Pharmacokinetic (PK) Differences Between Subcutaneous and Intramuscular Administration of Lanreotide: Results from a Phase I Study

Amandine Manon[1]; Edward M. Wolin[2]; Christophe Chassaing[3]; Laurent Bertocchi[3]; Joel Richard[3]; Alexandria T. Phan[4]

[1]Ipsen Innovation, Les Ulis, France; [2]Montefiore Einstein Center for Cancer Care, Bronx, NY, USA; [3]Beaufour Ipsen Industrie, Dreux, France; [4]Division of Hematology-Oncology, University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, USA

INTRODUCTION

- Lanreotide autogel/depot is indicated in the US and Europe for the long-term treatment of acromegaly (60, 90, and 120 mg Q4W) in patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy[1,2]
- Recently, it has also been indicated in the US and Europe for unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival (PFS). It is also approved for symptom control in Europe. Recommended dose is 120 mg Q4W as a deep subcutaneous (SC) injection.[1,2]
- The efficacy, safety, tolerability, and pharmacokinetics (PK) of lanreotide have been demonstrated, including rapid initial release and long half-life of 23-30 days[1,3]
- A 3-phased study with long-acting release octreotide (LAR), another injectable somatostatin analog, evaluated technical outcomes using intramuscular (IM) injection[4]
  - 328 injections in 115 patients (68% with carcinoid syndrome) were evaluated; 149 injections were evaluated retrospectively, 103 injections were evaluated after nurses were made aware of the problem, and 76 injections were evaluated after nurses received training
  - Of the 149 IM injections in 115 patients administered during the first retrospective observational phase of the study, only 52% of IM injections were administered correctly
  - Of all 328 intended IM injections, 62% were administered correctly and 38% were mistakenly given subcutaneously (SC)
- Because some errors were reported with the injections of octreotide LAR, the objective of this analysis was to assess whether the route of administration, either SC or IM, had an impact on PK of lanreotide in healthy volunteers

OBJECTIVE

- The objective of this study is to assess the PK parameters of SC vs IM routes of administration of lanreotide among healthy volunteers
- This analysis focuses on the groups receiving SC or IM lanreotide 60 mg 0.246 lanreotide/mg of autogel formulation (mg/mg)

METHODS

Study design

- This was a randomized, parallel, double-blind, phase 1 clinical study completed in 1998
- Healthy volunteers (18-45 years old; body weight within the ideal range ±20%) were divided into 7 groups of 6 subjects each (3 male/3 female)
- All volunteers received an initial lanreotide IV injection (1 mg/mL) and were randomized to one of the treatment groups (**Table 1**):
  - With different doses (60, 90, and 120 mg) to establish the linearity of the PK of lanreotide autogel/depot at a concentration of 0.246 mg/mg by intramuscular route
  - With different concentrations (0.205 mg/mg, 0.246 mg/mg, and 0.287 mg/mg) to compare the PK profile of different lanreotide autogel/depot formulations at the dose of 60 mg of lanreotide administered by IM and SC routes (IM route only for the 0.287 mg/mg)
  - With different routes of administration (SC or IM) to measure the influence of IM and SC administration on the PK and safety profiles of lanreotide autogel/depot 60 mg
- In this study, lanreotide 0.205 and 0.246 mg/mg 60 mg were administered via IM and SC while the 0.287 mg/mg formulation was by IM only because SC administration had already been included in a previous phase 1 study

Table 1. Summary of lanreotide treatments administered to healthy volunteers

Treatment Groups	1	2	3	4	5	6	7
Salt	Acetate						
Preparation concentration	0.246 mg/mg	0.246 mg/mg	0.246 mg/mg	0.246 mg/mg	0.287 mg/mg	0.205 mg/mg	0.205 mg/mg
Route of administration	IM	IM	IM	SC	IM	IM	SC
Dosage	60 mg	90 mg	120 mg	60 mg	60 mg	60 mg	60 mg
Dosage regimen	Single administration						

PK analysis

- Blood samples were collected to assess serum lanreotide levels using a validated radioimmunoassay method
- Serial blood samples were collected before treatment and over the 8 hours after lanreotide 1 mg IV bolus administration
- After administration of SC or IM lanreotide, blood samples were taken at 0, 1, 2, 4, 6 and 8 hours on Day 0, and then once a day on Days 1, 2, 3, and 4, then weekly during the first 2 months (Day 7, Day 14, Day 21, Day 28, Day 35, Day 42, Day 49, Day 56); and, finally, every 2 weeks during 2 months (Day 70, Day 84, Day 98, Day 112)
- For SC and IM administration of lanreotide, a non-compartmental PK analysis was performed using the software WinNonLin®. The estimated parameters were maximal concentration (C_{max}), the corresponding t_{max}, area under the curve (AUC_{last} and AUC_{inf}), clearance (CL/F), terminal half-life ($t_{1/2}$), mean residence time (MRT_{last} and MRT_{inf}). Bioavailability was estimated for each volunteer and for each product as the ratio of the SC or IM AUC_{inf} to IV AUC_{inf}, corrected by the respective doses.

Statistical analysis

- Comparisons between PK parameters estimates after SC and IM injections of lanreotide (0.246 mg/mg) were performed using Kruskal-Wallis non-parametric statistical test to assess treatment differences:
  - Criteria for statistically significant difference was $P < 0.05$
- Student Systat 7.0 software was used for conducting data analysis

RESULTS

- 42 healthy volunteers were included with mean age 25±5 years and weight 66±10 kg (**Table 2**)

Table 2. Average demographic characteristics of healthy volunteers (mean±SD)

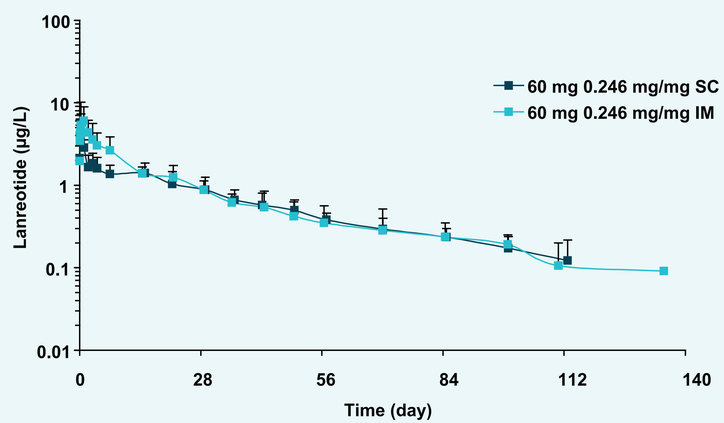
Gender	Age (year)	Race	Height (cm)	Weight (kg)
Female	25±6	21 Caucasian	166±5	59±6
Male	25±2	21 Caucasian	179±7	73±9
All	25±5	42 Caucasian	173±9	66±10

- In this analysis, 11 subjects received the same lanreotide dose/formulation (60 mg 0.246 mg/mg) either SC (n=5 [1 participant was excluded]) or IM (n=6), 30 received other doses/concentrations (results from these subjects are not included in this report)

Concentration-time profiles of lanreotide

- Between Days 14 and 112, comparable mean concentration-time profiles of lanreotide were observed for both IM and SC administration of lanreotide 60 mg 0.246 mg/mg (**Figure 1**)

Figure 1. Mean concentration-time profiles of lanreotide after IM and SC administration of lanreotide 60 mg 0.246 mg/mg



- Following SC and IM injections, the mean C_{max} (5.8±4 vs 6.8±3 µg/L), mean t1/2 (33±14 vs 23±9 d), and mean MRT_{last} (30±6 vs 23±11 d) were comparable (**Table 3**)
- Slightly lower but statistically significant AUC_{last} (1651±54 vs 2007±172 h•µg/L; P=0.006) and AUC_{inf} (1843±134 vs 2100±193 h•µg/L; P=0.03) were observed with SC vs IM injections

Table 3. Lanreotide pharmacokinetic parameters (non-compartmental analysis) after IM and SC administration of lanreotide 60 mg 0.246 mg/mg

Lanreotide treatment	C_{max} (µg/L)	t_{max} (h)	AUC_{last} (h•µg/L)	AUC_{inf} (h•µg/L)	F	Cl/F (L/h)	$t_{1/2}$ (days)	MRT_{last} (days)
60 mg 0.246 mg/mg SC n=5* (mean [SD])	5.8 (4)	6 (3)	1651 (54)	1843 (134)	0.63 (0.1)	33 (2)	33 (14)	30 (6)
60 mg 0.246 mg/mg IM n=6 (mean [SD])	6.8 (3)	15 (9)	2007 (172)	2100 (193)	0.79 (0.1)	29 (3)	23 (9)	23 (11)
Kruskal-Wallis (p-value)	0.4	0.2	0.006	0.03	0.05	0.03	0.2	0.2

C_{max}, maximum serum level; t_{max}, time of maximum serum level; AUC_{last}, area under the plasma drug concentration-time curve from time zero to the last measurable level; AUC_{inf}, area under the plasma drug concentration-time curve extrapolated to infinity; F, bioavailability; Cl/F, total apparent clearance after extra-vascular administration; $t_{1/2}$, elimination half-life; MRT_{last}, mean residence time.

*Lanreotide levels could not be determined after Day 15 for one volunteer (lanreotide 60 mg 0.246 mg/mg SC), who was therefore excluded from the pharmacokinetic analysis.

- Median T_{max} (8 vs 16 hours) and MRT_{last} in serum (28 vs 20 d) were also comparable
- Local tolerance at the IM and SC injection sites was generally good for lanreotide autogel and unloaded placebo microparticles

CONCLUSIONS

- There were similar PK profiles, maximal concentration, and terminal half-life between SC and IM injections of lanreotide autogel/depot 60 mg 0.246 mg/mg in this small cohort
- These data, which show slightly more lanreotide was available in the late-release phase after the SC injection (providing a better long-term release profile), support the SC administration now used in clinical practice
- In this study, lanreotide autogel/depot elicited an optimal release, as well as good local tolerance profiles, thus confirming the results obtained in previous phase 1 studies and observations from more than 10 years of use

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