

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		
Name of Active Ingredient(s): LANREOTIDE (L.N.N.) ACETATE	Volume: Page:	
<p><b>Statistical methods:</b></p> <p>The intent-to-treat (ITT) and safety populations include all randomized patients who received at least one dose of study medication. The per protocol (PP) population includes all randomized patients who received at least one dose of the study medication and who did not have major protocol deviations.</p> <p>Descriptive statistics, including mean, median, standard deviation, coefficient of variation, minimum and maximum values of the serum levels and the pharmacokinetic parameters as well as the confidence intervals at each sampling time (visit) were determined.</p> <p>Two different methodologies for assessing linearity were used (dose-normalized approach and the power model). In order to verify the dose-proportionality of lanreotide autogel at different dose levels, comparison of log-transformed <math>C_{max}</math>, <math>C_{min}</math> and <math>AUC_t</math> normalized by dose was performed at the first administration and comparison of log-transformed <math>C_{min, 75}</math>, <math>C_{max, 55}</math>, <math>C_{avg}</math> and <math>AUC_t</math> normalized by dose was performed at the last drug administration. All comparisons were conducted using analysis of variance (one way ANOVA procedure) taking into account the dose as fixed factor. Statistical significance was declared at <math>p &lt; 0.05</math>. A Scheffé multiple comparison test was performed in order to determine which comparisons among the doses were significant.</p> <p>A non-linear power model was also applied as an alternative method for evaluating linearity, fitting a linear relationship between log-transformed parameters and log dose. The key feature of the power model is the assumption of linearity between log-transformed values of parameters and doses. The mean slope of the log-transformed parameters against log dose were estimated and the corresponding 95% confidence intervals were constructed. The estimate of slope together with its 95% confidence intervals are presented to quantify the degree of non-proportionality.</p> <p>No primary efficacy endpoint was defined for this pharmacokinetic study. Secondary efficacy endpoints including the proportion of patients with mean GH <math>\leq 2.5</math> ng/mL and <math>\leq 5.0</math> ng/mL, normalized IGF-1, and changes from Baseline in mean GH and IGF-1 are tabulated for both the ITT and PP populations; changes from Baseline in acromegaly symptoms are analyzed only for the ITT population.</p> <p>All safety tabulations are based on the safety population and were descriptive in nature; no formal statistical testing was conducted.</p> <p><b>Summary - conclusions:</b></p> <p><u>Baseline data:</u></p> <p>The study population was comprised of 12 women (67%) and 6 men (33%); median age was 41.5 years with a range of 28 to 67 years. Sixteen (89%) of the 18 patients were Caucasian and 2 (11%) were Black.</p> <p>Median serum GH and IGF-1 levels at baseline were 25.4 and 747.0 ng/mL, respectively.</p>		

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Pharmacokinetic results:

The single dose pharmacokinetics of lanreotide autogel were dose-independent in the dose range 60 to 120 mg. Dose proportionality was observed in the pharmacokinetic parameters  $C_{min,1}$ ,  $C_{max}$  and  $AUC_T$ . With  $C_{min,1}$  values of 0.725, 0.973 and 1.406 ng·mL<sup>-1</sup>;  $C_{max}$  values of 1.650, 3.543 and 3.053 ng·mL<sup>-1</sup>; and  $AUC_T$  values of 22.27, 37.29 and 48.49 ng·mL<sup>-1</sup>·d obtained for the 60, 90 and 120 mg doses, respectively.

Lanreotide autogel exhibited linear pharmacokinetics after repeated doses over the range of 60 to 120 mg administered once every 28 days. Pharmacokinetic parameters  $C_{min,ss}$ ,  $C_{max,ss}$  and  $AUC_T$  increased in a dose-dependent linear manner.  $C_{min,ss}$  values of 1.822, 2.511 and 3.762 ng·mL<sup>-1</sup>;  $C_{max,ss}$  values of 3.821, 5.694 and 7.685 ng·mL<sup>-1</sup>; and  $AUC_T$  values of 68.79, 85.11 and 126.66 ng·mL<sup>-1</sup>·d were obtained for the 60, 90 and 120 mg doses, respectively. During the dosing interval, average steady state concentrations ( $C_{avg}$ ) of 2.457, 3.040 and 4.523 ng·mL<sup>-1</sup> were observed for the 60, 90 and 120 mg dose levels, respectively.

Four consecutive lanreotide autogel administrations produce a slight accumulation in the body independent of the dose level, with a mean accumulation index of approximately 2.7. This accumulation result is not unexpected considering the long half-life of lanreotide.

Peak-trough fluctuation (PTF) during the dosing interval was dose-independent in the dose range 60 to 120 mg, with values of 81, 108 and 86% for 60, 90 and 120 mg, respectively.

Negligible initial burst release and overall control over entire releases after single and multiple doses at the 3 dose levels (60, 90 and 120 mg) demonstrated the robustness of formulation drug release.

Efficacy results:

None of the 18 patients had mean GH ≤ 5.0 ng/mL or normalized IGF-1 (age-adjusted) at study baseline. At the end of the study (day 112), 6 (33%) of the 18 patients had mean GH levels ≤ 5.0 ng/mL, including 2 of 6 patients in the 60 mg group, 1 of 6 in the 90 mg group and 3 of 6 in the 120 mg group. Three (17%) of the 18 patients (17%) had mean levels ≤ 2.5 ng/mL; all 3 had received lanreotide 120 mg, and 5 patients (28%) had normalized IGF-1 levels, including 1 of 6 in each of the 60 and 90 mg groups and 3 of 6 in the 120 mg group. Three (17%) of the 18 patients had both mean GH ≤ 2.5 ng/mL and normalized IGF-1 (age-adjusted) by day 112; all 3 of these patients had received lanreotide 120 mg.

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

More than half of the 18 patients showed improvement by day 112 in the acromegaly

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<p>symptoms of perspiration (78% with improvement), swelling of extremities (61%), and headache (56%) and one-third or more showed improvement in fatigue (44%) and joint pain (33%).</p> <p><u>Safety results:</u></p> <p>All 18 patients experienced at least one adverse event during the study. The most commonly reported events were diarrhea (8 patients, 44%), flatulence (6, 33%), nausea (4, 22%), abdominal pain (3, 17%), vomiting (3, 17%), headache (3, 17%), constipation (2, 11%) and cholelithiasis (2, 11%). The latter events were reports of biliary sludge noted on gallbladder ultrasound for 2 patients in the lowest lanreotide dose group (60 mg). All other events were reported in only one patient each. There did not appear to be an increase in incidence of any adverse event across lanreotide dose.</p> <p>The majority of adverse events were mild to moderate in severity. Only one patient experienced an event (headache) that was assessed as severe in intensity by the investigator. There were no deaths or treatment-emergent serious adverse events reported during the study and no patients withdrew from the study due to adverse events.</p> <p>There were no clinically significant changes noted in clinical laboratory parameters, including hematology or chemistry, for any dose group or across all 18 patients. As well, no clinically significant changes were noted over time on study for any vital signs parameters. The presence of putative antibodies to lanreotide autogel was observed in one of the 18 patients in a sample obtained prior to study treatment. The sponsor confirmed that this patient had not received previous treatment with lanreotide; prior therapy with short-acting octreotide was reported.</p> <p>Based on centralized analysis of ECG and echocardiography data with review by a board certified cardiologist, electrocardiographic and echocardiographic analysis was unremarkable. Mean quantitative cardiac electrophysiologic and cardiac chamber dimensions were within normal ranges for the population and did not appear to exhibit any change over time. Valvular regurgitations were typical of those commonly seen in a general population and did not appear to show any change over time.</p> <p><u>Conclusion:</u></p> <p>In conclusion, the single-dose pharmacokinetics of lanreotide were dose-independent in the dose range 60 - 120 mg. Lanreotide autogel exhibited linear pharmacokinetics after repeated doses over the range of 60 to 120 mg administered once every 28 days. A slight accumulation of lanreotide in the body was observed at all dose levels, with mean accumulation index of ~2.7. These accumulation results are not unexpected values, considering the long half-life of lanreotide. Peak-trough fluctuation was dose-independent. Negligible initial burst release and overall control over entire releases was observed after single and multiple doses at the 3 dose levels demonstrating the robustness of the formulation.</p>		

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<p>Laureotide autogel, at doses of 60, 90 and 120 mg, effectively reduced mean serum GH and IGF-1 levels in ~ one-third of patients after 4 administrations separated by 28 days with a clear trend toward a dose-response relationship. As the patient sample size was limited, dose adaptation was not allowed, and duration of treatment was limited, as planned, no definitive efficacy conclusions can be drawn. Full assessment of lanreotide autogel efficacy should be based on larger and longer term studies.</p> <p>These 3 dose levels of lanreotide autogel were safe and well tolerated in a small number of patients with active acromegaly.</p> <p>Date of the report: 09 January 2003</p>		

**APPEARS THIS WAY  
ON ORIGINAL**

**Study E-54-52030-038**

<b>Name of company</b> Ipsen Biotech	<b>INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF THE DOSSIER</b>	<b>FOR NATIONAL AUTHORITY USE ONLY</b>
<b>Name of finished product</b> Lanreotide autogel		
<b>Name of active ingredient</b> Lanreotide	<b>Volume :</b>	<b>Page:</b>
<b>Study title:</b> Randomised, parallel, and double-blind phase I study in healthy volunteers, testing slow-release autogel formulations of the somatostatin analogue lanreotide		
<b>Investigators:</b> _____		
<b>Study centre(s):</b> _____		
<b>Publication (reference):</b> -		
<b>Studied period:</b> 112 days	<b>Clinical Phase:</b> Phase I	
<b>Date of first enrolment:</b> 30 October 1997		
<b>Date of last completed:</b> 15 June 1998		
<b>Study description:</b> Pharmacokinetics of lanreotide following the single administration of one of 7 different treatments/routes of administration of lanreotide autogel in 42 healthy volunteers (6 volunteers per treatment/route of administration).		
<b>Interaction analysis of lanreotide with ciclosporin and vitamin K</b>		
<b>Objectives:</b>		
<b>Primary objectives:</b>		
1) Evaluation of the linearity of the pharmacokinetics of lanreotide autogel following single i.m. injection of 60, 90 and 120 mg using 0.246 mg lanreotide/mg autogel formulation.		
2) Comparison of the pharmacokinetic profiles of lanreotide autogel 60 mg using the formulations containing _____ (i.m. and s.c. routes), 0.246 (i.m. and s.c. routes) and _____ (i.m. route) mg/mg lanreotide.		
3) Evaluation of the absolute bioavailability and disposition function of the lanreotide autogel formulations administered by subcutaneous and intramuscular route, with reference to an intravenous bolus of a lanreotide solution.		

<p><b>Objectives (continued):</b>  <b>Secondary objectives:</b></p> <ol style="list-style-type: none"> <li>1) Evaluation of the local and systemic tolerance and safety of lanreotide autogel.</li> <li>2) Evaluation of the pharmacokinetic interaction potential of lanreotide with ciclosporin and vitamin K. Results of the interaction study are presented in a separate report.</li> </ol>
<p><b>Methodology:</b> Parallel, randomised, double-blinded administration of different slow-release lanreotide autogel treatments as single s.c. or i.m. injection to healthy volunteers after administration of a single i.v. bolus of lanreotide to all volunteers.</p>
<p><b>Number of subjects:</b> 42 healthy volunteers (6 volunteers for each lanreotide autogel treatment).</p>
<p><b>Diagnosis and criteria for inclusion:</b> healthy volunteers from 18 to 45 years of age</p>
<p><b>Test product, dose and mode of administration, batch N°:</b>  Lanreotide 1 mg i.v., batch N° E001 (releasing numbers: FBNP)  Lanreotide autogel — mg/mg 60 mg s.c. and i.m., batch N° N70051  Lanreotide autogel 0.246 mg/mg 60 mg s.c. and i.m., batch N° N70050  Lanreotide autogel 0.246 mg/mg 90 mg i.m., batch N° N70052  Lanreotide autogel 0.246 mg/mg 120 mg i.m., batch N° N70053  Lanreotide autogel — mg/mg 60 mg i.m., batch N° N61007  Lanreotide placebo, batch N° F002 (releasing number FBNQ)</p>
<p><b>Duration of treatment:</b> 1) single doses of lanreotide solution i.v. bolus, 2) single doses of s.c. or i.m. lanreotide autogel injection.</p>
<p><b>Reference therapy, dose and mode of administration, batch N°:</b> n.a.</p>
<p><b>Criteria for evaluation:</b>  <b>Pharmacokinetics of lanreotide:</b> Main absorption and disposition parameters (<math>C_0</math>, <math>C_{max}</math>, <math>t_{max}</math>, <math>AUC_{last}</math>, <math>AUC_{inf}</math>, <math>k_e</math>, <math>F</math>, <math>CL</math>, <math>CL/F</math>, <math>V_z</math>, <math>V_{ss}</math>, <math>t_{1/2}</math>, <math>t_{1/2\alpha}</math>, <math>t_{1/2\beta}</math>, <math>t_{1/2\gamma}</math>, <math>MRT_{last}</math>, <math>MRT_{inf}</math>)  <b>Safety:</b> Local and systemic tolerance, standard biochemical and haematological analyses, physical examination, ECG</p>
<p><b>Statistical methods:</b> Non-parametric statistical tests (Kruskal-Wallis) were used to assess treatment differences in the pharmacokinetic parameters estimates for each treatment.  Results of laboratory safety measurements were expressed as percent change between Day 21 and pre-study (baseline) values and between post-study and pre-study (baseline) values. A paired t-test was performed to assess whether these percent changes were significantly different from 0.</p>

## SUMMARY - CONCLUSIONS:

### Pharmacokinetic results:

The lanreotide release profiles after the administration of lanreotide autogel are similar for all tested formulations (0.246, 0.205 mg/mg), routes of administration (i.m. (paraumbilical) or s.c. (paraumbilical)), and doses (60, 90 and 120 mg), except for lanreotide autogel 0.205 mg/mg 60 mg administered i.m., which elicited a different profile with a quicker release of lanreotide.

The absolute bioavailability of lanreotide after i.m. or s.c. administration of lanreotide autogel is of approximately 60 to 70 % for all tested formulations, routes of administration, and doses.

The terminal half-life of lanreotide after i.m. or s.c. administration of lanreotide autogel is approximately 4 weeks with all tested formulations, routes of administration, and doses, except after the i.m. administration of lanreotide autogel 0.205 mg/mg ( $t_{1/2}$  of  $12 \pm 4$  days).

A linear relationship is observed between the 60, 90 and 120 mg doses of lanreotide autogel 0.246 mg/mg i.m. and the measured lanreotide levels.

The formulation of lanreotide autogel does not influence the pharmacokinetic profile of lanreotide, except for the 0.205 mg/mg formulation which, when administered i.m., releases lanreotide more rapidly than after its s.c. administration.

In general, there is no marked influence of the route of administration (s.c. or i.m.) on the pharmacokinetic profile of lanreotide. However, the i.m. administration of lanreotide autogel 0.205 mg/mg 60 mg elicited a release of lanreotide of markedly shorter duration than with all other treatments.

The "apparent elimination" half life appears to be slightly longer in females than in males. The pharmacokinetic profile after the i.m. administration in females tends to be close to the ones observed after s.c. administration in males.

In 2 volunteers after the i.m. administration of 2 different formulations (0.205 mg/mg and 0.246 mg/mg) of lanreotide autogel 60 mg, lanreotide release is characterized by an abnormally high  $C_{max}$  and a short duration.

### Safety results:

Local and systemic tolerance after the extra-vascular administration of lanreotide autogel is good.

Local tolerance is better after the i.m. than after the s.c. administration of lanreotide autogel, with rare occurrences of redness, swelling, tenderness and indurations. Redness, swelling and tenderness are more rare and of lesser intensity after the s.c. administration of lanreotide autogel when compared to placebo unloaded PLGA microparticles administered s.c..

The frequency of indurations is equivalent after the paraumbilical s.c. administration of lanreotide autogel and placebo unloaded PLGA microparticles. Indurations were observed in almost all volunteers having received these treatments. Indurations are of greater surface area with placebo unloaded PLGA microparticles administered s.c., but are of much longer duration with lanreotide autogel administered s.c. in the paraumbilical region (9 volunteers still had nodules at the end of the study). No abnormal finding in systemic tolerance was observed with any dose of lanreotide autogel or with any route of administration.

Synopsis (continued)

**Conclusions:**

Lanreotide autogel elicits a prolonged lanreotide release and has a safety profile compatible with the requirements for a slow release formulation of lanreotide with a one month dosing interval.

Lanreotide release profiles are almost log-linear, the inter-individual variability appears to be low, the absolute bioavailability is approximately 60 to 70%, and the terminal half-life approximately 4 weeks.

There is a linearity between the 60, 90 and 120 mg doses (0.246 mg/mg) and the lanreotide serum concentration.

The lanreotide levels observed 29 days after the i.m. administration the 60, 90 and 120 mg doses (0.246 mg/mg) of lanreotide autogel are compatible with its use as a monthly dosing-interval formulation.

The 0.246 mg/mg formulation of lanreotide autogel is an optimum candidate, as it elicits similar lanreotide release profiles following i.m. and s.c. administrations, while the strength required for its injection is compatible with a clinical use.

A deep s.c. route of administration might combine the advantages of both the s.c. and the i.m. routes.

Date of report: 02 December 1998

E-92-52030-011

Name of Sponsor/Company :  / /	Individual Study Table Referring to Part IV A-2	(For national authority use only)
Name of Finished Product :	of the Dossier	
Name of Active Ingredient(s) : LANREOTIDE (I.N.N.) ACETATE	Volume : Page :	
<p><b>Title of study :</b> Pharmacokinetic profile of the somatostatin analogue lanreotide in patients suffering from severe chronic renal insufficiency. <i>(Perfil farmacocinético del análogo de la somatostatina BIM-23014 en pacientes afectados de insuficiencia renal crónica severa. Study code: 95/33. Spanish Ministry of Health).</i> <b>Study Number:</b> E-92-52030-011 (Beaufour-IPSEN Group Code) <b>Study Number:</b> 06-BIM23014-94 / 95/PKS/12</p>		
<b>Investigators :</b>		M <sup>a</sup>
<b>Study centre(s) :</b>		
<b>Publication (reference) :</b> None		
<b>Studied period (years) :</b> 2 Date of first enrolment: 25 / 09 / 1995 Date of last completed: 24 / 07 / 1997	<b>Phase of development :</b> Phase I study (pharmacokinetics, special population)	
<b>Objectives :</b> Following one intravenous bolus injection of 7 µg/kg of lanreotide to healthy volunteers and to patients suffering from severe chronic renal insufficiency, the time courses of serum lanreotide levels were assessed in order to compare between groups the values of the main pharmacokinetic disposition parameters: disposition rate constant ( $\lambda_d$ ), disposition half-life ( $t_{1/2}$ ), initial serum level (C(0)), area under the serum concentration time curve from time 0 to the last experimental time (AUC <sub>t</sub> ), area under the serum time curve from time 0 to infinity (AUC), mean residence time from time 0 to infinity (MRT), serum clearance (CL) and distribution volumes (V <sub>1</sub> , V <sub>z</sub> and V <sub>2</sub> ).		
<b>Methodology :</b> Open label and parallel pharmacokinetic clinical trial, with a control group of		

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healthy subjects.		
Number of patients (planned and analysed) : 13 patients and 12 healthy subjects. One patient (administered by i.v. infusion) was not included in the pharmacokinetic analysis.		
Diagnosis and criteria for inclusion : Severe chronic renal insufficiency (end-stage renal failure requiring haemodialysis).		
Test product, dose and mode of administration, batch number : Lanreotide, 7 µg/kg, i.v. (bolus) injection, batch no. D003.		
Duration of treatment : One intravenous bolus injection.		
Reference therapy, dose and mode of administration, batch number : Not applicable.		
Criteria for evaluation: <u>Pharmacokinetics</u> : The main pharmacokinetic disposition parameters evaluated were: disposition rate constant ( $\lambda_z$ ), disposition half-life ( $t_{1/2}$ ), initial serum level (C(0)), area under the serum concentration time curve from time 0 to the last experimental time ( $AUC_t$ ), area under the serum time curve from time 0 to infinity (AUC), mean residence time from time 0 to infinity (MRT), serum clearance (CL) and distribution volumes ( $V_1$ , $V_d$ and $V_z$ ). <u>Safety</u> : Clinical and laboratory standard examinations.		

**Statistical methods :**

**Pharmacokinetics:** The pharmacokinetic analysis was performed by a non-compartmental approach using the WinNonlin pharmacokinetic program (Scientific Consulting, Inc. 1995, Ver 1.1). The pharmacokinetic values were compared between groups by means of the Student t-test after log-transformation of data. Values of biochemical and haematological parameters were compared within groups (before and after drug treatment) by means of the paired t-test or the Wilcoxon Signed Rank test. The occurrences of adverse events were compared between groups by means of the Fisher exact test,  $P < 0.05$  was considered statistically significant.

**SUMMARY - CONCLUSIONS :**

**PHARMACOKINETIC RESULTS :** The main pharmacokinetic results are shown in the following table.

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	0.0196
$t_{1/2}$ hr	1.32	0.68	2.39	1.15	0.0015
AUC $ng.ml^{-1}.hr$	32.30	11.18	62.95	33.87	0.0020
MRT h	0.65	0.48	0.77	0.20	NS
CL $l.hr^{-1}.kg^{-1}$	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
$V_z$ $l.kg^{-1}$	0.458	0.289	0.442	0.205	NS

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

Statistically significant differences between the two population groups were found in most of the pharmacokinetic parameters analysed (except in  $V_{ss}$ ,  $V_z$  and MRT). As related to the values obtained in healthy subjects, total serum clearance values in patients with severe chronic renal insufficiency decreased by a factor of about 2. Conversely, values of  $t_{1/2}$  and AUC increased in patients with severe chronic renal insufficiency as compared with the corresponding values in healthy volunteers.

**SAFETY RESULTS :** Adverse events were recorded in 8 patients and in 6 healthy subjects. All events recorded were not serious. Their intensities were reported as mild or moderate and were related to the study medication according to the investigator's criteria. A great number of events were of gastrointestinal or vasomotor origins.

In relation to baseline, the i.v. bolus of 7  $\mu g/kg$  of lanreotide to chronic renal insufficient patients induced a clinically and statistically significant increase of diastolic blood pressure (with a concomitant decrease of heart rate values) at 5 and 10 minutes after the administration. The treatment did not lead to clinically significant changes in the laboratory parameters.

**CONCLUSION :**

A reduction in the total serum clearance and an increased half-life were observed in patients with severe chronic renal insufficiency treated with one single intravenous injection of 7  $\mu g/kg$  of lanreotide.

Date of the report : 24 August 1998

E-92-52030-012

Name of Sponsor/Company : <hr/>	Individual Study Table	(For national authority use only)
Name of Finished Product :	Referring to Part IV A-2 of the Dossier	
Name of Active Ingredient(s) : LANREOTIDE (I.N.N.) ACETATE	Volume : Page :	
<p><b>Title of study :</b> Pharmacokinetic profile of the somatostatin analogue lanreotide in elderly subjects. (<i>Perfil farmacocinético del análogo de la somatostatina BIM-23014 en el anciano. Study code: 95/32. Spanish Ministry of Health.</i>) <b>Study Number:</b> E-92-52030-012 (Beaufour-IPSEN Group Code) <b>Study Number:</b> 07-BIM23014-94 95/PKS/14</p>		
<p><b>Investigators:</b></p> <p>/ / / / /</p>		
<p><b>Study centre(s) :</b></p> <p>/ / / / /</p>		
<p><b>Publication (reference) :</b> None</p>		
<p><b>Studied period (years) :</b> 1 Date of first enrolment: 12 / 12 / 1995 Date of last completed: 09 / 02 / 1998</p>		<p><b>Phase of development :</b> Phase I (pharmacokinetics, special population)</p>
<p><b>Objectives :</b> Following one intravenous infusion of <math>7 \mu\text{g}\cdot\text{kg}^{-1}</math> of lanreotide to young healthy volunteers and to elderly subjects, the time courses of lanreotide serum levels were assessed to compare the values of the main pharmacokinetic disposition parameters between the groups: disposition rate constant (<math>\lambda_z</math>), disposition half-life (<math>t_{1/2\lambda_z}</math>), area under the serum</p>		

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concentration time curve from time 0 to the last experimental time (AUC <sub>t</sub> ), area under the serum concentration time curve from time 0 to infinity (AUC), mean residence time from time 0 to infinity following the infusion (MRT <sub>inf</sub> ) and adjusted for the infusion time (MRT <sub>total</sub> ), total serum clearance (CL) and distribution volumes (V <sub>d</sub> and V <sub>z</sub> ).		
<b>Methodology :</b> Open label and parallel pharmacokinetic clinical trial, with a control group of young healthy subjects.		
<b>Number of subjects (planned and analysed) :</b> 13 young and 12 elderly volunteers analysed (planned 12 and 12, respectively).		
<b>Diagnosis and criteria for inclusion :</b> Elderly subjects (over 65 years).		
<b>Test product, dose and mode of administration, batch number :</b> Lanreotide, 7 µg·kg <sup>-1</sup> , i.v. infusion administration, batches D003 and E001.		
<b>Duration of treatment :</b> One intravenous infusion (20 minutes).		
<b>Reference therapy, dose and mode of administration, batch number :</b> Not applicable.		
<b>Criteria for evaluation:</b> <b>Pharmacokinetics:</b> The main pharmacokinetic disposition parameters evaluated were: disposition rate constant ( $\lambda_z$ ), disposition half-life ( $t_{1/2\lambda_z}$ ), maximum serum concentration (C <sub>max</sub> ), time to reach maximum serum concentration (t <sub>max</sub> ), area under the serum concentration time curve from time 0 to the last experimental time (AUC <sub>t</sub> ), area under the serum concentration time curve from time 0 to infinity (AUC), mean residence time from time 0 to infinity (MRT <sub>inf</sub> ) following the infusion and adjusted by the infusion time (MRT <sub>total</sub> ), total serum clearance (CL) and distribution volumes (V <sub>d</sub> and V <sub>z</sub> ).		
<b>Safety:</b> Clinical and laboratory standard examinations.		

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**Statistical methods :**

**Pharmacokinetics:** The pharmacokinetic analysis was performed by a non-compartmental approach using the WinNonlin pharmacokinetic program (Scientific Consulting, Inc. 1995, Ver. 1.1). The statistical comparison of the main pharmacokinetic parameters between groups was performed by means of an unpaired Student t-test, after log-transformation of the data (with exception of  $t_{max}$ ). The U Mann-Whitney test was used in the case of  $t_{max}$ . Values of biochemical and haematological parameters were compared within groups (before and after drug treatment) by means of the paired t-test or the Wilcoxon Signed Rank test.  $P < 0.05$  was considered statistically significant.

**SUMMARY - CONCLUSIONS :**

**PHARMACOKINETIC RESULTS :** The main pharmacokinetic results are shown in the following table.

Parameter	Units	Young			Elderly			P
		MEAN	S.D.	n	MEAN	S.D.	n	
$t_{max}$	hr	0.33	-	13	0.33	-	12	NS
$C_{max}$	ng/ml <sup>-1</sup>	48.46	11.24	13	46.75	14.63	12	NS
$t_{1/2\alpha}$	hr	0.94	0.25	13	1.74	0.73	12	<0.05
AUC	ng·ml <sup>-1</sup> ·hr	26.18	5.50	13	29.17	9.41	12	NS
$V_d$	ml/kg <sup>-1</sup>	378.27	123.34	13	621.23	168.09	12	<0.05
CL	ml/hr <sup>-1</sup> ·kg <sup>-1</sup>	276.78	49.19	13	268.86	105.86	12	NS
MRT <sub>0-∞</sub>	hr	0.52	0.09	13	0.78	0.21	12	<0.05
MRT <sub>0-t</sub>	hr	0.69	0.09	13	0.93	0.21	12	<0.05
$V_{1\beta}$	ml/kg <sup>-1</sup>	146.29	41.48	13	203.33	97.81	12	<0.05

NS: p>0.05  
\* median values

Lanreotide pharmacokinetic profiles were similar within the group of young volunteers, with lanreotide serum levels detected up to 4-6 hours after the end of the infusion. Slightly more inter-individual variability was observed between the elderly subjects, with lanreotide serum levels detected longer, up to 6 to 12 hr after the end of the infusion.

Similar mean peak serum concentrations of lanreotide were observed following the intravenous infusion in both population groups. The corresponding values were  $48.46 \pm 11.24$

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<p>ng.ml<sup>-1</sup> in young volunteers and 48.75 ± 14.63 ng.ml<sup>-1</sup> in elderly subjects, respectively. A similitude between groups was also seen in relation to AUC values: 26.18 ± 5.50 ng.ml<sup>-1</sup>.hr and 29.17 ± 9.41 ng.ml<sup>-1</sup>.hr in young and elderly subjects, respectively.</p>		
<p>Statistically significant differences (P&lt;0.05) were detected when both half-life and MRT<sub>inf</sub> values were compared, with higher values observed in elderly subjects than in young volunteers (t<sub>1/2</sub>: 0.94 ± 0.25 hr in young vs 1.74 ± 0.73 hr in elderly subjects; MRT<sub>inf</sub>: 0.69 ± 0.09 hr in young vs 0.93 ± 0.21 hr in elderly subjects). On the other hand, no significant differences were found in CL values between both population groups (276.76 ± 49.19 ml/hr/kg in young vs 268.86 ± 105.96 (ml·hr<sup>-1</sup>·kg<sup>-1</sup> in elderly). Consequently, the longer elimination half-life in elderly subjects could be attributed to the statistically significant increase in the V<sub>d</sub> observed in the elderly compared to the young (146.29 ± 41.48 ml·kg<sup>-1</sup> in young vs 200.33 ± 97.61 ml·kg<sup>-1</sup> in elderly subjects), rather than to the elimination process. However, caution should be taken due to the greater inter-individual variability observed in the elderly group.</p>		
<p>The statistical comparison of the main pharmacokinetic parameters by gender did not show statistically significant results in elderly subjects.</p>		
<p><b>SAFETY RESULTS :</b> No serious adverse events were observed during or after the i.v. infusion of 7 µg·kg<sup>-1</sup> of lanreotide to young and elderly healthy subjects. The treatment did not lead to clinically significant changes in the laboratory parameters.</p>		
<p><b>CONCLUSION :</b> Lanreotide serum levels after one intravenous infusion of 7 µg·kg<sup>-1</sup> were detected longer in elderly subjects than in young volunteers. The intravenous infusion provided no statistically significant differences in mean C<sub>max</sub>, AUC and CL values of the population groups studied. However, statistically significant differences were found in t<sub>1/2α</sub>, MRT<sub>(0-∞, inf)</sub> and V<sub>d</sub> mean values between both groups, with these parameters being greater in elderly subjects. The greater half-life and MRT<sub>(0-∞, inf)</sub> values obtained in elderly subjects in relation to young volunteers could be attributed to the distribution phase rather than to the elimination process.</p>		
<p>Date of the report : 24 August 1998</p>		

E-92-52030-013

Name of Sponsor/Company :	Individual Study Table	<i>(For national authority use only)</i>
& BEAUFOR IPSEN INTERNATIONAL	Referring to Part IV A-2	
Name of Finished Product :	of the Dossier	
Name of Active Ingredient(s) : LANREOTIDE (I.N.N.) ACETATE	Volume : Page :	
<p><b>Title of study :</b> Pharmacokinetic profile of the somatostatin analogue lanreotide in patients suffering from hepatic insufficiency. <i>(Perfil farmacocinético del análogo de la somatostatina BIM-23014 en pacientes afectados de insuficiencia hepática).</i></p> <p><b>Study Number:</b> E-92-52030-013 (Beaufour-IPSEN Group Code)</p> <p><b>Study Number:</b> 08-BIM23014-94 95/PKS/13 /</p> <p><i>Study codes: 95/34, Spanish Ministry of Health and FAR-729, Czech Ministry of Health).</i></p>		
<p><b>Investigators:</b></p> <p>/ / / /</p>		
<p><b>Study centre(s) :</b></p> <p>/ / / / /</p>		
<p><b>Publication (reference) :</b> None</p>		
<p><b>Studied period (years) :</b> 1</p> <p>Date of first enrolment: 27 / 02 / 1996</p> <p>Date of last completed: 22 / 12 / 1997</p>		<p><b>Phase of development :</b> Phase I (pharmacokinetics, special population)</p>
<p><b>Objectives :</b> Following one intravenous infusion of 7 µg/kg of lanreotide to healthy volunteers and to patients suffering from moderate to severe hepatic insufficiency, the time courses of</p>		

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serum lanreotide levels were assessed in order to compare between groups the values of the main pharmacokinetic disposition parameters: disposition rate constant ( $\lambda_e$ ), disposition half-life ( $t_{1/2}$ ), area under the serum concentration time curve from time 0 to the last experimental time ( $AUC_e$ ), area under the serum time curve from time 0 to infinity ( $AUC$ ), mean residence time from time 0 to infinity (MRT), serum clearance (CL) and distribution volumes ( $V_d$ and $V_z$ ).		
Methodology : Open label and parallel pharmacokinetic clinical trial, with a control group of healthy subjects.		
Number of patients (planned and analysed) : 17 patients and 12 healthy subjects (12 patients and 11 healthy volunteers were included in the pharmacokinetic analysis).		
Diagnosis and criteria for inclusion : Patients with a B or C degree in the Child score of hepatic insufficiency.		
Test product, dose and mode of administration, batch number : Lanreotide, 7 $\mu$ g/kg, i.v. infusion administration, batches no. D003 and E001		
Duration of treatment : One intravenous infusion (20 minutes).		
Reference therapy, dose and mode of administration, batch number : Not applicable.		
Criteria for evaluation: <b>Pharmacokinetics:</b> The main pharmacokinetic disposition parameters evaluated were: disposition rate constant ( $\lambda_e$ ), disposition half-life ( $t_{1/2}$ ), area under the serum concentration time curve from time 0 to the last experimental time ( $AUC_e$ ), area under the serum time curve from time 0 to infinity ( $AUC$ ), mean residence time from time 0 to infinity (MRT), serum clearance (CL) and distribution volumes ( $V_d$ and $V_z$ ). <b>Safety:</b> Clinical and laboratory standard examinations.		

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**Statistical methods :**

**Pharmacokinetics:** The pharmacokinetic analysis was performed by a non-compartmental approach using the WinNonlin pharmacokinetic program (Scientific Consulting, Inc. 1997, Ver 1.5). The pharmacokinetic values were compared between groups (patients and volunteers) by means of the Student t-test after log-transformation of data and by the U-Mann-Whitney test for  $t_{max}$ .

**Safety:** Values of biochemical and haematological parameters were compared within groups (before and after drug treatment) by means of the paired t-test or the Wilcoxon Signed Rank test. The occurrences of adverse events were compared between groups by means of the Fisher exact test (not applicable, only one patient).  $P < 0.05$  was considered statistically significant.

**SUMMARY -- CONCLUSIONS :**

**PHARMACOKINETIC RESULTS :** The main pharmacokinetic parameters are shown in the following table:

Parameter	Units	Healthy Volunteers		Patients with Hepatic Insufficiency		STATISTICS	
		Mean	sd	Mean	sd	P	
$t_{max}$	hr	0.333	-	0.333	-		N.S.
$C_{max}$	ng ml <sup>-1</sup>	36.650	11.273	26.743	8.558		<0.0325
$t_{1/2}$	hr	1.348	0.344	1.856	0.487		0.0014
AUC	ng ml <sup>-1</sup> hr	22.449	5.476	20.024	4.248		N.S.
MRT	hr	0.230	0.138	0.688	0.205		<0.001
CL	l hr <sup>-1</sup> kg <sup>-1</sup>	0.332	0.058	0.262	0.084		N.S.
$V_{cl}$	l kg <sup>-1</sup>	0.184	0.077	0.322	0.089		<0.001
$V_d$	l kg <sup>-1</sup>	0.492	0.181	0.853	0.258		<0.001

\*Mean vs. N.S. Mean vs. Mean Student's t-test

Mean peak serum levels were significantly lower in patients than in healthy volunteers but lanreotide serum levels were detected for longer in patients than in healthy subjects (up to approx. 5 hours in healthy subjects vs. 9 hours in patients). The total clearance was not significantly different in patients with hepatic insufficiency than in healthy volunteers, suggesting that hepatic clearance plays only a minor role in lanreotide metabolism. However,

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<p>the volumes of distribution (<math>V_z</math> and <math>V_m</math>) were statistically higher in patients than in healthy volunteers. This fact can be explained both by the reduction of the plasma protein binding of lanreotide (lower albumin concentration in blood) and by the development of ascites which occurred in patients with moderate to severe hepatic insufficiency. Then, an increase of the free drug available for tissue distribution and, consequently, an increase of the distribution volumes were noted. As the elimination half-life is a secondary pharmacokinetic parameter, directly proportional to the <math>V_z</math>, higher values of <math>t_{1/2}</math> were noted in patients. Although no differences were observed in the AUC values of volunteers and patients, statistically significant differences were observed in MRT also due to the increase in the distribution volume of lanreotide when administered in a condition of hepatic insufficiency.</p>		
<p><u>SAFETY RESULTS</u> : Non serious adverse events (headache, nausea and vomiting after lunch) were observed in one patient approximately 3 hours after the i.v. infusion of 7 µg/kg of lanreotide. These symptoms of moderate intensity and possibly related to lanreotide disappeared spontaneously without any treatment. The treatment did not lead to clinically significant changes in the biochemical parameters. In relation to baseline, statistically significant reductions in haemoglobin and haematocrit levels, in erythrocyte, leukocyte and platelet counts and in total protein and albumin levels were observed in patients as a result of frequent blood sampling during the study.</p>		
<p><u>CONCLUSION</u> :</p> <p>The total clearance of lanreotide was not significantly different in patients with hepatic insufficiency than in healthy volunteers. In addition, the volumes of distribution and the elimination half-life were statistically higher in patients suffering from moderate to severe hepatic insufficiency than in healthy volunteers.</p>		
<p>Date of the report : 17 August 1998</p>		

E-38-52030-701

Name of Sponsor/Company: IPSEN - Biotech	Individual Study Table Referring to Part of the Dossier	<i>(For national authority use only)</i>
Name of Finished Product: Somatuline®		
Name of Active Ingredient: Lanreotide (L.N.N) immediate release form		
Volume: Page:		
Title of study: Pharmacokinetic profile of the somatostatin analogue BIM 23014 (lanreotide) in healthy volunteers and patients suffering from chronic impairment of hepatic function Study Number: E38 52030 701		
Investigators: _____		
Study centre: _____		
Publication (reference): Not applicable		
Studied period (years): Date of first enrolment: 15 <sup>th</sup> December 1997 Date of last completed: 21 <sup>st</sup> November 1998	Phase of development: I	
Objectives: Primary objective: to determine the main pharmacokinetic parameters following the administration of a single intravenous dose of 7 µg/kg of BIM 23014 over 20 minutes to patients suffering from chronic impairment of hepatic function, in comparison to those observed in a control group of healthy volunteers Secondary objective: to determine the tolerance of BIM 23014 in healthy volunteers and in patients suffering from chronic impairment of hepatic function.		
Methodology: This study was a single centre, open, phase I, clinical pharmacokinetic study of immediate release lanreotide (BIM 23014). The study included 12 patients suffering from chronic impairment of hepatic function and a control group of 12 healthy volunteers. Each trial subject was administered an intravenous infusion of 7 µg/kg of lanreotide over 20 minutes.		
Number of subjects (planned and analysed): Twenty-four subjects (12 healthy volunteers and 12 patients with impaired hepatic function) were planned and completed the study. This sample size was not based upon statistical considerations		
Diagnosis and criteria for inclusion: All studied subjects were Asian. • Healthy volunteers of both sexes, aged between 18 and 65. • Patients with hepatic impairment of B or C degree on the Child's Classification, of both sexes, aged between 18 and 65 years.		
Test product, dose and mode of administration, batch number: Study product: Lanreotide (BIM 23014). Route: i.v. infusion. Duration of treatment: a single dose of 7 µg/kg over 20 minutes. Batch numbers: FBL9 and GBDO.		

Name of Sponsor/Company: IPSEN – Biotech	Individual Study Table Referring to Part of the Dossier	<i>(For national authority use only)</i>
Name of Finished Product: Somatufine®		
Name of Active Ingredient: Lanreotide (LNN) immediate release form		
	Volume: Page:	
Reference therapy, dose and mode of administration, batch number: Not applicable		
<p>Criteria for evaluation:</p> <p><u>Pharmacokinetics:</u></p> <p><u>Blood sampling</u></p> <p>Fifteen minutes before the administration of the product, 5 mL of blood were extracted from every subject in order to obtain a blank serum sample. The blood sampling times for the pharmacokinetic analysis were:</p> <p><i>During the infusion period: 5 min, 10 min, 15 min and 20 min</i></p> <p><i>After the infusion period: 2 min, 15 min, 30 min, 1 h, 2 h, 3 h, 5 h, 7 h, 9h, 11 h and 24 h.</i></p> <p><u>Safety:</u></p> <p>Physical examination (at selection, prior to the beginning of infusion and 24 hours after the end of infusion), vital signs (at the end of infusion and 5, 10, 20, 40, 90 minutes, 4 and 6 hours after the end of infusion), ECG recording (at selection and 24 hours after the end of infusion), laboratory tests (blood chemistry and haematology at selection and 24 hours after the end of infusion), serology (at selection) and adverse events.</p>		
<p>Statistical methods:</p> <p><u>Pharmacokinetics</u></p> <p>Two populations were considered in order to perform the statistical analysis: Intention-To-Treat (ITT) population and Pharmacokinetic Per Protocol (PK-PP) population. Four patients, initially included, had hepatic impairment scores of 0 and 1, corresponding to a maximal Grade of A on Child Pugh's Classification. Therefore, these 4 patients were excluded from the pharmacokinetic analysis (PK-PP population) but were included in the safety analysis (ITT Population). Descriptive and inferential analysis were applied to both populations. Descriptive analysis: mean, median, standard deviation, coefficient of variation, minimum and maximum values and sample size were performed for the plasma concentrations of BLM 23014 at each sampling time and calculated for pharmacokinetic parameters. Statistical comparison analysis of the main pharmacokinetic parameters (log-transformed data values except for <math>T_{max}</math>) between two independent populations (healthy volunteers versus patients from ITT or PK-PP populations) was carried out by means of a two-sample t-test. For <math>T_{max}</math> the nonparametric Wilcoxon Rank-Sum Test (Mann-Whitney U) for differences in medians was used instead. In all cases, <math>p &lt; 0.05</math> was considered as a statistically significant difference.</p>		

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Name of Active Ingredient: Lanreotide (I.N.N) immediate release form		

Statistical methods (cont.):

Safety

Descriptive statistics by group and overall of both groups were provided for demographic and baseline characteristics.

Descriptive statistics by group and time evaluation were provided for safety parameters.

For biological parameters, in each group, the data at baseline were compared to the results after treatment using a paired Student t-test or Wilcoxon signed rank test.

Summary - conclusions:

Pharmacokinetic results

Pharmacokinetic parameters and results of statistical analysis of PK-PP population are summarised below:

Parameter	Units	Healthy Volunteers N=12		Patients N=8		Statistics <i>p</i>
		Mean	S.D.	Mean	S.D.	
<i>T<sub>max</sub></i>	hr	0.329	0.027	0.316	0.043	0.622872
<i>C<sub>max</sub></i>	ng·ml <sup>-1</sup>	37.345	13.883	34.394	8.514	0.695423
<i>t<sub>1/2</sub></i>	hr	1.015	0.194	2.908	1.041	0.000000
<i>λ<sub>z</sub></i>	hr <sup>-1</sup>	0.707	0.146	0.260	0.100	0.000000
<i>AUC</i>	ng·ml <sup>-1</sup> ·hr	21.704	6.360	30.090	4.610	0.002873
<i>AUC<sub>t</sub></i>	ng·ml <sup>-1</sup> ·hr	21.527	6.344	29.497	4.575	0.003683
<i>V<sub>ss</sub></i>	l·kg <sup>-1</sup>	0.205	0.060	0.348	0.135	0.004234
<i>V<sub>z</sub></i>	l·kg <sup>-1</sup>	0.489	0.085	1.036	0.442	0.000065
<i>Cl</i>	l·hr <sup>-1</sup> ·kg <sup>-1</sup>	0.343	0.079	0.237	0.035	0.002665
<i>MRT</i>	hr	0.597	0.066	1.464	0.468	0.000069
<i>MRT infusion</i>	hr	0.764	0.098	1.630	0.468	0.000148

After intravenous infusion of 7 µg/kg of BIM34014 over 20 minutes, the pharmacokinetic behaviour of lanreotide observed in healthy volunteers was different to that of patients suffering from chronic impairment of hepatic function. Differences in *Cl*, *V<sub>ss</sub>*, *V<sub>z</sub>*, *AUC*, *MRT* and *t<sub>1/2</sub>* between healthy volunteers and patient populations were statistically significant.

Clearance was lower in patients of the PK-PP population suffering from chronic hepatic impairment (0.237 l·hr<sup>-1</sup>·kg<sup>-1</sup>) compared to that of healthy volunteers (0.343 l·hr<sup>-1</sup>·kg<sup>-1</sup>). This represents only a 30.9% decrease suggesting that clearance of lanreotide does not depend on hepatic function only.

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Name of Active Ingredient: Lanreotide (I.N.N) immediate release form	Volume: Page:	
<b><i>Pharmacokinetic results (cont.)</i></b>		
<p><math>V_{ss}</math> and <math>V_z</math> increased from <math>0.205 \text{ l}\cdot\text{kg}^{-1}</math> and <math>0.489 \text{ l}\cdot\text{kg}^{-1}</math> respectively in healthy volunteers to <math>0.349 \text{ l}\cdot\text{kg}^{-1}</math> and <math>1.036 \text{ l}\cdot\text{kg}^{-1}</math> respectively in patients from the PK-PP population. The increase in these parameters is consistent with the low albumin values and the presence of ascites observed in some patients. An increase in the plasma unbound fraction is suggested.</p> <p>In healthy volunteers half-life was <math>1.0 \pm 0.2 \text{ h}</math> and in patients it was <math>3.0 \pm 1.0 \text{ h}</math>. An increase in the exposure and the mean residence time was also observed in patients.</p>		
<b><i>Safety results</i></b>		
<p>There was one serious adverse event during this study: one patient with a medical history of hepatic cirrhosis in a context of alcohol addiction experienced anorexia leading to his admission 7 days after initiating lanreotide treatment. This event was assessed not related to the study drug.</p> <p>During the course of the study one healthy volunteer experienced a non serious adverse event namely a transient episode of nausea and dizziness which developed 10 minutes after starting the infusion of lanreotide and a left hand swelling during blood sampling. Concerning the former the role of lanreotide was not excluded.</p> <p>No clinically significant laboratory parameter abnormality, no clinically significant change in vital signs were observed. ECG showed an incomplete right bundle branch block in one healthy volunteer. No relevant change from baseline was observed on physical examination. Lanreotide immediate-release formulation was generally well-tolerated in both healthy volunteers and patients with chronic hepatic insufficiency</p>		
<b>CONCLUSION:</b>		
<p>In Asian patients with chronic hepatic insufficiency following an intravenous <math>7 \mu\text{g}/\text{kg}</math> infusion of immediate-release formulation of lanreotide over a 20-minute period, clearance was significantly lower than in healthy volunteers. This was associated with a significantly higher distribution volume as well as a longer half-life and a greater serum exposure. Safety/tolerance did not show any clinically significant symptom either in healthy volunteers or in patients suffering from chronic hepatic impairment.</p>		
Date of report: 28 <sup>th</sup> February 2002		

## Study E-54-52030-134

### 1.0 SUMMARY

#### 1.1 Objective

The main purpose of this study was to evaluate the pharmacokinetics of lanreotide in the steady-state of two doses previously employed in two different clinical trials. The effect of lanreotide on serum glucose and glucagon concentrations and plasma IGF-I, testosterone, LH and insulin levels were also evaluated. Plasma testosterone and LH concentrations were determined in male volunteers only. Liver and kidney function tests and other blood chemistry were performed before, during and one week after treatment. Adverse events and side effects were also recorded throughout the trial.

#### 1.2 Study Design

This pharmacokinetic study was conducted as an open-label and parallel evaluation. Twenty volunteers were divided into two groups. The first group of 10 volunteers received the low dose and the second group of 10 volunteers received the high dose. Lanreotide was administered as a continuous 5-day subcutaneous (s.c.) infusion. On Day -1, prior to the start of infusion, within 24 hours, a baseline assessment was performed on all volunteers. The infusion started at Day 0 and continued through Days 1, 2, 3 and 4. During the five days of the infusion, volunteers were continuously monitored as per protocol. Volunteers were followed up as out-patients for seven days after the infusion ended.

Study volunteers were assigned to one of the two treatment groups. The first ten volunteers were assigned to the low dose treatment group, lanreotide 0.75 mg per day for 5 days. The next ten volunteers were assigned to the high dose treatment group lanreotide 3.0 mg per day, escalated to 6.0 mg per day after 24 hours and continuing for an additional four days. Twenty-four hours after the beginning of the continuous infusion, a booster injection of 0.375 mg and 1.5 mg was administered s.c. for the low and high dose groups, respectively.

#### 1.3 Results

##### 1.3.1 Safety

##### 1.3.1.1 Adverse Events

No serious adverse events were reported during this pharmacokinetic study. The most frequently reported adverse event was diarrhea. Fifteen out of 20 volunteers reported this event including 8 in the low dose group and 7 in the high dose group. The second most frequently reported adverse event was abdominal pain (n = 9), with 5 volunteers in the low dose group and 4 in the high dose group. Headache was reported by 5 volunteers, 4 in the low dose group and 1 in the high dose group. Other reported adverse

events included flatulence (reported in 5 volunteers, 1 in the low dose group and 4 in the high dose group) and nausea (4 volunteers, 2 in each dose group). The adverse events were not dose dependent and were all considered expected and most probably related to the medication. These adverse events were episodic, lasting only for few hours and with a good response to symptomatic treatment.

The frequency of occurrences of adverse events was:

- 1) Eighteen occurrences of diarrhea, 9 in each dose group: 3 volunteers reported multiple occurrences.
- 2) Eleven occurrences of abdominal pain, 6 in the low dose group and 5 in the high dose group: 2 volunteers reported multiple occurrences. Treatment was required in only 3 of these events.
- 3) Seven occurrences of headache, 5 in the low dose group and 2 in the high dose group. Treatment with acetaminophen was required in 5 of these events.
- 4) Six occurrences of flatulence, 1 in the low dose group and 5 in the high dose group: 1 volunteer reported multiple occurrences.

#### 1.3.1.2 Hematology

Hematocrit, hemoglobin and red blood cell count decreased over time in the two dose groups. Ten volunteers experienced below normal range hematocrit values including 6 in the low dose group and 4 in the high dose group. In 7 of these volunteers, the hematocrit was below the normal range at Day 11 and 2 of these 7 volunteers had hematocrit values below normal range prior to beginning the infusion. Hemoglobin levels below normal range were observed in 7 volunteers, including 5 in the low dose group and 2 in the high dose group. Below normal red blood cell counts were reported in 11 volunteers: 6 in the low dose group and 5 in the high dose group. None of these abnormalities in hematocrit, hemoglobin and red blood cell counts were considered statistically or clinically significant. However, the difference between the baseline for hematocrit, hemoglobin and red blood cell counts, and the maximum change observed post-treatment was statistically significant for the high dose group ( $p < 0.01$ ). This was attributable to the greater number of blood samples taken from the high dose group compared to the low dose group. No abnormalities in platelet counts were observed during this trial.

Abnormalities in total white blood cell and differential counts were observed during the trial. The distribution of the white blood cell count abnormalities were random and no significant differences were found