

Lanreotide Bioequivalence Study

Information on the bioequivalence study comparing Lanreotide ADVANZ PHARMA 60 mg, 90 mg or 120 mg solution for injection in a prefilled syringe to the brand Somatuline® Autogel® injection is briefly summarized below and subsequently discussed in more detail.

Lanreotide ADVANZ PHARMA 60 mg, 90 mg and 120 mg solution for injection in a prefilled syringe has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on 23 November 2023 following a decentralised procedure with Denmark as Reference Member state [1,2].

Lanreotide ADVANZ PHARMA is indicated for [2]:

- The treatment of individuals with acromegaly when the circulating levels of Growth Hormone (GH) and/or Insulin-like Growth Factor-1 (IGF-1) remain abnormal after surgery and/or radiotherapy, or in patients who otherwise require medical treatment.
- The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease.
- The treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.

SUMMARY

- Lanreotide ADVANZ PHARMA 60 mg, 90 mg and 120 mg solution for injection in a prefilled syringe is a generic medicinal product of the reference medicinal product Somatuline Autogel® (Lanreotide), IPSEN Pharma Biotech.
- Both formulations contain the same active ingredient and the same excipient (glacial acetic acid, used for the pH adjustment) in equivalent quantities.
- Bioequivalence of Lanreotide ADVANZ PHARMA to the reference product has been achieved via a biowaiver, based on equivalent molecular, structural, and thermodynamic properties as the reference listed product [3, 4].
- A bioequivalence (BE) study (Study PHG-P2-584) has been performed as a single dose, parallel comparative bioavailability study of a single dose of 2 different formulations of lanreotide 120 mg subcutaneous (SC) injection in healthy male and female subjects. As per the study design, all 3 PK parameters (C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$) had to meet strict BE criteria range of 80-125% [5].
- Lanreotide met BE criteria for both AUC_{0-T} , and $AUC_{0-\infty}$. It did not achieve BE in this study because the upper limit of the 90% CI for C_{max} was outside of the strict 80-125% BE criteria range. A likely reason for this is the high inter-individual variability in C_{max} values observed (90.7% and 186%, for the test and reference products, respectively) [5].
- PK simulations of BE studies of lanreotide and the reference product have been conducted, using distributions of PK outcomes (e.g., C_{max} and AUC) observed in the bioequivalence study, with the goal to evaluate whether lanreotide would be bioequivalent to Somatuline Autogel® if a larger number of subjects had been studied and if different bioequivalence acceptance criteria had been used for C_{max} [6]. Simulation analysis of 1000 lanreotide BE trials demonstrated that the likely reason for the failed bioequivalence in C_{max} is the high variability in the C_{max} and the SC absorption process. Further, application of strict BE criteria (80-125%) to C_{max} is likely to have set a high,

unattainable BE bar when a widened acceptance range (70-143%) would have been more appropriate due to the high variability in C_{max} .

- A further set of simulations were conducted [6] using a published distribution of Somatuline Autogel in healthy subjects receiving a single subcutaneous (SC) dose of 120 mg as the reference [7] and observed test data from study PHG-P2-584 suggested that Somatuline Autogel itself would fail to meet strict BE criteria for C_{max} (BE achieved in $\leq 15\%$ of simulated trials), but easily achieves BE for AUC_{0-T} and $AUC_{0-\infty}$. Although the percent success is numerically different for Somatuline Autogel itself, compared to the test product, the difference is not clinically significant, and both numbers indicate an exceedingly low probability of success in terms of meeting BE criteria of 80-125% for C_{max} .
- Simulation of lanreotide pharmacokinetics (PK) based on a published population PK model demonstrated that both Test and Reference concentrations generally fall within the 90% prediction interval for expected lanreotide concentrations, with high variability observed during the first 24 h post-dose [6]. Given the similarities in observed concentrations to expected lanreotide concentrations, differences in clinical safety, tolerability and efficacy are not expected for lanreotide compared to Somatuline Autogel.
- In the BE study PHG-P2-584, the incidence of TEAEs was similar for subjects dosed with the Test and the Reference (86% and 89%, respectively). Drug-related TEAEs were also reported with a similar incidence for subjects dosed with the Test and the Reference (86% and 87%, respectively).

➤ **Bioequivalence of Generic Lanreotide via the Biowaiver Approach**

A Biowaiver means that *in vivo* bioavailability (BA) and/or bioequivalence (BE) studies may be waived (= not considered necessary for product approval). The criteria to claim a biowaiver of strength is provided in section 4.1.6 of the Guideline on the Investigation of BE [3]. Lanreotide ADVANZ PHARMA fulfils the required criteria, including the following. The Sameness study has demonstrated equivalence between the test and reference product [4].

- The qualitative and quantitative composition of the different strengths is the same. In particular, the content of all strengths comes from the same bulk and differs only in the amount introduced into each syringe.
- The development of lanreotide autogel has been based on similarity with Somatuline Autogel®. Similarity has been applied with respect to all critical process parameters and critical quality attributes recognized to reflect the *in vivo* behavior of the product.
- The dissolution profiles are similar between the bio-strength and the additional strengths
- Pharmacokinetic linearity has been established for Somatuline Autogel for all strengths up to 120 mg.

➤ **Lanreotide Bioequivalence study Study PHG-P2-584 Background [5]**

Study PHG-P2-584 was a single dose, parallel comparative bioavailability study of a single dose of two different formulations of lanreotide 120 mg subcutaneous (SC) injection in 140 healthy male and female subjects under fasting conditions. The test product was lanreotide (produced by ADVANZ PHARMA) and the reference product was Somatuline® Autogel® (produced by Ipsen). Following SC injection, blood for pharmacokinetic (PK) analysis was collected for 112 days. Concentration in human plasma was analyzed using a validated high performance liquid chromatography with tandem mass spectrometry detection assay and concentration over time data was analyzed using standard non-

compartmental methods to derive the following PK parameters: C_{max} , C_{tau} , T_{max} , AUC_{0-T} , $AUC_{0-\infty}$, Residual Area, λ_z , and T_{half} .

Statistical analysis for bioequivalence (BE) was based on an analysis of variance model of the In-transformed PK parameters (C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$). The ratio of geometric least square means with corresponding 90% confidence interval (CI) was calculated from the exponential of the difference between the test and reference product for the In-transformed parameters (C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$). In order to establish BE, the 90% CI for all 3 parameters were to be within the 80-125% BE range.

➤ Study PHG-P2-584 Pharmacokinetic Results [5]

A total of 137 subjects were included in the pharmacokinetic and statistical analysis of treatments with the test and reference product. Lanreotide failed to establish BE in this study because the upper limit of the 90% CI for C_{max} was slightly outside of the 80-125% range (Ratio test/reference: 108.09; 90% Confidence Limits: 86.91% -134.43%), however both AUC_{0-T} (Ratio test/reference: 107.43; 90% Confidence Limits: 98.29% -117.23%) and $AUC_{0-\infty}$ (Ratio test/reference: 106.79; 90% Confidence Limits: 98.41% -115.89%) met BE criteria (Table 2).

Table 2. Intersubject Variability of Study PHG-P2-584

Parameter	Inter-Subject C.V. (%)	Geometric LSmeans ^a		Ratio (%)	90% Confidence Limits (%)	
		Test (n=68) ^b	Reference (n=69) ^c		Lower	Upper
C_{max}	90.0	6983.8	6461.1	108.09	86.91	134.43
AUC_{0-T}	31.5	3546654.7	3304089.8	107.34	98.29	117.23
$AUC_{0-\infty}$	28.1	4211699.8	3943898.0	106.79	98.41	115.89

The likely reason for exceeded upper confidence interval limit of C_{max} is the high variability in the C_{max} and the SC absorption process. Further, application of strict BE criteria (80-125%) to C_{max} is likely to have set a high, unattainable BE bar when a widened acceptance range (70-143%) would have been more appropriate. Wider BE criteria are acceptable for drugs with high variability ($\geq 50\%$) in C_{max} , where replicate design is recommended, as appropriate [3]. Although replicate design is not feasible for lanreotide, given its long half-life, wider BE criteria are acceptable given the high CV% observed in study PHG-P2-584 for C_{max} (90.7% and 186%, for the test and reference products, respectively [5]).

Thus, because this study was designed in a way that required for all 3 PK parameters (C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$) to meet strict BE criteria range of 80-125%, BE to Somatuline Autogel was not met. If the study had been designed to establish BE for C_{max} using the 70-143% range, while maintaining the 80-125% range for AUC, it is likely (though not certain) that BE to Somatuline Autogel would have been established.

➤ Study PHG-P2-584 Tolerability Results [5]

One hundred twenty-two subjects (87%) reported a total of 474 treatment-emergent Adverse Events (TEAEs) over the course of the study. Table 3 summarizes the AEs of all dosed subjects as a function of the treatments they received over the course of the study. The incidence of TEAEs was similar for subjects dosed with the Test and the Reference (86% and 89%, respectively). Drug-related TEAEs were also reported with a similar incidence for subjects dosed with the Test and the Reference (86% and 87%, respectively). The TEAEs experienced during the study were deemed mild (388/474; 82%), moderate (46/474; 10%) and severe (40/474; 8%) in intensity. Of the severe TEAEs, 18 were

experienced following the administration of the Test and 22 were experienced following the administration of the Reference. Severe TEAEs were mostly events of diarrhoea, with 18 events reported by 16 subjects (23%) after administration of the Test and 17 events reported by 14 subjects (20%) after administration of the Reference. Most of the severe TEAEs experienced during the study were considered drug-related (37/40; 93%). All severe TEAEs were resolved by the end of the study.

No deaths were reported in any of the subjects dosed in this study. Two subjects (1%) reported 3 SAEs following administration of the reference product, of which one was judged unexpected and related to study drug (SAEs of deep vein thrombosis and pulmonary embolism of severe intensity). No subject was withdrawn by the investigator due to a TEAE (safety reason).

Table 3. Overview of Adverse Events in the Bioequivalence study PHG-P2-584 [5]

Parameter	Test (N=70)	Reference (N=70)
TEAEs reported [n]	244	230
Subjects with at least one TEAE [n (%)] [1]	60 (86)	62 (89)
Subjects with at least one drug-related TEAE [n (%)] [1] [3]	60 (86)	61 (87)
TEAEs relationship [2]		
Related [n (%)] [3]	239 (98)	210 (91)
Not related [n (%)]	5 (2)	20 (8)
SAEs reported [n] [2]	0	3 (1)
Subjects with at least one SAE [n (%)] [1]	0	2 (3)
Subjects with at least one drug-related SAE [n (%)] [1] [3]	0	1 (1)
Deaths [n (%)] [1]	0	0

AEs: Adverse events; TEAEs: Treatment-Emergent Adverse Events; SAEs: Serious Adverse Events

N = number of subjects who received a specific treatment

[1] Percentages are based on the number of subjects in the safety population in each treatment group.

[2] Percentages are based on the total number of TEAEs reported in each treatment group.

[3] Drug-related TEAE was reported as: Reasonable Possibility.

➤ Pharmacokinetic Simulations of Bioequivalence Trials

Observed PK parameters (C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$) for the test and reference formulations from Study PHG-P2-584 were fit using log-normal distributions, and parameters for spread and central tendency were derived. PK parameters were simulated from these distributions for 70 Test (lanreotide) and 70 Reference (Somatuline Autogel®) subjects in each of 1000 trials. As was done in Study PHG-P2-584, an ANOVA on ln-transformed PK parameters was performed for each of the 1000 trials to test for BE of Test compared to Reference. The BE acceptance criteria for C_{max} were 80-125% and 70-143%; the BE acceptance criteria for AUC_{0-T} and $AUC_{0-\infty}$ was 80-125%. BE was met if the 90% CI of the ln-transformed PK parameter was contained within each BE range. The percent of studies where BE was met was calculated and reported.

To explore whether or not BE to Somatuline Autogel would have been established if different BE criteria were set for C_{max} , PK simulations were conducted. One thousand (1000) trials were simulated for 70 healthy subjects receiving a single SC injection of either lanreotide or Somatuline Autogel. C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$ were simulated from the observed distributions of those parameters in study PHG-P2-584. Resulting ln-transformed PK parameters were analyzed in the same statistical manner as was done for study PHG-P2-584. The proportion of studies where BE was achieved was tabulated. Results shown in **Table 4** suggest that BE criteria would be met in greater than 90% of simulated studies for both AUC_{0-T} and $AUC_{0-\infty}$. However, C_{max} would have achieved BE in <7% of studies using the 80-125% range. Relaxing the C_{max} BE criteria to 70-143% would have resulted in achieving BE in ≥63% of simulated trials.

Table 4. Results of 1000 PK trial simulations for bioequivalence between lanreotide and Somatuline Autogel

Pharmacokinetic Parameter	Bioequivalence Criteria	
	80-125%	70-143%
C _{max}	6.8%	63%
AUC _{0-T}	90%	N/A
AUC _{0-∞}	96%	N/A

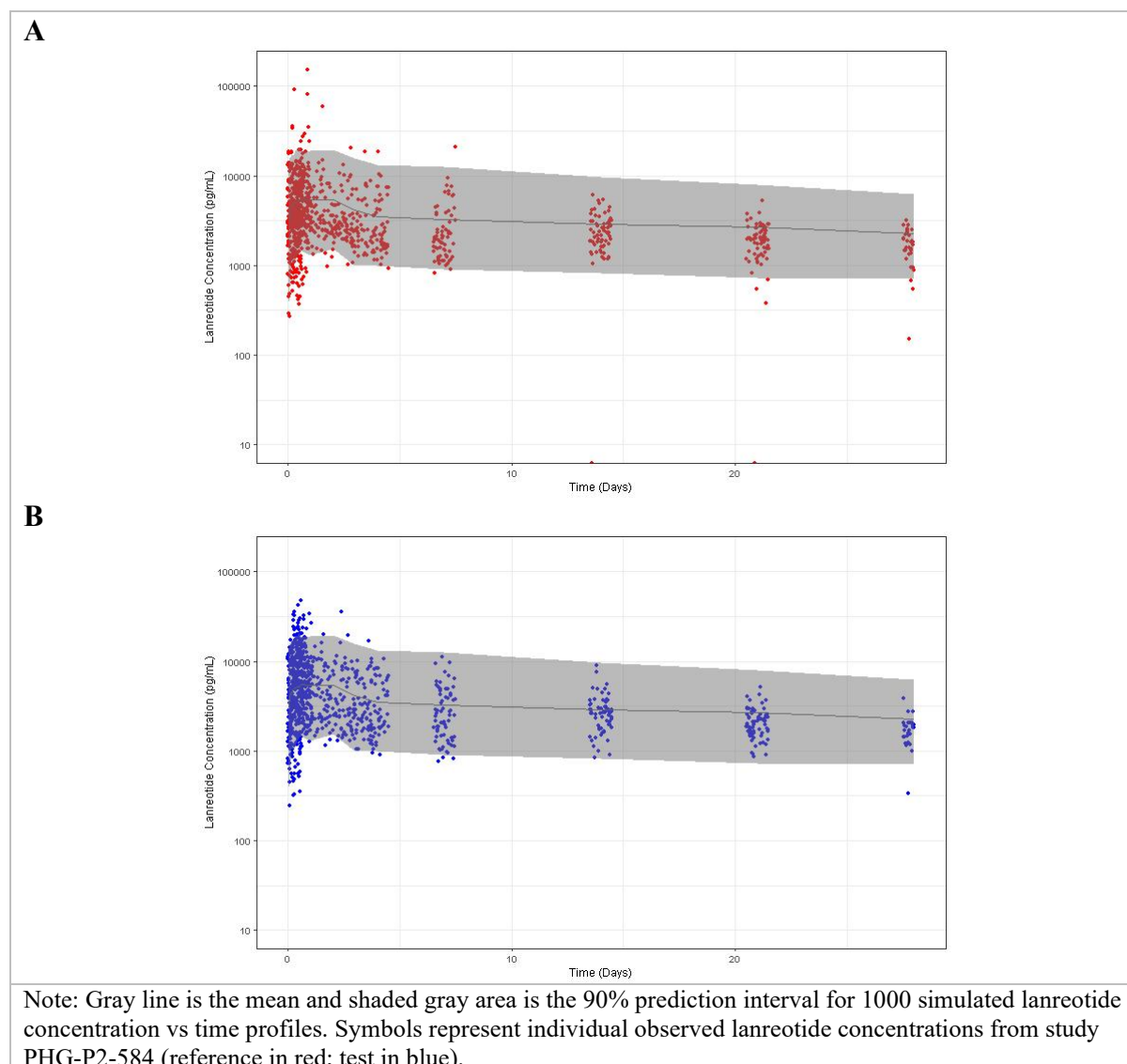
A further set of simulations were conducted using the published distribution of Somatuline Autogel in healthy subjects receiving a single SC dose of 120 mg as the reference (mean [SD], 6.785 [3.641] ng/mL) [7] and observed test data from study PHG-P2-584. Results suggest that Somatuline Autogel itself would fail to meet strict BE criteria for C_{max} (BE achieved in ≤15% of simulated trials), but easily achieves BE for AUC_{0-T} and AUC_{0-∞}. Although the percent success is numerically different for Somatuline Autogel itself, compared to the test product, the difference is not clinically significant, and both numbers indicate an exceedingly low probability of success in terms of meeting BE criteria of 80-125% for C_{max}.

➤ Population PK Simulations

It is possible that concentrations observed in Study PHG-P2-584 were different than expected concentrations of Somatuline Autogel. In order to compare test and reference concentrations observed in study PHG-P2-584 to expected lanreotide concentrations following administration of a single SC dose of 120 mg Somatuline Autogel, a published population PK model for subcutaneous administration was used to simulate expected concentration values [8 - Buil-Bruna]. The published model is a one-compartment model with linear clearance (CL/F) and two absorption processes: 1) first-order absorption (KA [input rate, 1/h], F1) and 2) zero-order absorption (D0 [input rate, mg/h], F2). Bioavailability was split between these two processes such that F2 = 1-F1. Inter-individual variability was included on CL/F, volume of distribution (V/F), KA, and F1. Body weight and sex were covariates influencing CL/F and F1, respectively. While the interpatient variability (IPV) in this model was low for clearance (27 %), it was found moderate to high for volume of distribution (150 %) and the absorption constant (61 %) [8 - Buil-Bruna]. The model was fit to log-transformed concentration data with an additive residual error model. Using this model, concentration versus time data were generated for 1000 patients simulated with equal distribution of sex (50% female) and normal distribution of body weight (mean=73.7 and SD=13.9 kg, based on observed body weight distribution from Study PHG-P2-584). Simulations were plotted as median, 90% prediction interval (PI) along with observed concentrations from Study PHG-P2-584.

Figure 1 shows the mean and 90% prediction interval ([PI]; similar to a 90% CI, but for simulated data) of expected lanreotide concentrations along with the observed test and reference concentrations from study PHG-P2-584. Observed test and reference lanreotide concentrations are mostly contained within the 90% PI of the expected Somatuline Autogel values. Observed concentrations during the first 24 h post-dose demonstrate high variability (several observed values fall outside the 90% PI). Following 24 h, observed concentrations generally fall within the 90% PI. High variability observed during the first 24 h post-dose and low variability thereafter, further support that whereas AUC (governed by data beyond the first 24 h) is likely to achieve BE, the variability in C_{max} precludes achieving BE, especially when using strict BE criteria.

Figure 1. Simulated and observed lanreotide plasma concentrations following a single subcutaneous dose of 120 mg lanreotide: A) Reference (red), B) Test (blue).



➤ Effect of C_{max} variability between Generic Lanreotide and Somatuline Autogel on Safety and Efficacy

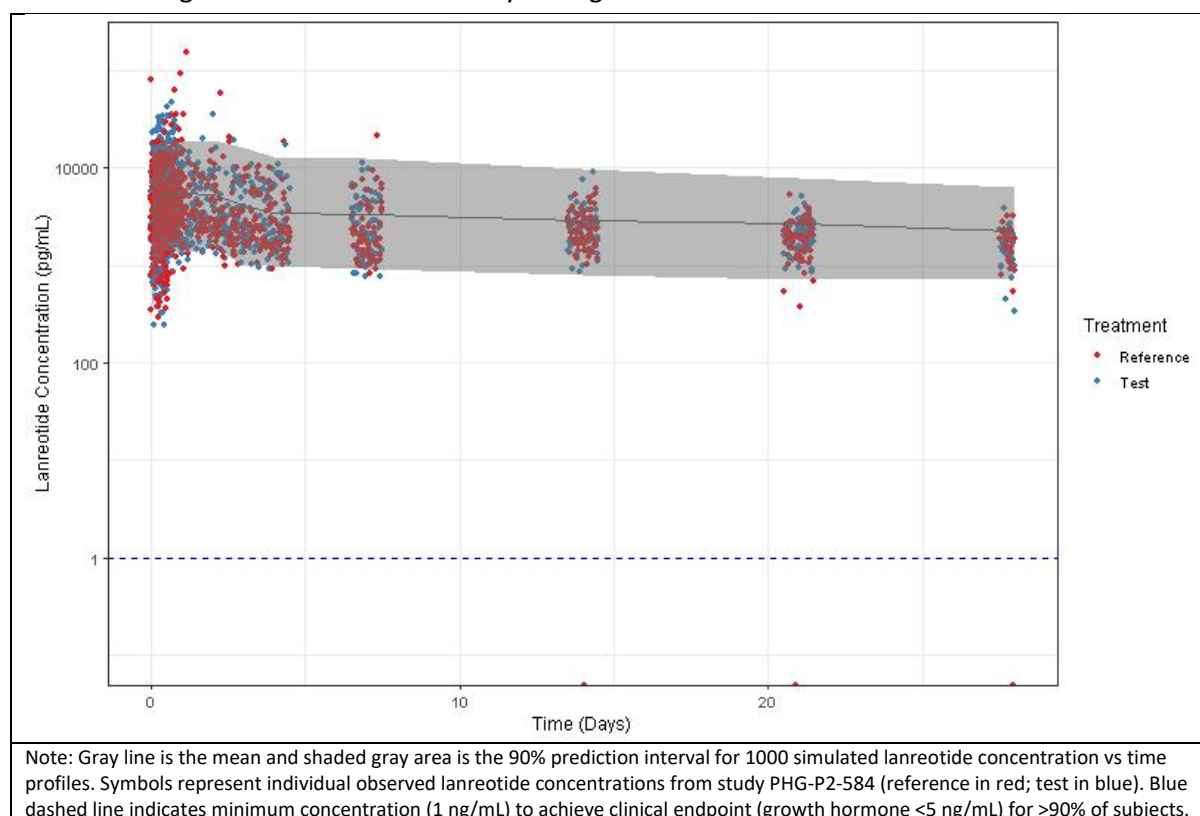
Lanreotide is a well-tolerated drug with a long clinical use history. Publicly available data [9] describing the undesirable effects of Somatuline Autogel list the most common ($\geq 1/10$) effects as gastrointestinal (diarrhea and abdominal pain) and liver disorders (cholelithiasis), and injection site reactions, which are easily manageable and transient. Common ($\geq 1/100$ – $<1/10$) undesirable effects (e.g., hypo and hyperglycemia, dizziness, headache, etc.) are likely unrelated to C_{max} , and are easily monitored. Population pharmacodynamics analysis published by Cendros et al [10] showed that the relationship between either formulations of lanreotide (Somatuline LA and Somatuline Autogel) and serum growth hormone (GH) concentrations was best described using an inhibitory maximum response (E_{max}) model that allowed for the possibility of an incomplete inhibition of GH. The effectiveness of treatment was demonstrated by the median serum concentration of lanreotide 1.13 ng/mL, required to lower GH to

2.5 ng/mL or less. With higher serum concentrations of lanreotide (up to 12 ng/mL), no further decrease of GH levels was observed in this model [10].

In Study PHG-P2-584, the geometric mean ratio of lanreotide compared to Somatuline Autogel was 108% [5]; this slight increase in C_{max} for the test product is unlikely to be clinically meaningful where safety and tolerability are concerned. Given the monitorable and benign nature of undesirable effects, along with only a slight increase in C_{max} , it is not expected that the generic lanreotide formulation would have a different safety or tolerability profile compared to the reference product.

Where efficacy is concerned, clinical response (suppression of growth hormone to <5 ng/mL) is achieved in >60% of subjects when lanreotide concentrations are maintained above 1 ng/mL over the dosing interval [8]. Simulated lanreotide concentrations (**Figure 2**) show that this benchmark is achieved in most subjects (observed and simulated) following a single 120 mg SC dose of lanreotide over the 28-day dosing interval and is thus likely achieved following dosing to steady state. Therefore, it is not expected that the generic lanreotide formulation would result in any differences in clinical efficacy compared to the reference product.

Figure 2. Simulated and observed lanreotide plasma concentrations following a single subcutaneous dose of 120 mg lanreotide over the 28-day dosing interval



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Last revision: 28 January 2028

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