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

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INTRODUCTION
• Lanreotide autogel/depot is indicated in the US and Europe for the long-term treatment of acromegaly (60, 90, and 120 mg QM) in patients who have an inadequate response to or cannot be treated with surgery and/or radiotherapies.1

• Recently, it has also been indicated in the US for severe, well-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 QM as a deep subcutaneous (SC) injection.7

• The efficacy, safety, tolerability, and pharmacokinetics (PK) of lanreotide have been demonstrated, including initial release and long half-life of 23-30 days.1

• A 3-phased study with long-acting release octreotide (LAR), another injectable somatostatin analog, was conducted to evaluate different doses (60, 90, and 120 mg) to establish the linearity of the PK of lanreotide autogel/depot. The efficacy, safety, and tolerance of lanreotide were demonstrated.8

• 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.1

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 mg/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 (38-45 years old; body weight within the ideal range of 20%) were divided into 7 groups of 6 subjects each (3 male/3 female).

• All volunteers received an initial lanreotide IV injection (0.1 mg/kg) 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 were administered IM and SC while the 0.287 mg/mg formulation was IM only because SC administration had already been included in a previous phase 1 study.

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, and 8 hours on Day 0, and then once a day on Days 2, 3, 4, and 5, until the first 4 weeks (Day 2, Day 4, Day 6, Day 8, Day 10, and, finally, every 2 weeks during 2 months (Day 70, Day 84, Day 91, Day 112).

• For SC and IM administration of lanreotide, a non-compartmental PK analysis was performed using the software WinNonLin8. The estimated parameters were maximal concentration (Cmax), the corresponding tmax under the curve (AUC0-t) and AUCinf, clearance (CL/F), terminal half-life (t1/2), mean residence time (MRT0-t and MRTinf), and bioavailability were estimated for each volunteer and for each product as the ratio of the area under the plasma drug concentration-time curve from time zero to the last quantifiable concentration (AUCinf).

RESULTS
• 42 healthy volunteers were included with mean age 25 ± 6 years and weight 66 ± 9 kg (Table 2).

• In this analysis, 11 subjects received the same dose formulation (60 mg 0.246 mg/mg) either SC or IM (3 participants were excluded) or IM (n=10) received other dose/formulations (results from these subjects are not included in this report).

• 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 Cmax (0.844 ± 0.834 μg/mL), mean t1/2 (33.44 ± 23.49 d), and mean MRT0-t (67.95 ± 23.43 d) were comparable (Table 3).

• Slightly lower but statistically significant AUC0-t (7861.845 ± 202772 μg·h/mL; P=0.008) and AUCinf (6743.265 ± 290259 μg·h/mL; P=0.03) were observed with SC vs IM injections.

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-phase of SC injection, thus confirming the results obtained in previous phase 1 studies and observations from more than 10 years of use.

REFERENCES

ACKNOWLEDGMENTS
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Table 1. Average demographic characteristics of healthy volunteers (n=42±5)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>25.4 (2.9)</td>
<td>59.4 (11.2)</td>
</tr>
<tr>
<td>Male</td>
<td>25.1 (2.6)</td>
<td>66.0 (12.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>SC</th>
<th>IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>60 mg 0.246 mg/mg SC</td>
<td>56.9 (10.2)</td>
<td>57.8 (10.7)</td>
</tr>
<tr>
<td>2.</td>
<td>60 mg 0.246 mg/mg IM</td>
<td>57.6 (11.0)</td>
<td>62.5 (12.8)</td>
</tr>
<tr>
<td>3.</td>
<td>60 mg 0.246 mg/mg SC</td>
<td>55.0 (10.0)</td>
<td>56.0 (10.1)</td>
</tr>
<tr>
<td>4.</td>
<td>60 mg 0.246 mg/mg IM</td>
<td>56.1 (10.9)</td>
<td>65.3 (13.4)</td>
</tr>
<tr>
<td>5.</td>
<td>60 mg 0.246 mg/mg SC</td>
<td>56.5 (11.1)</td>
<td>57.2 (10.7)</td>
</tr>
<tr>
<td>6.</td>
<td>60 mg 0.246 mg/mg IM</td>
<td>58.5 (12.3)</td>
<td>61.4 (11.8)</td>
</tr>
<tr>
<td>7.</td>
<td>60 mg 0.246 mg/mg SC</td>
<td>57.2 (11.2)</td>
<td>58.0 (11.0)</td>
</tr>
</tbody>
</table>

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