous or intramuscular administration of a prolonged release semisolid formulation of the somatostatin analogue BIM23014	18	116 of 330	
	E54-52030-029 Open phase I study of lanreotide (30 mg) kinetics, after one intramuscular injection in 12 healthy volunteers. A monocentre, open, non comparative study, carried out on healthy volunteers	19	117 of 330	
	E-54-52030-098 Pilot study of lanreotide acetate (30 mg) pharmacokinetics after one single intramuscular injection in healthy volunteers	20	118 of 330	
	E-92-52030-176 Part A: Tolerance and pharmacokinetic study of Lanreotide (BIM 23014) after a single intravenous administration Part B: Lanreotide prolonged release formulation: tolerance and pharmacokinetic study after a single intramuscular administration	21	119 of 330	
	E-54-52030-086 A pilot study on the kinetics of lanreotide (30 mg) administered intramuscularly as a single dose in the healthy volunteer	21	119 of 330	
	E-92-52030-177 / 178 Study of the pharmacokinetic parameters of BIM23014 (slow-release formulation) and of the pharmacodynamic effect on IGF-1 after a single administration in healthy volunteers	22	120 of 330	
	E-54-52030-040 Open phase I study of lanreotide (60 mg) kinetics, after one intramuscular injection in 12 healthy volunteers	22	120 of 330	

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	E-28-52030-051 Open labeled phase I monocentre study of lanreotide (60 mg) kinetics, after a single intramuscular injection in 12 healthy subjects	22	120 of 330	
	E-54-52030-106 Pharmacokinetic of lanreotide acetate (60 mg) after a single intramuscular injection in healthy volunteers - an open - labeled phase I study	22	120 of 330	<i>Case Report Forms</i>
	E-54-52030-092 Pilot study of the kinetic properties of lanreotide acetate (40 mg) after two intramuscular injections in healthy volunteers	23	121 of 330	
	E-92-52030-016 / 019 Pharmacokinetic study in healthy volunteers: administration of a new release formulation of the somatostatin analogue BIM-23014 (Parts I & II)	24	122 of 330	
	E-54-52030-082 Study of the pharmacokinetic properties and tolerance levels of lanreotide pamoate administered as a single dose to a healthy subject	25	123 of 330	
	E-54-52030-088 Pilot study of the kinetics of lanreotide pamoate (40 mg), after two intramuscular injections in healthy volunteer subjects	26	124 of 330	
	E-54-52030-091 Lanreotide slow release formulation pharmacokinetic study after two intramuscular administrations in twelve healthy volunteers	27	125 of 330	<i>Case Report Forms</i>
5.3.3.2	<i>Patient PK and Initial Tolerability Study Reports</i>	28	126 of 330	
	E-28-52030-076 Phase II, randomized, parallel groups, double-blind pharmacokinetic study of lanreotide Autogel (60, 90 or 120 mg) after 4 deep subcutaneous injections (administered every 28 days) in acromegalic patients	28	126 of 330	<i>Datasets</i>
	E-92-52030-017 A pharmacokinetic study in acromegalic patients: a single administration of a prolonged release formulation of the somatostatin analogue BIM-23014	33	131 of 330	

Module/ Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	E-92-52030-096 A pharmacokinetic study in acromegalic patients: multiple dose administration of the prolonged release formulation of the somatostatin analogue BIM-23014.	33	131 of 330	Case Report Forms
	E-92-52030-179 Evaluation of the efficiency (clinical and laboratory parameters) and safety of BIM 23014 (prolonged-release formulation) in patients with active acromegaly. Study of pharmacodynamic and pharmacokinetic parameters	34	132 of 330	Case Report Forms
5.3.3.3.	<i>Intrinsic Factor PK Study Reports</i>	35	133 of 330	
	E-92-52030-011 Pharmacokinetic profile of the somatostatin analogue lanreotide in patients suffering from severe chronic renal insufficiency	35	133 of 330	
	E-38-52030-701 Pharmacokinetic profile of the somatostatin analogue BIM 23014 (lanreotide) in healthy volunteers and patients suffering from chronic impairment of hepatic function	35	133 of 330	Case Report Forms
	E-92-52030-013 Pharmacokinetic profile of the somatostatin analogue lanreotide in patients suffering from hepatic insufficiency	35	133 of 330	
	E-92-52030-012 Pharmacokinetic profile of the somatostatin analogue lanreotide in elderly subjects	35	133 of 330	
	E-55-52030-146 Phase I, single centre, randomised, double-blind, cross-over, placebo controlled study, to show the pharmacokinetic equivalence and to assess the tolerance of lanreotide immediate release formulation 7 mcg/kg administered as intravenous infusion to Caucasian and Japanese healthy volunteers	36	134 of 330	

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	2 SS 52030 162 A phase I, single centre, randomised, double-blind, cross-over study to determine the absolute bioavailability, the pharmacokinetic profile, the safety and tolerability of lanreotide immediate release formulation administered by short i.v. infusion at 7 mcg/kg and by s.c. administration at 7, 21 and 42 mcg/kg in Japanese male healthy volunteers	37	135 of 330	
	E-47-52030-607 A phase I, open multicentre study of the pharmacokinetics and safety of a somatostatin analogue lanreotide in hepatic impaired patients (UK LAN 96-125)	37	135 of 330	Case Report Forms
	06/PKR/033 Effect of race or ethnicity on the pharmacokinetics of lanreotide after repeated deep s.c. administration of lanreotide Autogel (60, 90, or 120 mg) every 28 days in acromegalic patients included in clinical study E-28-52030-717	37	135 of 330	
5.3.3.4	Extrinsic Factor PK Study Reports	37	135 of 330	
	Drug-drug interactions associated with the somatostatin octapeptide analogs lanreotide and octreotide: a review of current scientific literature	37	135 of 330	
5.3.3.5	Population PK Study Reports	37	135 of 330	
5.3.4	Report of Human Pharmacodynamic (PD) Studies	38	136 of 330	
5.3.4.1	Healthy Subject PD and PK/PD Study Reports	38	136 of 330	
	E-54-52030-132 Evaluation in healthy volunteers of the pharmacodynamic effects of BIM 23014, administered s.c. in single injection at increasing doses (125,250,500 mcg) or in continuous infusion (pump) at a dose of 2000mcg, on nocturnal secretion of GH (spontaneous or GH-RH stimulated), digestive hormones (motilin, secretin, pancreas polypeptide) and TSH	38	136 of 330	
	E-92-52030-173 Evaluation of the effect of BIM 23014, administered in a single dose of 1000 mcg by s.c. route on tolerance to carbohydrates, cortisol, and plasma GH, in orally induced hyperglycaemia in healthy volunteers in comparison with a placebo. Study of the PK parameters	38	136 of 330	

Module/ Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	E-92-52030-174 Evaluation of the effect of BIM 23014, administered in a single increasing dose (1000 - 2000 - 3000 mcg/24h) by continuous subcutaneous route (pump), on tolerance to carbohydrates and plasma GH in healthy volunteers in comparison with placebo. Study of the pharmacokinetic parameters	39	137 of 330	
	E-54-52030-135 Comparisons of efficacy (pharmacokinetics and pharmacodynamics) after subcutaneous injections of 2 doses of 2 batches of angiopeptin: a randomized, double blind study	40	138 of 330	
	E-54-52030-133 Evaluation of the effect of continuous s.c. administration (pump) of BIM23014 at 2000 mcg/24h for 7 days on carbohydrate tolerance determined during orally induced hyperglycaemia and on IGF-1, pancreatic polypeptide, motilin and plasma GIP in healthy volunteers compared with placebo	40	138 of 330	
	E-47-52030-147 A phase I, single-blind, placebo controlled, cross-over study investigating the safety and effect of Somatuline SR on gastric acid output in healthy volunteers	41	139 of 330	
	E-92-52030-005 A clinical trial in healthy volunteers: effects of the slow-release formulation of the somatostatin analogue BIM-23014 on renal haemodynamics	41	139 of 330	
	E-47-52030-154 A phase I, single blind, placebo controlled, cross-over study investigating efficacy and pharmacokinetics of Somatuline SR in inhibition of exocrine pancreatic responses in healthy human subjects	42	140 of 330	
	E-47-52030-403 A phase I, double blind, randomized, placebo - controlled cross-over study investigating the haemodynamic responses of a long acting somatostatin analogue - lanreotide - upon meal-stimulated splanchnic blood flow in healthy subjects	42	140 of 330	

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	E-54-52030-070 Evaluation of the effect of lanreotide on the digestion of a liquid meal and the duodenal-caecal transit time in healthy volunteers	42	140 of 330	
	E-54-52030-031 Jejunal secretions of water, electrolytes and peptides during immuno-suppression linked to HIV; examination in the basal state and during the administration of an analogue of somatostatin - study in the healthy volunteer	43	141 of 330	
	E-54-52030-109 Pharmacokinetic and pharmacodynamic effects of BIM 23014, a somatostatin analogue, in healthy male subjects (Four-way- cross-over study in 8 subjects)	43	141 of 330	
	E-54-52030-131 Pharmacokinetic and pharmacodynamic effects of BIM 23014, a somatostatin-analogue, in healthy male subjects	44	142 of 330	
	E-54-52030-126 Evaluation in healthy volunteers of the pharmacodynamic effects of BIM 23014, administered subcutaneously in singly injection at increasing doses (0, 125, 250 and 500 micrograms twice daily), on growth hormone secretion	44	142 of 330	
	E-47-52030-408 A phase I, double-blind, randomised, placebo-controlled study investigating the effects of three doses of a somatostatin analogue - lanreotide - upon meal - stimulated renal and splanchnic blood flow in healthy subjects	45	143 of 330	
	E-92-52030-182 A clinical pharmacokinetic study in healthy volunteers: administration of a new immediate release formulation of the somatostatin analogue BIM-23014	46	144 of 330	
	E-47-52030-703 A phase I, open, single centre study of the haemodynamic responses of lanreotide 60 mg on meal-stimulated splanchnic blood flow in healthy volunteers	47	145 of 330	

Module / Section	Report Number / Report Title	Module Volume	Comprehensive Volume	Electronic Elements
	E-47-52030-041 A phase I, double blind, randomized, cross-over study investigating the effects of a somatostatin analogue – lanreotide – on post-prandial splanchnic blood flow when given as a bolus i.v. injection compared to the effects when given as a continuous i.v. infusion in healthy volunteers	47	145 of 330	Case Report Forms
	E-47-52030-508 A phase I, double-blind, randomized placebo-controlled study to investigate the safety and effects of three doses of a somatostatin analogue - lanreotide - on gastric acidity in healthy subjects	48	146 of 330	
	E-47-52030-603 A phase I, open, randomized study investigating the effects of a somatostatin analogue – lanreotide – on vasoactive intestinal peptide-induced jejunal secretion and small intestinal motility (UK LAN 96 – 119)	49	147 of 330	Case Report Forms
5.3.4.2	Patient PD and PK/PD Study Reports	50	148 of 330	
	E-54-52030-127 Suppression of growth hormone secretion and release by BIM 23014 (5 healthy volunteers and 5 acromegalics, 250 and 500 mcg)	50	148 of 330	
	01/PKR/050 Pharmacokinetic and population pharmacokinetic / pharmacodynamic analysis of lanreotide Autogel	50	148 of 330	
	01/PKR/025 Population pharmacokinetic and pharmacodynamic analysis of lanreotide studies A-47-52030-705/88-52030-044 and E-54-52030-065	51	149 of 330	
	E-88-52030-012 Open phase I safety and efficacy study of angiopeptin on glucose, insulin, glucagon and growth hormone levels in patients with diabetes mellitus	52	150 of 330	
	A-93-52030-055 Cross-over, randomized, double blind, placebo-controlled trial to assess the effects of a single administration (0.5 mg) of BIM 23014 on exocrine pancreatic secretion in humans	52	150 of 330	
5.3.5	Reports of Efficacy and Safety Studies	53	151 of 330	

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/s/

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