ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetic Analysis of Lanreotide Autogel® in Healthy Subjects
Evidence for Injection Interval of Up to 2 Months

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Abstract

Background and objective: Lanreotide is a somatostatin analogue used for the treatment of acromegaly and neuroendocrine tumours. The objective of this study was to develop a pharmacokinetic model for the sustained-release formulation lanreotide Autogel® after deep subcutaneous administration in healthy subjects, and to explore the potential effect of covariates, especially sex and dose.

Subjects and methods: This was an open-label, single-centre, randomized, dose-ranging, parallel-group study, with a follow-up period of 4–7 months following drug administration in healthy subjects. Healthy Caucasian subjects aged 18–45 years were included. Subjects received a rapid intravenous bolus of 7 μg/kg of an immediate-release formulation of lanreotide (lanreotide IRF). After a 3-day washout period, participants were randomized to receive a single deep subcutaneous injection of lanreotide Autogel® at a dose of 60, 90 or 120 mg.

Pharmacokinetic and statistical analysis: Blood samples for lanreotide determination were obtained during the first 12 hours after the intravenous bolus injection and during the 4- to 7-month follow-up period after deep subcutaneous administration of lanreotide Autogel®. Data after intravenous and subcutaneous administration were fitted simultaneously using the population approach in NONMEM® version VI software. The model was validated externally using data from patients with acromegaly.

Results: In total, 50 healthy subjects (24 women and 26 men) received a single intravenous dose of lanreotide IRF. Of these, 38 subjects (18 women and 20 men) received a single subcutaneous dose of lanreotide Autogel® 3 days after intravenous lanreotide IRF. The disposition of lanreotide was described by a three-compartment open model. The estimates of the total volume of distribution and serum clearance were 15.1 L and 23.1 L/h, respectively. The estimates of interindividual variability were <40%. To evaluate lanreotide Autogel® pharmacokinetics, the absorption rate was modelled to decrease exponentially as a function of the natural logarithm of time. The absolute bioavailability after deep subcutaneous administration of lanreotide Autogel® was 63%. The rate of absorption and bioavailability of lanreotide Autogel® were independent of the administered dose in the range from 60 to 120 mg, and no significant effect of covariates (sex, dose, age or bodyweight) was found (p > 0.05).

Conclusions: Population analysis allows a full description of the disposition of lanreotide after rapid intravenous bolus administration of lanreotide IRF (7 μg/kg) and the pharmacokinetics of lanreotide Autogel® after a single deep subcutaneous injection (60, 90 or 120 mg) in healthy subjects. The model-based simulations provide support for the feasibility of extending the dosing interval for lanreotide Autogel® to 56 days when given at 120 mg. The absorption profile of lanreotide Autogel® was independent of the dose and was not affected by sex.

Background

Lanreotide is a synthetic octapeptide somatostatin analogue used to treat acromegaly and neuroendocrine tumours; it binds preferentially to pituitary somatostatin receptors, inhibits growth hormone secretion and reduces insulin-like growth factor I levels.[1] An earlier extended-release lanreotide formulation based on microparticles of lactide-glycolide copolymer allowed the release of the peptide over 7–14 days after intramuscular administration.[2] The development of lanreotide Autogel® (Somatuline Autogel®, Beaufour Ipsen, Dreux, France), a supersaturated solution containing only lanreotide and water, for subcutaneous injection, extended the duration of release to a more convenient dosing interval of at least 28 days.[3] This formulation, supplied as a ready-to-use preparation (of 60, 90 or 120 mg) in pre-filled polypropylene syringes, has good effectiveness and is well tolerated in patients; the main side-effects, which are of a gastrointestinal nature,[4-6] have been similarly reported with other somatostatin analogues given at therapeutic doses.[7]

A population model has recently been developed that relates lanreotide serum concentrations at steady state after administration of lanreotide microparticles or lanreotide Autogel® with growth hormone levels, estimating parameters associated with baseline growth hormone levels, hormonal effectiveness and potency, as well as their corresponding degree of interindividual variability (IIV).[8] The pharmacodynamic properties of lanreotide were independent of the formulation. However, a pharmacokinetic model relating the lanreotide serum concentration to the dose and time has not been developed; so far, only descriptors such as the maximum serum concentration (C_{max}), minimum serum concentration (C_{min}) and area under the serum concentration-time curve (AUC) have been reported.[4,9] Such a model, when combined with the pharmacodynamic model, could be used to explore the relationship between growth hormone levels and time in different clinical scenarios, taking into account the IIV in both pharmacokinetic and pharmacodynamic processes. Therefore, the main objective of the current analysis was to develop a population pharmacokinetic model after a single deep subcutaneous injection of lanreotide Autogel®, quantifying the degree of IIV in the pharmacokinetic parameters. Differences in the pharmacokinetic properties between males and females in the case of the subcutaneous administration could be expected because of higher subcutaneous fat levels in women.[10] Therefore, the study of the potential effect of covariates of sex, in addition to the dose level, was also part of the main objective of the analysis. To estimate the absolute bioavailability of lanreotide Autogel® and serum disposition para-

meters, the design included a rapid intravenous bolus injection of an immediate-release formulation of lanreotide (lanreotide IRF).

Study Participants and Methods

This was an open-label, single-centre, randomized, pharmacokinetic phase I study involving three parallel groups of healthy subjects. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was reviewed and approved by the local ethics committee, and all participants gave their written informed consent.

Participants

Inclusion of 54 healthy subjects was planned. Caucasian men and women fulfilling the following criteria were included: age between 18 and 45 years; bodyweight within 10% of the ideal height/frame; normal physical and laboratory test results; women with a negative pregnancy test who were not breastfeeding and who were using appropriate contraceptive methods; willingness and ability to understand and sign an approved informed consent form.

The exclusion criteria were a history of alcohol (ethanol) or drug abuse; smoking of >10 cigarettes/day; history of cholelithiasis or gastrointestinal, renal, hepatic, pulmonary or cardiovascular disease; history of epilepsy, asthma, diabetes mellitus, psychosis or glaucoma; history of an allergic response to lanreotide or related drugs; blood donation of ≥250 mL or participation in a clinical trial in the 3 months before study initiation; practising vegetarian diet, abnormal diet or substantial changes in eating habits within the previous 4 weeks; treatment with any known enzyme-inhibiting or enzyme-inducing agents in the 4 weeks before study medication; and positive tests for HIV and/or hepatitis B and C.

Drug Administration and Sample Collection

Participants received a single intravenous dose (7 μg/kg) of lanreotide IRF by rapid intravenous bolus injection (less than 10 seconds), followed by 3 days of washout and then randomization to one of three single deep subcutaneous doses of lanreotide Autogel® (60, 90 or 120 mg) administered to the superior-external quadrant of the buttock. Lanreotide was administered in the morning, and fasting conditions were not required.

Lanreotide IRF was obtained by reconstituting lanreotide lyophilisate with diluent (mannitol 40 mg/1 mL water for injections) immediately before administration. The lanreotide Autogel® formulation consists of lanreotide acetate and water (lanreotide base,

0.246 mg/mg of solution); the hydration of the peptide leads to the formation of a supersaturated solution.

Blood samples for determining serum lanreotide concentrations were obtained at the following times after the intravenous bolus injection: at 0, 5, 15 and 30 minutes, then at 1, 1.5, 2, 4, 6, 8 and 12 hours. After deep subcutaneous administration, samples were taken for at least 6 months at 0, 1, 2, 4, 6, 8 and 12 hours during the first day after administration and then on days 2, 3, 4, 5, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98 and 112, and afterwards if necessary, until a serum concentration below the lower limit of quantification was reached.

Determination of Serum Lanreotide Concentrations

A previously validated radioimmunoassay (RIA) procedure was used to determine serum lanreotide concentrations.[9] The lower limit of quantification was 0.078 ng/mL, and the overall precision (inter- and intra-assay), expressed as the coefficient of variation (CV), was 2.3–13.6% for concentrations between 0.1 and 10 ng/mL.

Data Analysis

All analyses were performed under the population approach using the Laplacian numerical estimation method with interaction and the nonparametric option implemented in NONMEM® version VI software (Icon Development Solutions, Ellicott City, MD, USA).[11]

All observations were fitted simultaneously; however, in the first step, the model describing the disposition characteristics of lanreotide in serum was developed using only the data obtained after intravenous administration. Then the disposition model parameters were re-estimated when the intravenous and subcutaneous observations were fitted together. In the analyses, the data were logarithmically transformed. Approximately 10% of the observations at later times after administration were below the lower limit of quantification (BLQ). BLQ observations were kept in the dataset and were treated as censored observations (according to method 3 in Beal).[12] The method used to handle BLQ observations in the current analyses was implemented in NONMEM® version VI based on recent documentation.[13] IIV was modelled exponentially, and residual variability was initially modelled with a combined error model; if one of the components (additive or proportional) of the residual error was negligible, it was deleted from the model.

Model selection was done using the minimum objective function value (MOFV), provided by NONMEM®, as a guide. A difference in the MOFV of 3.84 and 6.63 points between two nested models differing by one parameter was considered significant at the 5% and 1% levels, respectively. Since some of the models that were compared were not nested, the MOFV was not used directly for comparative purposes, and the value of the Akaike Information Criteria (AIC)[14] computed as MOFV + 2 × Np, where Np is the number of the parameters in the model, was used instead. The model with the lowest value of the AIC, given that the precision of the model parameters and data description was adequate, was selected.

Drug disposition was described with compartmental models parameterized in apparent volumes of distribution, and distribution and elimination clearances. Different absorption models,[15] including time-dependent absorption rate constants (k_a), the Weibull model[16] and the transit compartment model,[17] were tested to describe the absorption process after administration of lanreotide Autogel®.

Demographic characteristics (age, bodyweight, sex) and the dose level were first investigated one by one for any potential effect of covariates on all parameters associated with IIV. Significant covariates were then incorporated (starting with the covariate leading to the largest drop in the MOFV) one at a time until the full covariate model was obtained. If a covariate was added but did not cause a significant decrease in the MOFV, it was removed. This was followed by a backward-elimination process, whereby covariates that were found not to be significant were dropped one by one until no more could be eliminated. The levels of significance used during the forward inclusion and backward elimination were 5% and 1%, respectively.

Model parameters were expressed as the corresponding estimate with the relative standard error (RSE; i.e. the ratio between the standard error provided by NONMEM® and the parameter estimate). The degree of IIV was expressed as the %CV and the additive residual variability as the standard deviation.

A predictive check was used to assess the performance of the selected population model by looking at the C_{max} of lanreotide and the AUC from time zero to time of the last measurable concentration (AUC_{last}). One thousand studies were simulated with the selected pharmacokinetic model, and for each simulated dataset, the mean C_{max} and AUC_{last} were calculated for each dose level and sex. Then the overall mean values of the C_{max} and AUC_{last} across the 1000 simulated studies were computed, as well as the 2.5th and 97.5th percentiles, and compared with the observed mean values.

The final model was further evaluated internally and externally using the visual predictive check method.[18] For each dose level,

1000 virtual individuals were generated on the basis of the estimates of the fixed- and random-effect parameters obtained from the selected model. The intervals including 95% of the simulated concentrations and the profile corresponding to the median were constructed and represented together with (i) the observed concentration values from the healthy subjects (internal validation) and (ii) the serum lanreotide values obtained from a phase II, multicentre, double-blind, placebo-controlled, repeated-dose, dose-ranging trial involving 105 patients with acromegaly (external validation).[19] The schedule corresponding to the fixed dose part of this phase II study consisted of three phases: (i) washout (weeks −12 to 0) – required only for patients who had been treated previously; (ii) double-blind, placebo-controlled (weeks 0–4) – a single deep subcutaneous injection of placebo or lanreotide Autogel® 60, 90 or 120 mg; (iii) single-blind, fixed-dose (weeks 4–20) – four consecutive deep subcutaneous injections of lanreotide Autogel® 60, 90 or 120 mg every 28 days. Blood samples for serum lanreotide determination were taken 4 weeks after the first injection and 1, 2, 3 and 4 weeks after the third or fourth lanreotide Autogel® injection.[19]

Results

Study Participants

Fifty healthy subjects received a single intravenous dose of lanreotide IRF. Twelve subjects withdrew after this dose but before lanreotide Autogel® was administered (one withdrew because of adverse events [AEs; nausea, vomiting, diarrhoea and headache]; one because of a concurrent illness [tonsillitis]; and ten

Table I. Demographic and study characteristics for healthy subjects and patients with acromegaly who were included in the study used for the external model validation

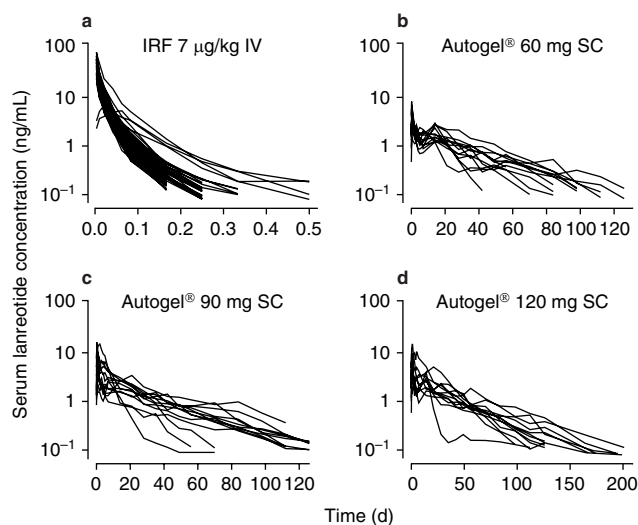| Parameter	Healthy subjects	Patients with acromegaly
Age (y)[a]	27.6 (5.8)	53.3 (13.8)
Bodyweight (kg)[a]	67.1 (12.4)	83.8 (17.0)
Sex [n (%)]		
female	24 (48)	56 (53)
male	26 (52)	49 (47)
Deep subcutaneous dose [n (%)]		
60 mg	13 (34)	34 (32)
90 mg	13 (34)	36 (34)
120 mg	12 (32)	35 (33)
a Values are expressed as mean (SD).		

Fig. 1. Individual serum lanreotide concentrations following a rapid intravenous (IV) bolus dose of 7 µg/kg of the immediate-release formulation (IRF) of lanreotide (**a**) or deep subcutaneous (SC) administration of lanreotide Autogel® at doses of 60 mg (**b**), 90 mg (**c**) or 120 mg (**d**).

withdrew consent after other subjects described gastrointestinal AEs). Therefore, 38 subjects were randomized to receive a single subcutaneous dose of lanreotide Autogel®. As one volunteer subsequently withdrew from the study because of a serious AE (described in the Safety section), 37 subjects completed the study according to the protocol. Table I lists the demographic and design characteristics of the current study.

Description of the Data

Individual observed lanreotide serum concentration-time profiles for a single intravenous bolus of lanreotide IRF 7 µg/kg (24 women and 26 men) and for a single deep subcutaneous injection of lanreotide Autogel® (18 women and 20 men; 60 mg, n = 13; 90 mg, n = 13; 120 mg, n = 12) are shown in figure 1.

Safety

More subjects in the lanreotide Autogel® groups had AEs than in the lanreotide IRF group, but there were no specific dose-related trends across the lanreotide Autogel® groups. Gastrointestinal events were the most frequent AEs in all groups (lanreotide IRF and lanreotide Autogel®); in particular, nausea in the lanreotide IRF group, and diarrhoea, abdominal pain, abdominal distension and vomiting in the lanreotide Autogel® groups. One serious AE was reported, in which biliary colic occurred approximately 3 months after the single deep subcutaneous dose of lanreotide Autogel® 60 mg and resolved after cholecystectomy.

Pharmacokinetic Modelling

A total of 500 serum samples (109 were BLQ observations) from 50 subjects were used to initially select the disposition pharmacokinetic model of lanreotide after rapid intravenous bolus administration. The pharmacokinetic profiles from two subjects resembled an extravascular administration and therefore were treated accordingly.

Lanreotide disposition was best described by a three-compartment open model compared with the one- and two-compartment open models (p < 0.01). IIV was significant for total serum clearance (CL) and the apparent volume of distribution of the shallow peripheral compartment (V_{p1}; p < 0.01). Table II lists the results from the four main models fitted to the intravenous data. Inclusion of IIV on the rest of the disposition parameters did not lead to a significant decrease in the MOFV (p > 0.05). The off-diagonal elements of the variance-covariance Ω matrix were found to be non-significant (p > 0.05). The residual error was modelled with an additive model.

Once the disposition model for lanreotide was selected, intravenous and subcutaneous data were fitted simultaneously using a total of 1404 serum samples (143 were BLQ observations). The concentration-time profiles (figure 1) showed a similar pattern of drug release for the three dose levels of lanreotide Autogel® and a limited initial burst effect. The C_{max} occurred 7–12 hours after injection. The mean C_{max} values were 4.2, 8.4 and 6.8 ng/mL for the 60, 90 and 120 mg doses, respectively. From day 1 to the end of the study (98, 112 and 112 days for the 60, 90 and 120 mg doses, respectively), lanreotide serum concentrations decreased gradually according to a pseudo first-order elimination profile, reflecting prolonged release of the active compound from the depot.

Table II lists the main results obtained during the selection of the best absorption model. A zero-order absorption rate model performed significantly worse than model 6 in table II. Models based on two parallel absorption processes, or on sequential zero

Table II. Results from the key models fitted to the data obtained during the development of the population pharmacokinetic model of lanreotide Autogel® in healthy subjects

Model	Model structure	ΔMOFV
Disposition models		
1	One compartment; $\omega^2_{CL,Vc}$	
2	Two compartments; $\omega^2_{CL,Vc}$	−190[a]
3	Three compartments; $\omega^2_{CL,Vp1}$	−350[a]
4	Three compartments; $\omega^2_{CL,Vc,Vp1}$	−350[a]
Absorption models		
5	First-order absorption model; $\omega^2_{ka,F}$	
6	First-order absorption model, lag time; $\omega^2_{ka,F}$	−7.3[b]
7	Weibull model, lag time; $\omega^2_{\alpha,\beta,F}$	−277.1[b]
8	Transit compartment model; $\omega^2_{N,MTT,ka,F}$	−35.1[b]
9	First-order absorption model [$k_a = k_b \times e^{-kc \times ln(t)}$], lag time; $\omega^2_{kb,kc,F}$	−304.1[b]
Covariate models		
10	Model 9; CL related to sex	−0.66[c]
11	Model 9; F related to sex	−0.394[c]
12	Model 9; k_b related to sex	−3.16[c]
13	Model 9; F related to dose	0.0[c]

a   Change in MOFV with respect to model 1.

b   Change in MOFV with respect to model 5.

c   Change in MOFV with respect to model 9.

α = scale parameter in the Weibull model; β = shape parameter in the Weibull model; **ΔMOFV** = change in the minimum objective function value provided by NONMEM®; ω^2 = variance of random effects; **CL** = total serum clearance; **F** = total bioavailability; k_a = first-order absorption rate constant; k_b = first-order absorption rate constant 24 h after administration; k_c = first-order rate constant governing the exponential decrease in the k_b as a function of ln(t); **MTT** = mean transit time; **N** = number of transit compartments; **t** = time after drug administration; V_c = apparent volume of distribution of the central compartment; V_{p1} = apparent volume of distribution of the shallow peripheral compartment.
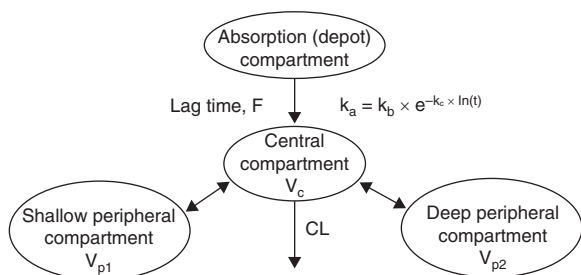
Fig. 2. Schematic representation of the model describing serum lanreotide kinetics after intravenous or deep subcutaneous administration. **CL** = total serum clearance; **F** = total bioavailability; k_a = first-order rate constant of absorption; k_b = value of the k_a 24 h after administration; k_c = first-order rate constant governing the exponential decrease in the k_b as a function of $\ln(t)$; t = time after drug administration; V_c = apparent volume of distribution of the central compartment; V_{p1} = apparent volume of distribution of the shallow peripheral compartment; V_{p2} = apparent volume of distribution of the deep peripheral compartment.

and first-order absorption processes, did not perform significantly better than model 6 (table II).

Three additional absorption models were also tested, and all of them fitted the data significantly better than model 6 (first-order absorption model). Model 9, where the k_a was modelled as a function of time after administration, represented the best model, with a decrease in the MOFV of 27 and 269 points with respect to the Weibull model (model 7) and the transit compartment model (model 8), respectively. In model 9, the k_a was modelled as an exponential decrease (to prevent the k_a from being negative) using equation 1:

$$k_a = k_b \times e^{-k_c \times \ln(t)}$$

(Eq. 1)

where k_b is the value of the k_a 24 hours after administration, k_c is the first-order rate constant governing the exponential decrease in the k_b as a function of $\ln(time)$ and t represents the time after drug administration. Model 9 provided a decrease in the MOFV of 264.7 points with respect to the model where the k_a was modelled as equation 2:

$$k_a = k_b \times e^{-k_c \times t}$$

(Eq. 2)

The inclusion of a lag time and incomplete absolute bioavailability (F) were both significant ($p < 0.01$). The data supported the incorporation of IIV on F, k_b and k_c ($p < 0.01$) in addition to CL and V_{p1}. A different estimation of the variance in the additive residual error between the intravenous and subcutaneous data was included in the model. Figure 2 represents the model structure corresponding to model 9 in table II and shows all of the estimated parameters in the model.

Models 10–13 in table II list some of the results obtained when covariates were incorporated into model 9. All of the covariates tested (bodyweight, age, sex and dose level) elicited only very marginal decreases in the MOFV with respect to model 9 ($p > 0.05$), and therefore none of them were incorporated into the model.

The data supported the estimation of five diagonal elements of the Ω matrix. In order to test the presence of covariance between the diagonal elements, the corresponding correlation coefficients were computed from the full Ω matrix obtained in the nonparametric step. All correlation coefficients were below 0.3, with the exception of the ones corresponding to CL versus F and k_b versus k_c, with values of 0.52 and 0.53, respectively. When those two off-diagonal elements were tested in NONMEM®, both were non-significant ($p > 0.05$).

Table III lists the population model parameter estimates of the selected population pharmacokinetic model represented in figure 2. All parameters were estimated with good precision and, when

Table III. Population pharmacokinetic model parameter estimates of lanreotide in healthy subjects after rapid bolus intravenous administration of an immediate-release formulation of lanreotide and after deep subcutaneous administration of lanreotide Autogel®

Parameter	Estimate[a]	IIV [%CV][a]
CL [L/d]	554 (0.045)	20 (0.24)
V_c [L]	5.29 (0.12)	NE
CL_{D1} [L/d]	358 (0.14)	NE
V_{p1} [L]	4.99 (0.19)	38 (0.43)
CL_{D2} [L/d]	51.4 (0.12)	NE
V_{p2} [L]	4.86 (0.06)	NE
k_b [d^{-1}]	0.038 (0.12)	42 (0.32)
k_c [d^{-1}]	0.079 (0.30)	96 (0.58)
Lag time [d]	0.036 (0.03)	NE
Bioavailability [%]	63 (0.09)	30 (0.27)
Residual error (SD) – intravenous	0.21 (0.053)	NA
Residual error (SD) – subcutaneous	0.31 (0.02)	NA

a Values in parentheses are relative standard errors.

CL = total serum clearance; **CL_{D1}** = distribution clearance between the central and shallow peripheral compartments; **CL_{D2}** = distribution clearance between the central and deep peripheral compartments; **IIV** = interindividual variability; **k_b** = first-order rate constant of absorption 24 h after administration; **k_c** = first-order rate constant governing the exponential decrease in the k_b as a function of $\ln(time)$; **NA** = not applicable; **NE** = not estimated in the model; **SD** = standard deviation in log scale; **V_c** = apparent volume of distribution of the central compartment; **V_{p1}** = apparent volume of distribution of the shallow peripheral compartment; **V_{p2}** = apparent volume of distribution of the deep peripheral compartment.
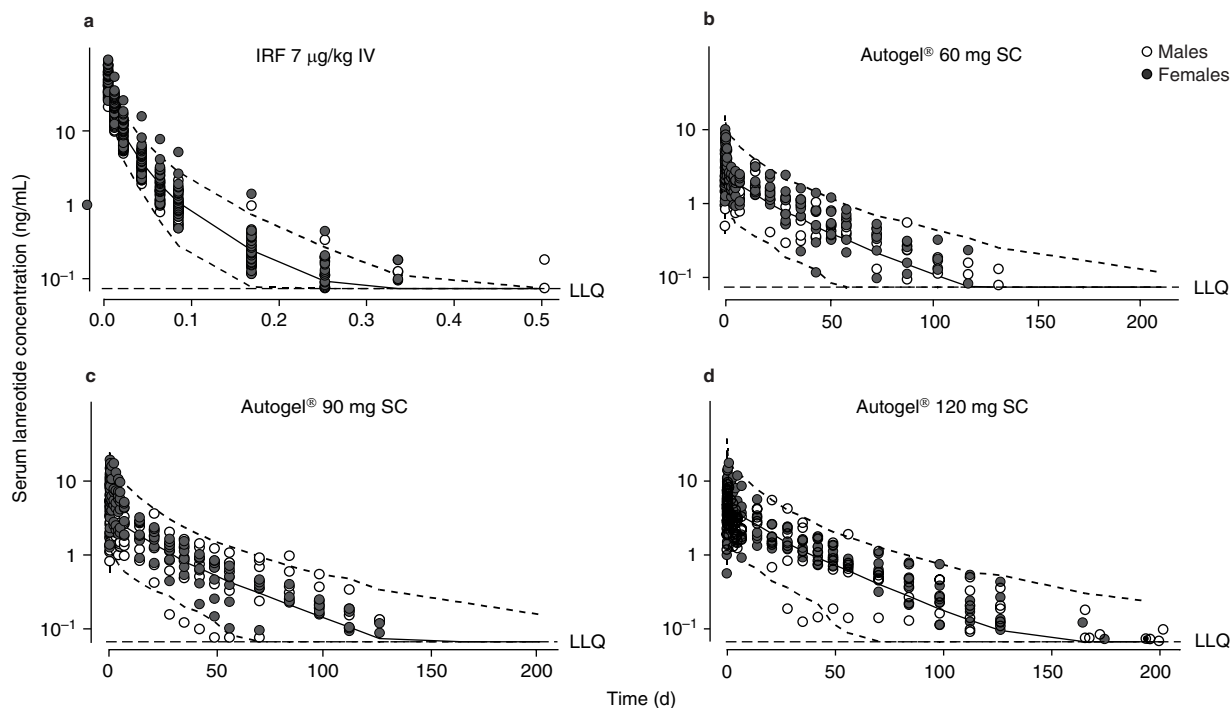
Fig. 3. Results of the internal visual predictive check, showing individual serum concentration-time profiles following a rapid intravenous (IV) bolus dose of 7 µg/kg of the immediate-release formulation (IRF) of lanreotide (**a**) or deep subcutaneous (SC) administration of lanreotide Autogel® at doses of 60 mg (**b**), 90 mg (**c**) or 120 mg (**d**). The solid lines represent the median concentration-time profiles obtained from 1000 model-based simulations. The dashed lines represent the area covering 95% of the simulated observations. **LLQ** = lower limit of quantification.

they were compared with those computed using the results from the nonparametric step, the differences were negligible.

Figures 3 and 4 show the results of the internal visual predictive check, where it can be observed that the selected model is capable of describing the mean tendency of the data, as well as the observed variability. The plot in figure 5 representing the results of the external visual predictive check suggests that the absorption and disposition properties of lanreotide Autogel® are very similar between healthy subjects and acromegalic patients.

The results of the predictive check are shown in table IV, confirming the adequacy of the model to capture two important data descriptors such as the C_{max} and AUC_{last}. It should be noted that in the case of intravenous administration, the dose of lanreotide was adjusted by bodyweight (mean bodyweight in females = 58.8 kg; mean bodyweight in males = 74.7 kg), which explains the 30% decrease in the AUC in females.

The total value of the apparent volume of distribution, calculated as the sum of the apparent volumes of distribution of the central, shallow peripheral and deep peripheral compartments, was 15.14 L, a value lower than the physiological water volume. The estimate of CL was 23.1 L/h and its IIV was approximately 20%. The absolute bioavailability after deep subcutaneous lanreotide

Autogel® administration was 63% and showed moderate IIV (30%). The parameter governing the decrease in the k_a as a function of ln(time) was associated with a high value of IIV (96%), resembling the variability observed in the serum concentration-time profiles (figure 1).

Figure 6a represents the typical profile of the k_a versus time after drug administration predicted by the model. This figure shows that the selected model, with a relatively simple equation, could account for the initial fast subcutaneous release, where the k_a achieves the highest values during the first days of treatment, followed by prolonged release from the depot, where the k_a was approximately constant from day 10 to the end of the study.

In figure 6b, the typical model predicting lanreotide serum concentration-time profiles during 1 year of treatment with lanreotide Autogel® administered subcutaneously once monthly at doses of 60, 90 and 120 mg is presented.[8] The predicted mean C_{min} values at steady state (1.80, 2.70 and 3.60 ng/mL for the 60, 90 and 120 mg doses, respectively) were similar to those observed in patients with acromegaly at the same three dose levels (1.949, 2.685 and 3.575 ng/mL, respectively). It should be noted that after four once-monthly lanreotide Autogel® injections, the fraction of steady state achieved was approximately 94%.
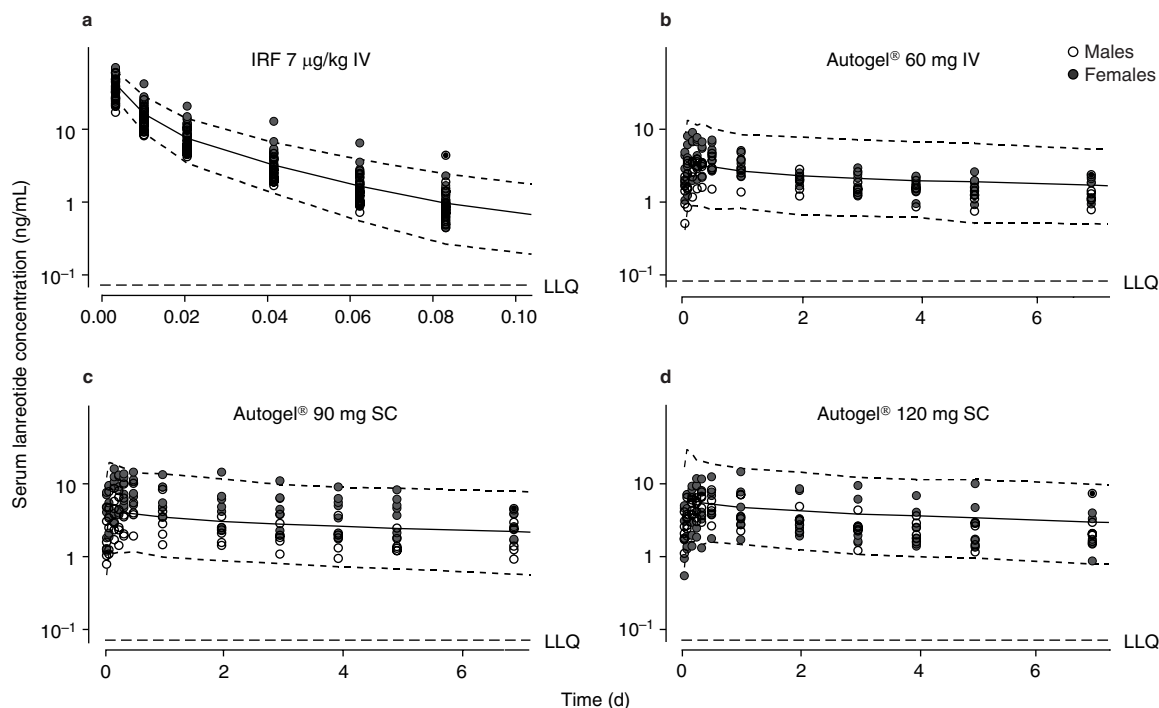
Fig. 4. Results of the internal visual predictive check, showing individual serum concentration-time profiles during the first hours after rapid intravenous (IV) bolus administration of the immediate-release formulation (IRF) of lanreotide (**a**) and during the first week after deep subcutaneous (SC) administration of lanreotide Autogel® at doses of 60 mg (**b**), 90 mg (**c**) or 120 mg (**d**). The solid lines represent the median concentration-time profiles obtained from 1000 model-based simulations. The dashed lines represent the area covering 90% of the simulated observations. **LLQ** = lower limit of quantification.

Discussion

This study represents the first population pharmacokinetic analysis of lanreotide Autogel® in which parameters representing disposition in serum and absorption processes were estimated and the IIV was quantified.

The disposition parameters of lanreotide after rapid intravenous bolus administration of 7 μg/kg have been characterized previously using a noncompartmental approach in 12 healthy subjects; CL was 17 L/h,[9] a value slightly lower than that in the current analysis (23.1 L/h). It is possible that such a discrepancy might have been caused by differences in the design (e.g. sampling times, number of subjects) and the methodology of the data analysis. IIV could only be estimated in CL and V_{p1} and was of moderate-to-low variability. Renal elimination seems to be important for lanreotide[9] and may account for the low estimate of the variability in CL (20%).

The value of CL, together with the small apparent volume of distribution, is responsible for the rapid decline in serum lanreotide concentrations following an intravenous bolus injection.[20] When lanreotide was injected as extended-release formulations, such as micro-particles or Autogel®, a flip-flop situation occurred.[21] This phenomenon prevents estimation of the disposition parameters for extended-release formulations and justifies the design used in the current study where, during the first period, lanreotide was given as an intravenous bolus.

Disposition of lanreotide in serum could be described using a standard three-compartment open model; however, the model for absorption required some elaboration.

Lanreotide acetate can form three-dimensional ordered structures (liquid crystals) at high concentrations in water, and lanreotide Autogel® is a simple formulation comprising lanreotide acetate in water for injection at 0.246 mg of active base per milligram of formulation.[22,23] When lanreotide Autogel® has been extravascularly injected, the contact of the formulation with the physiological medium is thought to cause precipitation (depot formation). Burst control and prolonged release of lanreotide Autogel® over >4 weeks was achieved because of the immediate formation of this depot at the injection site, resulting in a slow release into the circulation from the depot by passive diffusion.

Different absorption models were fitted to the data[15-17] and, finally, a modification of the standard first-order input model, where the absorption rate decreases exponentially as a function of the natural logarithm of time, was selected. The inclusion of only one extra parameter in the absorption model allows the description

of the two sequential absorption phases: (i) the initial fast subcutaneous release, in which the drug that had not precipitated was immediately absorbed into the bloodstream during the first days of treatment; and (ii) the prolonged release of the active compound

Fig. 5. Results of the external visual predictive check, showing individual serum concentration-time profiles (depicted as solid circles) after deep subcutaneous (SC) administration of lanreotide Autogel® at doses of 60 mg (**a**), 90 mg (**b**) or 120 mg (**c**). The solid lines represent the median concentration-time profile obtained from 1000 model-based simulations. The dashed lines represent the area covering 90% of the simulated observations. The arrows indicate the drug administration times.

from the depot by passive diffusion according to a slow pseudo first-order constant rate (see figure 6a). This model resembles the physical changes occurring in the lanreotide Autogel® formulation within the depot compartment when it has been subcutaneously injected. The limited initial burst release and controlled release over several weeks after administration at the three dose levels (60, 90 and 120 mg) demonstrated the robustness of the drug release from the formulation.

Although one might expect a difference in the bioavailability and rate of absorption due to differences in body composition between males and females at the injection site, no clinically relevant covariate effects of sex were found. A similar result was found recently after subcutaneous administration of recombinant human growth hormone.[24] The lack of involvement of body-weight and sex in the IIV of population pharmacokinetic parameters of this model supports the use of fixed dosing and confirms the appropriateness of the deep subcutaneous route of administration for both sexes.

Our population model has been validated. Usually, because of the lack of new data, only internal validation is performed. In this study, an external validation method was also performed. The new data came from a study in which patients with acromegaly received the same doses as in the current analysis, but given in a multiple-dosing schedule (once every 4 weeks).[19] The visual inspection of figure 5 confirms that the model that was developed adequately captures the mean tendency as well as the dispersion of the data. This result indicates also that the pharmacokinetics of lanreotide Autogel® do not differ between healthy subjects and patients with acromegaly, and that they are independent of time after the start of treatment.

Figure 7 is the result of the combination of the population pharmacokinetic model selected in the present study and the population pharmacodynamic model established recently,[8] and allows an exploration of the mean and dispersion of steady-state response-time profiles. These model predictions indicate that after administration of lanreotide Autogel® (120 mg every 28 days) at this steady state, approximately 53% of patients with acromegaly will have a controlled growth hormone level (<2.5 ng/mL) throughout the dosing interval. In addition, in the clinical study performed in patients with acromegaly,[8] it was established that a typical serum lanreotide concentration of 1.13 ng/mL reduced serum growth hormone levels to <2.5 ng/mL. Taking into account the model predictions for the C_{min} at steady state ($C_{min,ss}$), the percentage of subjects who would achieve lanreotide concentrations higher than this threshold at steady state are 69%, 86% and
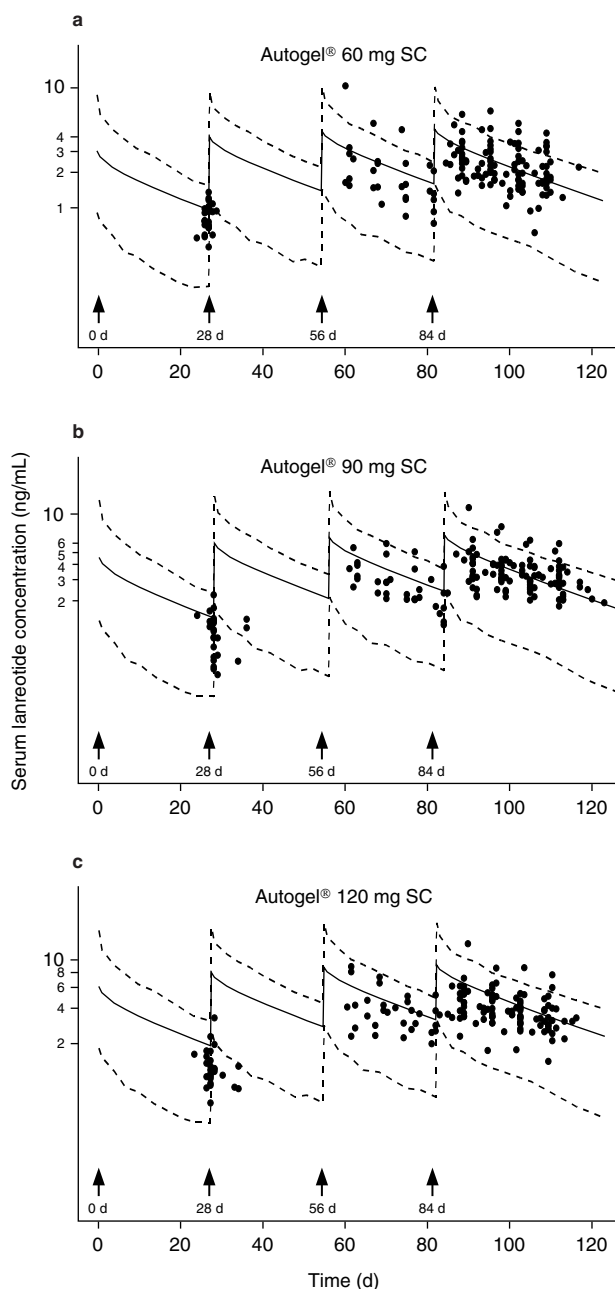
Table IV. Results from the predictive check obtained from 1000 simulations with the selected population pharmacokinetic model

Lanreotide dose	C_max (ng/mL)			AUC_last (ng • day/mL)		
	observed[a]		simulated[b]	observed[a]		simulated[b]
	female	male		female	male	
7 µg/kg				0.72	1.0	Female: 0.74 (0.68, 0.8) Male: 0.94 (0.88, 1.01)
60 mg	3.2	5.1	4.8 (2.5, 10)	64.5	74.3	61.6 (44, 83.5)
90 mg	5.1	11.2	8 (3.6, 13.8)	97.4	115.7	95.4 (68.6, 129.6)
120 mg	6.1	7.5	8.6 (4.7, 16.6)	127.3	137	133.7 (96.3, 178.7)

a   Values are expressed as mean.

b   Mean with 2.5th and 97.5th percentiles in parentheses.

AUC_last = area under the serum concentration-time curve from time zero to the time of last measurable concentration; **C_max** = maximum serum concentration.

92% for 60, 90 and 120 mg, respectively, administered every 28 days.

Mean lanreotide concentrations remain higher than 0.44, 0.54 or 0.81 ng/mL at 56 days after a single lanreotide Autogel® injection of 60, 90 or 120 mg, respectively. These results suggest that extending the dosing interval from 28 to 56 days could

Fig. 6. (**a**) Absorption rate constant (k_a) versus time relationship predicted from the population model. (**b**) Typical model-predicted lanreotide serum concentration-time profiles during treatment with lanreotide Autogel® administered subcutaneously once monthly at doses of 60, 90 or 120 mg. The arrows indicate the drug administration times.

provide therapeutically effective drug concentrations at steady state. Simulation after repeated lanreotide Autogel® injections at a dose of 120 mg every 56 days was performed using the pharmacokinetic model that was developed (figure 8). The predicted $C_{min,ss}$ (1.14 ng/mL [95% CI 0.19, 2.64]) was slightly lower than the predicted drug concentration after 60 mg every 28 days (1.80 ng/mL [95% CI 0.48, 3.04]), showing that 81% of subjects treated with 120 mg every 56 days will have lanreotide concentrations higher than 0.48 ng/mL (the lower CI limit after 60 mg every 28 days). The mean predicted lanreotide concentration (1.14 ng/mL) is in the same range as that found in a clinical study of patients with active acromegaly (1.6 ng/mL), in which effectiveness was demonstrated with 120 mg of lanreotide Autogel® every 56 days.[25] In addition, 95% of subjects treated with 120 mg every 56 days will have $C_{min,ss}$ values higher than the lanreotide concentration that produced a 50% decrease in the maximum reduction in growth hormone (EC_{50}; 0.206 ng/mL) established in a previous publication.[8] These findings provide evidence that it is feasible to extend the dosing interval for lanreotide Autogel® 120 mg to 56 days (1.14 ng/mL) to achieve a response in the growth hormone reduction similar to that achieved after 60 mg every 28 days. The primary benefit will be a substantial reduction in the number of lanreotide Autogel® injections required to achieve a therapeutic effect.[8]

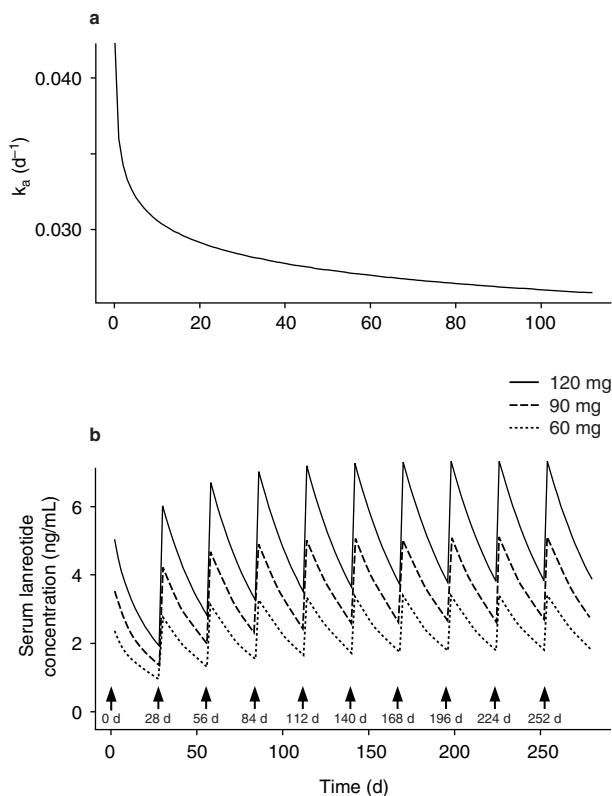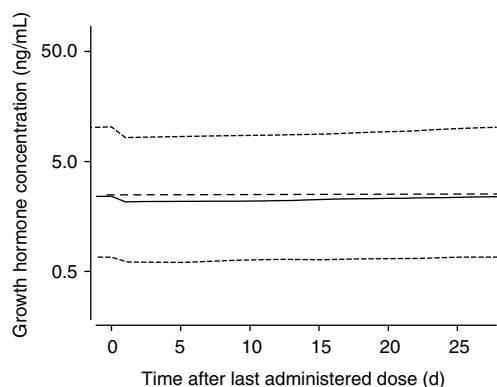## Conclusions

The disposition characteristics of lanreotide administered as a rapid intravenous bolus injection of 7 µg/kg were best described with a three-compartment open model. Estimates of IIV were moderate (<40%). The total apparent volume of distribution (15.1 L) was lower than the physiological water volume, and the estimate of CL was 23.1 L/h.

Fig. 7. Simulated response-time profiles after the last administration of 6 months' treatment of deep subcutaneous lanreotide Autogel® 120 mg every 28 days. The solid line corresponds to the median of the simulated response-time after last dose profiles, and the dashed lines represent the 5th and 95th percentiles of the simulated response data. The dotted line shows the value corresponding to controlled growth hormone concentrations (<2.5 ng/mL).

The use of mixed-effects modelling allowed a good description of the pharmacokinetics of deep subcutaneous lanreotide Autogel® in healthy subjects. Using a simple modified first-order rate constant of absorption, the model was adequate to describe the course of lanreotide release over at least a 6-month postadministration period. The absorption rate constant decreased exponentially as a function of ln(time), resembling the changes occurring within the lanreotide Autogel® formulation following subcutaneous injection. Limited initial burst release and controlled release over a period of several weeks after single-dose administration dem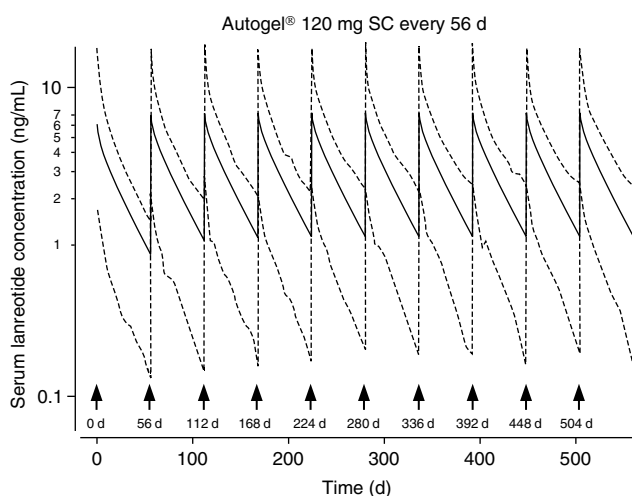onstrated the feasibility of the lanreotide Autogel® formulation for longer-term treatment, with administration at least every 4 weeks. The rate and extent of absorption of lanreotide after deep subcutaneous Autogel® injection was not dependent on the administered dose in the range of 60–120 mg. The bioavailability was 63% of the administered dose and showed low IIV (27%). No clinically relevant relationship with any of the demographic covariates that were tested (age, bodyweight, sex, dose level) was found in the absorption and disposition properties.

The model-based simulations provide evidence that it may be clinically feasible to extend the dosing interval for lanreotide Autogel®. A dose of 120 mg given every 56 days would achieve a similar response in growth hormone reduction to that achieved with 60 mg every 28 days.

Acknowledgements

Fig. 8. Simulated pharmacokinetic profile after repeated lanreotide Autogel® administration at a dose of 120 mg every 56 days. The solid line corresponds to the typical pharmacokinetic profile and the dashed lines represent the area covering 90% of the simulated pharmacokinetic profiles. The arrows indicate the drug administration times.

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