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ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetic Analysis of Lanreotide Autogel®/Depot in the Treatment of Neuroendocrine Tumors: Pooled Analysis of Four Clinical Trials

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Abstract

Background and Objectives Lanreotide Autogel® (lanreotide Depot in the USA) has demonstrated anti-tumor activity and control of the symptoms associated with hormone hypersecretion in patients with neuroendocrine tumors. The objectives of this study were to describe the pharmacokinetics of lanreotide Autogel® administered 4-weekly by deep subcutaneous injections of 60, 90, or 120 mg in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), to quantify the magnitude of inter-patient variability (IPV), and to identify those patient characteristics that impact on pharmacokinetics.

Methods Analyses were based on pooled data from clinical trials. A total of 1541 serum concentrations from 290 patients were analyzed simultaneously by the population approach using NONMEM® version 7.2. Covariates evaluated included demographics, renal and hepatic function markers, and disease-related parameters.

Results Serum profiles were described by a one-compartment disposition model in which the absorption process was characterized by two parallel pathways following first- and zero-order kinetics. The estimated apparent volume of distribution was 18.3 L. The estimated apparent total serum clearance for a typical 74 kg patient was 513 L/day, representing a substantial difference in clearance in this population of patients with respect to healthy volunteers that could not be explained by any of the covariates tested. Body weight was the only covariate to show a statistically significant effect on the pharmacokinetic profile, but due to the overlap between the pharmacokinetic profiles of patients with lower or higher body weights the effect of body weight on clearance was not considered clinically relevant. The IPV was low for clearance (27 %) and moderate to high for volume of distribution (150 %) and the absorption constant (61 %).

Conclusions Using two mechanisms of absorption, the pharmacokinetics of lanreotide Autogel® were well-described in patients with GEP-NET. None of the patient characteristics tested were of clinical relevance to potential dose adjustment in clinical practice.

Key Points

A population PK model for Lanreotide autogel® has been established in patients with gastroenteropancreatic neuroendocrine tumors.

Elimination of lanreotide in this type of patient population is reduced compared to healthy volunteers and patients with acromegaly.

Body weight showed statistical effect of the apparent total clearance which was not considered clinically relevant.

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1 Background

Somatostatin analogs are the treatment of choice for hormone-related syndromes associated with functioning neuroendocrine tumors (NETs), such as carcinoid syndrome. Lanreotide Autogel® (known as lanreotide Depot in the USA) is a synthetic octapeptide analog of somatostatin with a longer half-life than the native molecule and with selectivity for somatostatin receptor (SSTR) 2 and, to a lesser extent, SSTR 5 [1]. Lanreotide Autogel® was launched in the UK in 2001 and is now approved in more than 60 countries worldwide for indications including acromegaly and clinical symptoms associated with NETs, and also for improvement of progression-free survival in patients with unresectable, well- or moderately differentiated, and locally advanced or metastatic gastroenteropancreatic NETs (GEP-NETs) [2].

The pharmacokinetic properties of lanreotide Autogel® in healthy volunteers and patients with acromegaly have been reported previously [3]. This formulation, subcutaneously injected, acts as depot providing a slow and controlled release over 4 weeks with 60–70 % absolute bioavailability (F). The apparent volume of distribution (V_d/F) and the total clearance were estimated to be 15 L and 23 L/h, respectively, and were not modified by repeat dosing. Lanreotide is thought to be eliminated mainly by renal metabolism and biliary excretion, and the renal serum clearance of lanreotide was found to be reduced in patients with severe chronic renal insufficiency when compared with healthy subjects [4].

To date, the pharmacokinetics of lanreotide Autogel® in patients with functioning and non-functioning GEP-NETs has not been reported. Such evaluation is essential for both dose adjustment and a complete understanding of clinical response to treatment. The objectives of the current analysis were to describe the pharmacokinetic characteristics of deep subcutaneous injections of lanreotide Autogel® administered as 60, 90, or 120 mg every 4 weeks in patients with functioning and non-functioning GEP-NETs, to quantify the degree of inter-patient variability (IPV) in the pharmacokinetic parameters, and to identify patient characteristics that may influence the pharmacokinetic properties. Data from four clinical studies of patients with GEP-NETs were pooled to determine the influence of demographic factors, clinical characteristics, and disease parameters on the IPV of the pharmacokinetics of lanreotide Autogel® in this patient population.

2 Methods

All patients provided written informed consent consistent with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice (ICH–GCP) and local legislation. All studies were performed in accordance with the Declaration of Helsinki and were approved by the institutional review board of the ethics committee at each study site.

2.1 Overview of Clinical Study Designs

2.1.1 Study 1: CLARINET

CLARINET (Controlled study of Lanreotide Antiproliferative Response In NeuroEndocrine Tumors) [5] was a phase III, randomized, double-blind, placebo-controlled study conducted over 96 weeks in 204 patients at 48 centers worldwide; lanreotide Autogel® 120 mg was administered every 4 weeks in patients with non-functioning GEP-NETs.

Serum lanreotide concentrations were measured at (1) baseline; (2) 4 weeks before first drug administration; (3) between the first and second injections (between week 1 and week 4): patients were randomized 1:1 to either (a) two blood samples at 4 h (range 2–12 h) and 7 days (range 6–8 days) after drug administration or (b) two blood samples at 3 days (range 2–4 days) and 14 days (range 12–16 days) after drug administration; (4) between the sixth and seventh injections (between week 20 and week 24) using the same schedule as described in (3); and (5) prior to drug administration at all treatment period visits including completion or withdrawal. Putative anti-lanreotide antibodies were measured at weeks 1, 24, 48, 72, and 96.

2.1.2 Study 2: ELECT

ELECT [6] was a phase III–IV 48-week study consisting of a 16-week, double-blind, randomized, placebo-controlled phase in which lanreotide Autogel® 120 mg or placebo was administered, followed by a 32-week initial open-label phase in which all patients received lanreotide Autogel®. Patients with gastrointestinal NETs and a history of carcinoid syndrome ($n = 115$) were randomly allocated to study drug or placebo at 39 centers worldwide.

Serum lanreotide concentrations and putative anti-lanreotide antibodies were measured at week 16 before and 4 h (±2 h) after drug administration, at week 20 before drug administration, and at the end of the initial open-label phase (week 48).

2.1.3 Study 3

A phase II, single-arm, open-label study was conducted at 17 Spanish centers [7]. Patients ($n = 30$) with progressive functioning/non-functioning gastrointestinal, pancreatic, and lung NETs received lanreotide Autogel® 120 mg every 4 weeks over ≤92 weeks, to a maximum of 23 injections.

Serum lanreotide concentrations and putative anti-lanreotide antibodies were measured before drug administration and every 12 weeks from week 8 to week 92.

2.1.4 Study 4

An open-label, dose-titration study was conducted in patients with symptomatic carcinoid NETs ($n = 71$) [8]. Lanreotide Autogel® was given at titrated doses every 4 weeks over 6 months: the first two injections were of 90 mg, after which the dose was increased to 120 mg in patients who did not respond to treatment and decreased to 60 mg in those who did respond. Patients on 120 mg remained at that dose, others continued the titration scheme until study end.

Serum lanreotide concentrations were measured before drug administration and every 4 weeks from week 4 to week 24.

2.2 Bio-Analytical Method

Serum lanreotide was measured by using a validated radioimmunoassay[4] with a lower limit of quantification of 0.078 ng/mL, overall precision (inter- and intra-assay) and reproducibility expressed as percentage coefficient of variation (CV) of 2.3–13.6 %, and a CV of 6.2–13.2 % for concentrations in the range 0.1–10 ng/mL. Accuracy was >89 %. When stored at −20 °C, serum lanreotide was stable for 28 months.

2.3 Study Population

All patients providing at least one valid serum concentration and receiving active treatment with lanreotide Autogel® were included in the analysis.

Covariates included in the population pharmacokinetic analysis were age, alanine aminotransferase (SPGT), serum albumin (ALB), anti-lanreotide antibodies, aspartate aminotransferase (SGOT), body weight (BW), body mass index (BMI), creatinine clearance (CL_{CR}) calculated using the Cockroft-Gault expression, ethnicity (RACE), functioning/non-functioning classification of the endocrine tumor (FNTC), gender (SEX), total bilirubin (BILI), cholecystectomy (CYST), and primary tumor location (TLOC).

2.4 Population Pharmacokinetic Model Building

Data were transformed logarithmically and NONMEM® version 7.2 [9] software (Icon Development Solutions, Ellicott City, MD, USA), using first-order conditional estimation and the INTERACTION option, was used to fit all serum concentration data simultaneously. Model development was performed in three steps: (1) a base population model, defined as a population model providing proper data description without incorporating covariates, was built; (2) the covariate model was developed by selecting those patient characteristics that showed significant impact on the model parameters; and (3) the selected model was evaluated.

IPV was modeled exponentially. Non-diagonal elements of the Ω variance–covariance matrix were also considered. As full pharmacokinetic profiles were not obtained in all studies at every visit, inter-occasion variability was not considered. Residual variability was modeled considering an additive error in the logarithmic domain of the transformed data.

2.4.1 Model Selection Criteria

Selection between models was based on the evaluation of different statistical and graphical criteria: precision of parameter estimates obtained from the analysis of 1000 bootstrap datasets using the software Perl-speaks-NONMEM (PsN) [10], goodness-of-fit plots, and minimum value of the objective function value provided by NONMEM® and approximately equal to $-2 \times \log$ (likelihood) ($-2LL$). Differences between two hierarchical (nested) models were compared with a Chi squared (χ^2) distribution in which a decrease of 3.84, 6.63, 7.88, or 11.87 points in $-2LL$ was considered significant at the 5, 1, 0.5, and 0.1 % levels for one extra parameter in the model, respectively. Non-nested models were compared using the Akaike information criteria (AIC) [11] calculated as $-2LL + 2 \times NP$, where NP is the number of parameters in the model. The model with the lowest value of AIC, given the precision of model parameters and an adequate description of the data, was selected.

2.4.2 Base Population Model

Because of the complex absorption profile of lanreotide in healthy volunteers [3], the initial model consisted of an absorption model including two input parallel mechanisms accounting for first- and zero-order rate input processes each associated with a corresponding latency time. Other absorption models including two parallel first-order processes, or simpler models such as the zero- or first-order input models were also explored. Drug disposition was described by compartmental models parameterized in apparent volumes of distribution and elimination clearances.

2.4.3 Covariate Model Development

Covariate selection was performed using the stepwise covariate modeling (SCM) implemented in the PsN software [10]. Significance levels were set to 0.05 and 0.005 for the forward inclusion and backward deletion

approaches, respectively. The stepwise modeling selection approach was performed with the covariate information gathered at baseline. For those covariates that changed during the period of the study and were significant in the SCM, the impact of that change on pharmacokinetics was evaluated [12].

2.4.4 Final Model Evaluation

The final model was challenged to determine whether further simplification was possible, or if there were aspects that could be improved. Parameter precision was evaluated by performing 1000 non-parametric bootstrap analyses using PsN [10] and Xpose [13].

The selected model was evaluated by performing predictive checks based on computer simulation exercises. A total of 500 datasets with the same study design characteristics as the original were simulated. The 2.5th, 50th, and 97.5th percentiles of the simulated observations in each dataset were computed for all time intervals and the 95 % prediction interval of each calculated percentile was obtained and plotted against the 2.5th, 50th, and 97.5th percentiles obtained from the raw data.

Individual serum concentrations were simulated and the following pharmacokinetic descriptors were obtained: maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), average serum concentration within the dosing interval (C_{avg}), and the area under the serum concentration–time curve (AUC) within the dosing interval at steady state (AUC_{τ}).

The summary statistics of the pharmacokinetic descriptors defined above were performed for the whole population and sub-categories of the population: (1) body weight ≤62, ≥70 to ≤77, and ≥89 kg; (2) gender. Those three categories were chosen as they correspond to the 20th, 50th, and 80th percentiles of the weight distribution in the studied population.

3 Results

3.1 Description of the Data

Patients received a median (range) of 24 (1–24), 18 (2–74), 12 (2–12), and 24 (4–46) lanreotide Autogel® injections in studies 1, 2, 3, and 4, respectively. Analyses were performed on 1541 serum lanreotide concentration values from 290 patients. The number of samples per patient ranged from 1 to 11, with mean values ranging approximately from three to eight samples between the different clinical trials.

A total of 101 (Study 1), 104 [Study 2; comprising 59 in the double-blind phase (56 of whom continued to the initial open-label phase) and 45 in the open-label phase randomized to placebo], and 30 patients (Study 3) received lanreotide Autogel® 120 mg, corresponding to 793, 286, and 111 serum samples, respectively. In the dose-titration study (Study 4), a total of 71 patients received the 60 mg ($n = 17$), 90 mg ($n = 67$), and/or 120 mg ($n = 46$) doses from which 57, 148, and 146 corresponding serum concentration values were derived.

Eleven serum lanreotide samples obtained from six patients revealed the presence of anti-lanreotide antibodies at concentrations of lanreotide of 4.7–8.19 ng/mL.

Figure 1 shows individual serum lanreotide concentration as a function of time for each clinical trial. No outliers were identified.

3.2 Covariates Tested for Significance

Covariates tested for significance are listed in Table 1. A number of patients were missing information for BW (2), CL_{CR} (2), and BMI (86). BMI was not tested for significant covariate effects. For the two patients with BW and CL_{CR} values missing, covariate effects were ignored. The three non-continuous covariates tested were SEX, FNTC, and TLOC. As the majority of the patients were white, RACE was not tested as a significant covariate.

Most continuous covariates changed for individual subjects over the course of the studies. The CV was calculated for each continuous covariate, and varied up to 108 % (BILI).

Exploratory analysis of the covariates revealed that, as expected, there were apparent correlations between BW and CL_{CR}, and between age and CL_{CR} (data not shown). The number of patients with normal renal function (>90 mL/min) was 130, while the number of patients with mild (60–89 mL/min), moderate (30–59 mL/min), or severe (<30 mL/min) renal impairment was 100, 58, and 2, respectively.

3.3 Population Pharmacokinetic Model Building

3.3.1 Base Population Model

Attempts to model the absorption process using zero-, first-, or two parallel first-order inputs yielded a poorer description of the data than the model based on two parallel mechanisms representing first- and zero-order rate input processes ($p < 0.001$). Inclusion of the latency times associated with each input mechanism did not improve the fit significantly ($p > 0.05$).

As drug disposition was described equally well by the one-compartment model and the more complex two-compartment model ($p > 0.05$), the former was selected for further development. The structure of the population

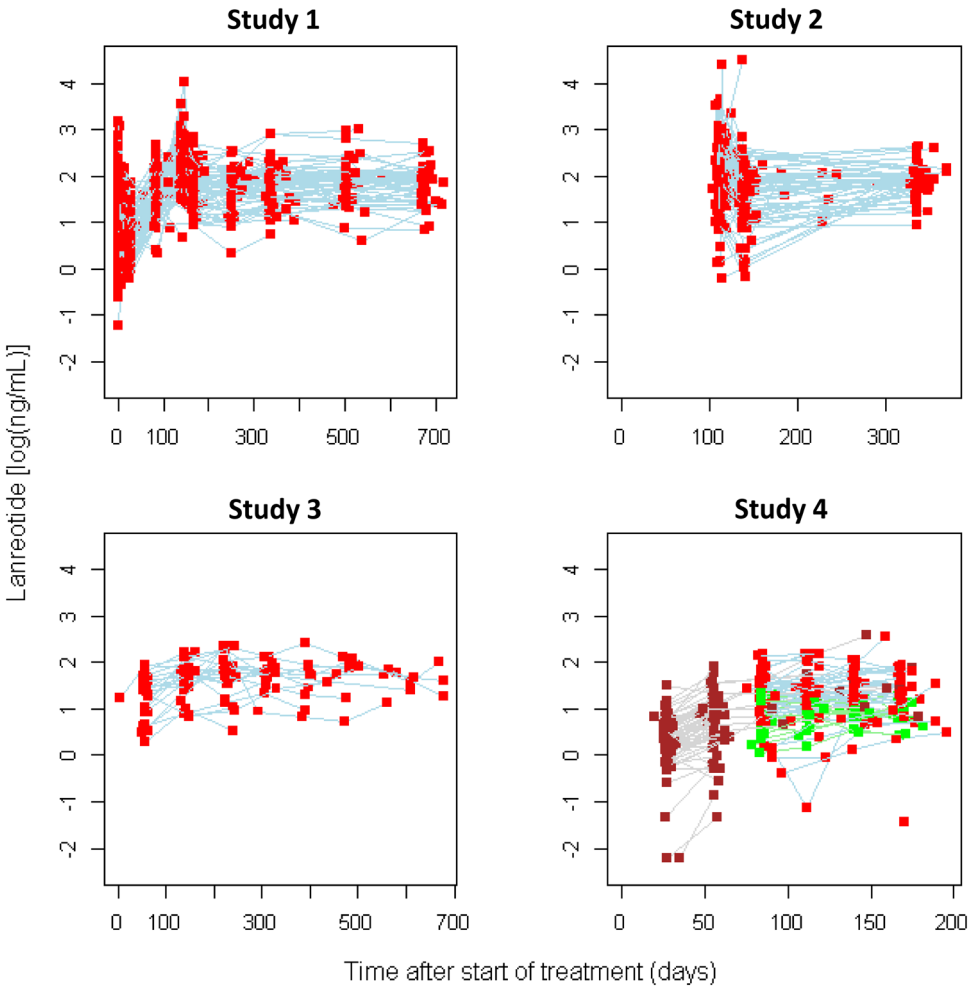

Fig. 1 Serum lanreotide concentration–time profiles corresponding to each of the clinical trials involved in the current evaluation: *Study 1* CLARINET [5], *Study 2* ELECT [6], *Study 3* [6], and *Study 4* [8]. *Symbols in green*, *brown*, and *red* represent concentrations of lanreotide in serum corresponding to doses of 60, 90, and 120 mg, respectively

pharmacokinetic model selected for lanreotide Autogel® is represented schematically in Fig. 2.

IPV was included on the first-order rate constant of absorption (k_a), the V_d/F, apparent total serum clearance (CL/*F*), and the fraction of the dose absorbed following the first-order rate process (F_1). The fraction of the absorbed dose following a zero-order process (F_2) was calculated as $1 - F_1$. Inclusion of IPV on *F* and on the parameter representing the duration of the zero-order rate input process (D_0) did not affect the results significantly ($p > 0.05$). Similar results were obtained when the non-diagonal elements of the Ω variance–covariance matrix were estimated ($p > 0.05$).

Typical estimates corresponding to F_1 and F_2 were 98.5 and 1.5 %, respectively. The zero-order rate process takes place during the first 2.96 days after injection, and the first-order input process occurs slowly with a k_a of 0.0161 day^{-1}, corresponding to a half-life of 43.6 days. CL/*F* and V_d/F were 516 L/day and 20.2 L, respectively. The estimates of IPV were 2.5 % (F_1), 61 % (k_a), 33 % (CL/*F*), and 142 % (V_d/F).

For some parameters (V_d/F, k_a, and F_1) in the model the percentage shrinkage was high (>20 %), indicating that the empirical Bayes estimates were not informative [14]. No major trends were identified in the goodness-of-fit plots and parameters were estimated with high precision (data not shown).

3.3.2 *Covariate Model Selection*

The set of covariates tested for each parameter in the model were: (1) CL/F ~ SEX, AGE, BW, SGPT, SGOT, BILI, ALB, CL_{CR}, TLOC, FCTN; (2) V_d/F ~ SEX, AGE, BW, BILI, ALB, TLOC, FCTN; (3) k_a ~ SEX, AGE, BW; and (4) F_1 ~ SEX, AGE, BW. These choices were based on standard pharmacokinetic principles taking into account route of administration. For continuous covariates, both linear and non-linear relationships were explored.

The selected full covariate model obtained in the forward-inclusion approach comprised the following covariate effects: (1) BW and SEX on F_1; and (2) BW, TLOC, AGE, and BILI on CL/*F*.

Table 1 Summary of patient characteristics measured at baseline

Covariate	Study 1 [5] ($n = 96$)	Study 2 [6] ($n = 98$)	Study 3 [7] ($n = 69$)	Study 4 [7] ($n = 27$)	Pooled data ($n = 290$)
Continuous[a]					
Age (years)	63.3 (15.4)	58.5 (19.3)	59.7 (20)	62.3 (16.6)	60.7 (18.2)
BW (kg)	78 (21.4)	75.5 (22.3)	72.4 (23.5)	69.3 (18.6)	75.1 (22.2)
SGPT (IU/L)	28.3 (78)	26.4 (75.6)	31.3 (51.7)	26.7 (44.2)	28.2 (68.3)
SGOT (IU/L)	29.4 (63)	27.6 (51.7)	28.1 (40.9)	26.3 (33.3)	28.1 (52.5)
BILI (mg/dL)	0.65 (91)	0.54 (79.8)	0.55 (58.6)	0.7 (44.4)	0.59 (77.8)
ALB (g/L)	4.3 (7.9)	4.3 (9.9)	4.0 (11.7)	4.1 (7.1)	4.2 (10.1)
CL_{CR} (mL/min)	88.9 (35.2)	95.5 (37.1)	87.1 (38.2)	77.5 (33.3)	89.8 (36.9)
Non-continuous[b]					
SEX					
Male	50	41	35	14	140
Female	46	57	34	13	150
FCTN					
Nonfunctioning	96	0	0	10	106
Functioning	–	98	69	17	184
RACE					
Asian	2	8	0	0	10
African American	1	8	1	0	10
White	93	81	68	27	269
Other	0	1	0	0	1
TLOC					
Pancreas	39	0	0	7	46
Foregut	0	0	4	6	10
Midgut	31	0	46	10	87
Hindgut	11	0	1	1	13
Other	1	0	12	0	13
Unknown	14	98	6	3	121

ALB serum albumin, *BILI* total bilirubin, *BW* body weight, CL_{CR} creatinine clearance calculated using the Cockroft-Gault expression, *FCTN* functioning/non-functioning status of neuroendocrine tumor, *SGOT* aspartate aminotransferase, *SGPT* alanine aminotransferase, *TLOC* primary tumor location

[a] Values are expressed as mean [coefficient of variation (%)]

[b] Values are listed as total number per category

During the backward-deletion approach, the covariate BW showed no significant effects on F_1. The selected covariate model has the following structure (Eqs. 1 and 2):

$$F_1 = \theta_{F_1} \times (1 + \theta_{SEX}) \quad (1)$$

where $\theta_{\mathrm{SEX}} = 0$ for females.

$$CL/F = \theta_{CL} \times [1 + \theta_{BW\_CL} \times (BW - 74)] \times \left(\frac{AGE}{62}\right)^{\theta_{AGE}} \times e^{\theta_{BILI} \times BILI} \times (1 + \theta_{TLOC}) \quad (2)$$

where 74 and 62 are the median BW (kg) and AGE (years), respectively, in the population studied, and θ_{TLOC} corresponds to different estimates based on primary tumor location.

IPV magnitude was reduced from 32 to 22 % for CL/F and from 2.5 to 1.1 % for F_1. V_d/F and k_a estimates of variability remained almost unchanged between the base population model and the final covariate model. The resulting value of −2LL was 129.61 lower than the one obtained for the base population model.

3.3.3 Final Population Model

As 46 % of the patients had unknown ($n = 121$) or 'other' primary tumor location, and taking into account that the greatest TLOC effects on CL/F were estimated for 'foregut' ($n = 10$), 'hind gut' ($n = 13$), and 'other' ($n = 13$), the covariate effects of TLOC were questionable and were removed from the model.

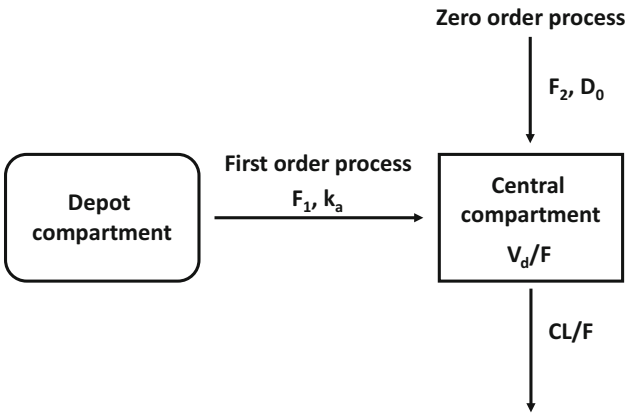

Fig. 2 Schematic representation of the pharmacokinetic model for lanreotide. *CL/F* apparent total serum clearance, D_0 duration of the zero-order input process, *F* absolute bioavailability (not known and arbitrarily set to 1), F_1 and F_2 fractions of the absorbed dose following a first- and a zero-order rate absorption process, respectively, k_a first-order rate constant of absorption, V_d/F apparent volume of distribution

For the effects of SEX on F_1, the final covariate model provided estimates of F_1 for males and females of 0.974 and 0.994, respectively, which has a negligible effect on F_1 but a large impact on F_2 [2.6×10^{-2} (males), 6×10^{-3} (females)], the derived parameter governing C_{max} values.

BW rather than CL_{CR} was selected for CL/*F*; although both covariates were highly correlated, the dataset contained 14 CL_{CR} values >150 mL/min (these were probably non-physiological).

The covariate effects of BILI and AGE were not significant ($p > 0.05$) once the covariate TLOC was removed from the model, but the effect of BW on CL/*F* continued to be significant ($p < 0.001$).

Changes in BW during the study were accounted for by using the approach suggested by Wählby et al. [12]. The value of −2LL was reduced by 7.96 points, but there was no reduction in IPV and the remaining parameters remained unchanged. The dose of lanreotide administered appeared to have no effect on CL/*F* ($p > 0.05$). Estimates of CL/*F* for the 60 and 90 mg doses were increased by 13 and 24 %, respectively, when compared with the 120 mg dose, indicating the absence of a monotonic relationship between CL/*F* and dose. However, the number of patients receiving 60 and 90 mg was far lower than the number receiving the 120 mg dose of lanreotide Autogel®.

Table 2 lists the corresponding estimates of the model parameters. Goodness-of-fit plots are shown in Electronic Supplementary Material Figure S1.

According to the selected model, the mean V_d/F was 18.3 L (no effects of covariates were found for V_d/F). The mean CL/*F* was 513 L/day for a 74 kg subject, and the mean k_a was 0.0159 day^{-1}, corresponding to an absorption half-life of 43.6 days. IPV of CL/*F* decreased from 33 to 27 % in comparison with the base population model when BW measured at the beginning of the study was included as a covariate. Incorporation of SEX effects on F_1 reduced the IPV of F_1 from 2.5 to 1.05 %. The IPV value that is marginal with respect to F_1 has a non-negligible impact on individual differences in F_2. IPV was moderate for all parameters with the exception of V_d/F. Typical population estimates of the different parameters were very similar between the base model and the final model.

Results of the bootstrap analysis indicated that all parameters in the model were estimated with adequate precision. η-Shrinkage values were >20 % and the ε-shrinkage was 17.5 %. One explanation for the high shrinkage percentage values is that there were few data-points in two of the clinical trials evaluated. The substantial shrinkage values reported in Table 2 indicate that (1) empirical Bayes estimates should not be used to drive the covariate selection process; and (2) the individual predictions versus observations plot is uninformative, and other type of model diagnostics are advisable.

Figure 3 shows the results of the prediction-corrected visual predictive checks. The model performs adequately in capturing the central trend and the spread of the data for each of the clinical trials. Individual lanreotide serum concentration profiles for a sample of patients from each of the four clinical trials are shown in Electronic Supplementary Material Figure S2.

The relationship between conditional weighted residuals and individual covariate values is illustrated in Electronic Supplementary Material Figure S3, demonstrating the absence of trends when BW and SEX were incorporated as selected covariates for CL/*F* and F_1 in the final model.

3.4 Exploration of Covariate Effects

Figure 4 explores the covariate effects of BW and SEX on serum lanreotide profiles during a 1-year treatment period with 4-weekly lanreotide Autogel® 120 mg. The plot predicts a high degree of overlap between the panels. The impact of SEX on the serum profiles is minor, whereas BW has a greater effect. The values of the weights chosen in this simulation exercise correspond to the 2.5th, 50th, and 97.5th percentiles of the weight distribution in males and females.

Figure 5a shows the pharmacokinetic profiles for those patients who were positive for anti-lanreotide antibodies. The profiles were superimposed on the 5th and 95th percentiles of the remaining patient population. The resulting graphic confirms that the presence of anti-lanreotide antibodies have no effect on the pharmacokinetic profile. RACE effects were not tested during the pharmacokinetic model building process. However, an overlay of the 90 %

Table 2 Population pharmacokinetic parameter estimates of lanreotide Autogel® administered to patients with functioning and non-functioning endocrine tumors

Parameter/covariate model	Estimates	2.5th to 97.5th[a]	Shrinkage (%)
CL/F (L/day) $= \theta_{CL} \times [1 + \theta_{BW} \times (\text{weight} - 74)]$	$\theta_{CL} = 513$	491 to 537	–
	$\theta_{BW} = 9.77 \times 10^{-3}$	$(6.95 \text{ to } 0.12) \times 10^{-3}$	
V_d/F (L)	18.3	10.2 to 41.5	–
k_a (day^{-1})	1.59×10^{-2}	$(1.44 \text{ to } 1.82) \times 10^{-2}$	–
$F_1 = \theta_{F1} \times (1 + \theta_{SEX})$	$\theta_{F1} = 0.994$	0.977 to 0.996	–
	$\theta_{SEX} = -0.024$ (males)	−0.0058 to −0.058	
	$\theta_{SEX} = 0$ (females)		
D_0 (day)	2.96	2.05 to 3.03	–
$IPV_{CL/F}$ (%)	27	21 to 32	24.2
$IPV_{V/F}$ (%)	150	107 to 197	63.0
IPV_{k_a} (%)	61	49 to 70	22.0
IPV_{F1} (%)	1.05	1.07 to 1.3	42.9
Residual error [log(ng/mL)]	0.275	0.25 to 0.3	17.5

BW body weight, *CL/F* apparent total serum clearance, D_0 duration of the zero-order input process, F_1 fraction of the absorbed dose following a first-order rate absorption process, *IPV* inter-patient variability, k_a first-order rate constant of absorption, V_d/F apparent volume of distribution

[a] 95 % confidence intervals calculated from 1000 bootstrap datasets

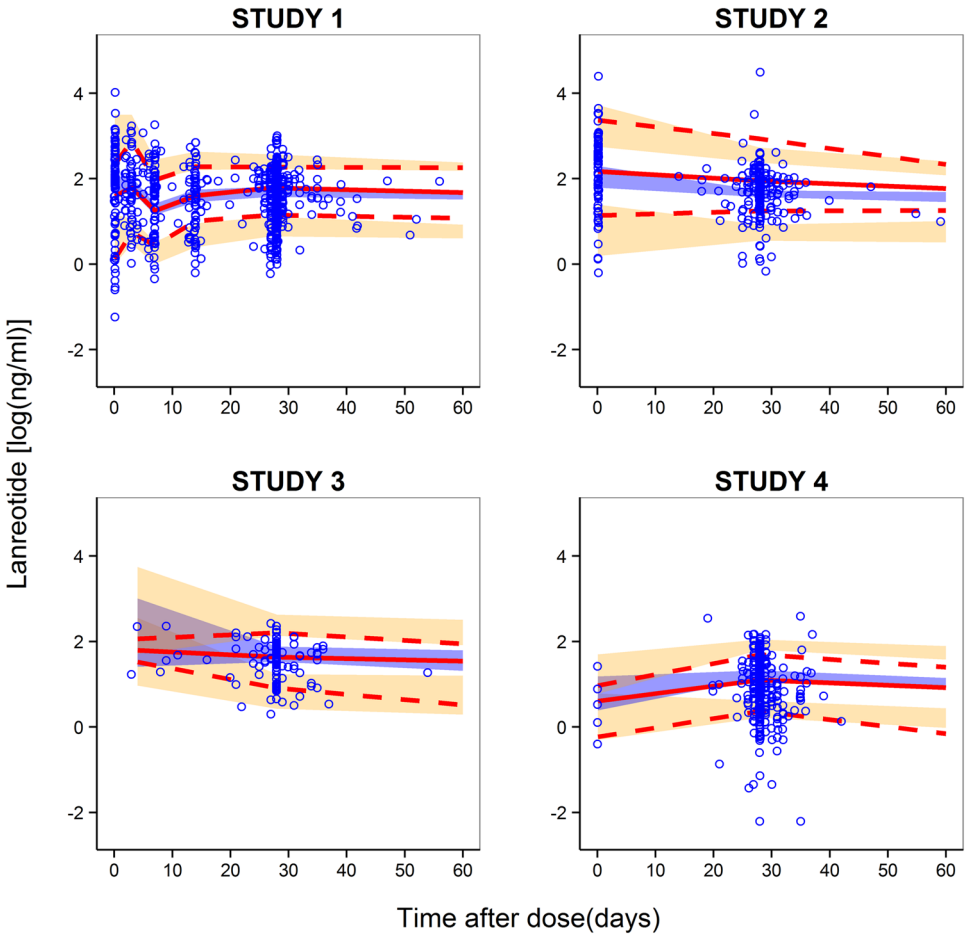

Fig. 3 Results of the predicted-corrected visual predictive checks from 500 simulated profiles. *Points* represent raw data and *red lines* correspond to the 2.5th, 50th, and 97.5th percentiles. *Shaded areas* represent the 95 % prediction intervals of the 2.5th–50th–97.5th percentiles of 500 simulated datasets

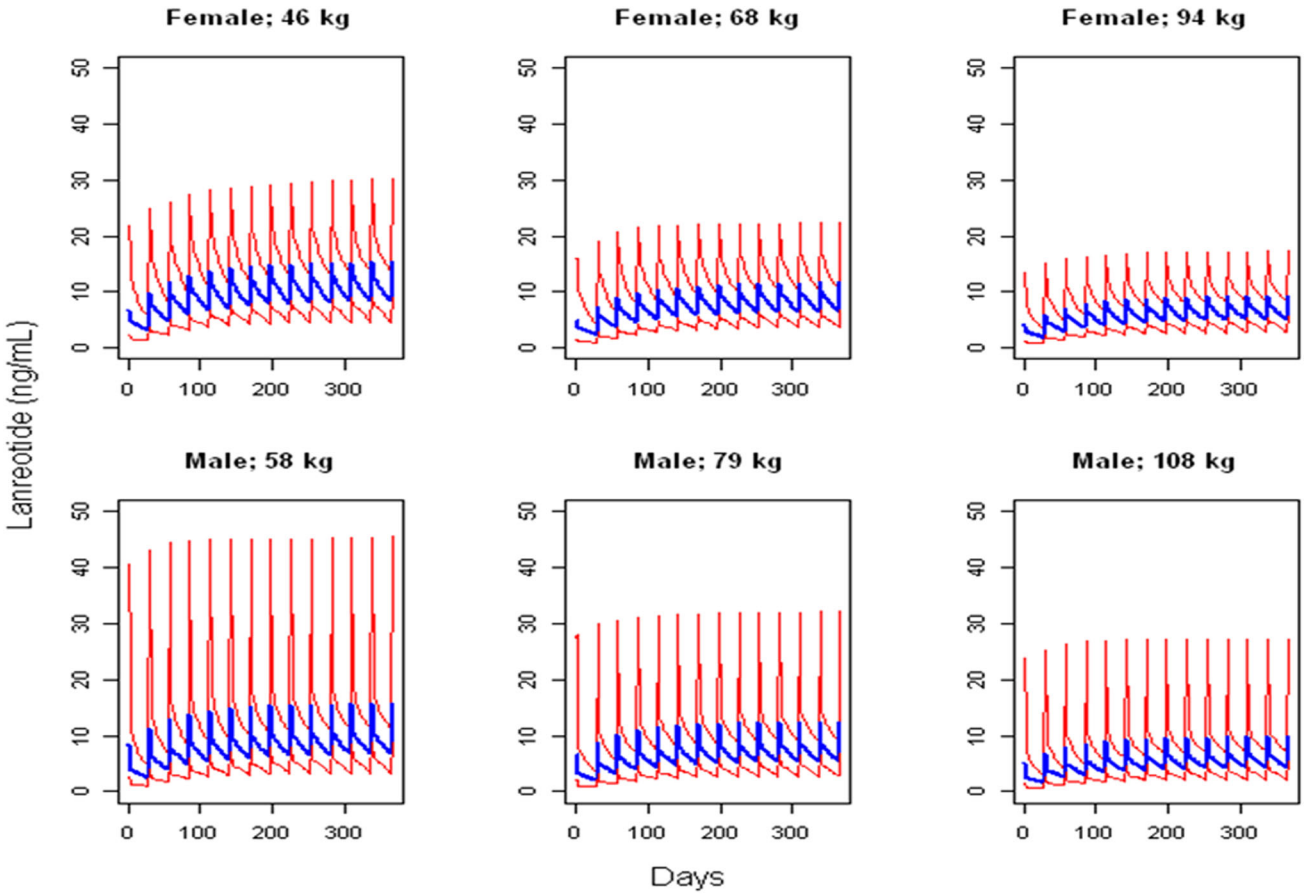

Fig. 4 Serum lanreotide profiles after 4-weekly lanreotide Autogel® 120 mg over 1 year. The panels summarize the profiles obtained from 1000 simulated patients for each gender (SEX) and body weight (BW) condition: median (*thick blue lines*), 2.5th–97.5th percentiles (*thin red lines*)

prediction interval of the pharmacokinetic timeline with the concentrations observed in Asian and black/African American patients is shown in Fig. 5b. Most of the serum lanreotide concentrations lay within the 90 % prediction interval calculated using the serum pharmacokinetic profiles obtained in white patients. Finally, Fig. 6a, b shows the median and 95 % prediction intervals of the serum concentration profiles from 1000 simulated patients ($n = 500$ females) after a single dose or assuming 4-weekly subcutaneous administration of lanreotide Autogel® 120 mg.

3.5 Pharmacokinetic Descriptors

Table 3 shows the summary statistics for the calculated pharmacokinetic descriptors for the overall population stratified by the corresponding categories in the two selected covariates. With respect to BW, typical C_{max} and AUC_{τ} were decreased by 35 % in patients over 89 years of age compared with patients younger than 62 years. C_{max} and AUC_{τ} were decreased by approximately 15 % in females compared with males.

4 Discussion

We have used a population pharmacokinetic model to describe the serum concentration–time profiles of lanreotide following subcutaneous injection of lanreotide Autogel® in patients with functioning and non-functioning NETs. The selected model consists of an absorption process characterized by simultaneous first- and zero-order rate input, and a one-compartment model to account for disposition of the drug in the body. This type of absorption model is commonly used when characterizing extended-release formulations [15, 16]. Previously, in healthy volunteers, the first-order rate constant of absorption was modeled to decrease exponentially as a function of the natural logarithm of time, implying a faster value at early times after dosing [3]. Using time as a covariate affecting a pharmacokinetic process has limitations, e.g., at the time to simulate profiles after multiple dosing. In the current analysis, we present a model in which time effects are substituted by a more elaborate absorption model. The faster initial absorption rate is now represented by the zero-order process lasting 2.96 days.

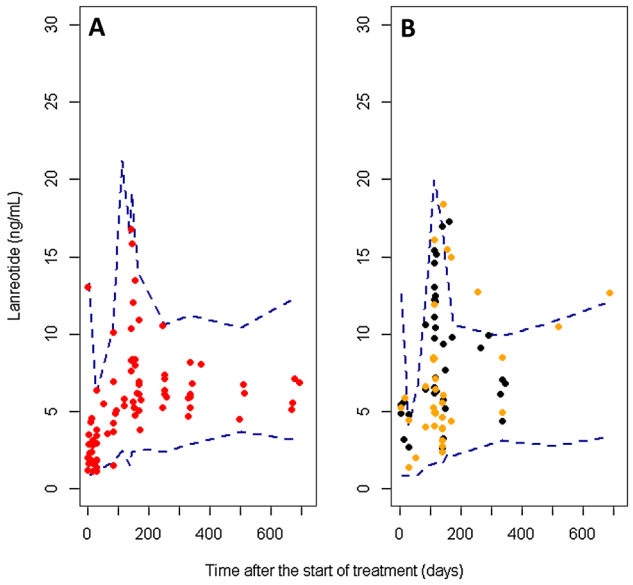

Fig. 5 Observed lanreotide serum concentration–time profiles **a** of patients positive for lanreotide antibodies (*filled red circles*) and **b** corresponding to Asian ($n = 10$) and black/African American ($n = 10$) patients (*filled black circles* and *filled orange circles*, respectively). The *dashed blue lines* show the 5th and 95th percentiles of the observed lanreotide concentrations in the remaining patient population

Most of the (unknown) fraction of the absorbed dose followed the first-order process (99.4 % in females, 97 % in males), with a typical absorption half-life of 43.6 days. Such a long half-life implies flip-flop kinetics, but the model-derived typical value for elimination half-life calculated as $0.693 \times \frac{V_d/F}{CL/F}$ was 0.59 h. This apparent discrepancy can be explained by the fact that the sampling schedule adopted in study A allowed the capture of the rapid decline in serum concentration (just after the zero-order input process finished [typically 2.96 days after administration]), as observed in several of the individual profiles shown in Electronic Supplementary Material Figure S2. The decline of serum lanreotide concentrations was also rapid following intravenous administration to healthy volunteers (estimated elimination half-life 0.45 h) [3].

Assuming that F is similar between healthy volunteers and patients with functioning and non-functioning NETs (approximately 70 %) [3], the CL/F and V_d/F are 359.1 L/day and 12.81 L for patients with NETs, respectively. When compared with CL/F and V_d/F estimates reported for healthy volunteers (554 L/day and 15.1 L, respectively) [3], it is evident that although the distribution properties of lanreotide appear to be unaltered between healthy volunteers and patients with functioning and non-functioning NETs, elimination seems to be impaired in the latter. It has to be taken into consideration that although in the current analysis a one-compartment model was selected to describe drug disposition, a three-compartment model is closer to the true disposition characteristics, based on the analysis performed in healthy volunteers with an extensive sampling design. In the current scenario, more information on the ADME (absorption, distribution, metabolism, and excretion) properties would have been gained if rich sampling or single-dose studies data had been available at the time of analysis. The 35 % decrease in CL/F in patients with NETs cannot be explained by differences in CL_{CR}. Half of the patient population in the current evaluation had CL_{CR} values within the normal range, and CL_{CR} did not show significant covariate effects. A NETs-related impaired active secretion process might explain the reduced clearance; however, we are not aware of any literature data supporting that hypothesis.

Interestingly, the variability in CL/F and in k_a was similar to that reported in healthy volunteers; on the other hand, the variability obtained for V_d/F was much greater (150 vs. 23 %). The reason for this may be that in the current model the three compartments (one central and two peripheral) identified in the analysis of healthy volunteers data were combined into a single one, and part of the variability in the absorption process is reflected in V_d/F (note that variability in the duration of the zero-order input process could not be estimated).

Figure 6c shows serum lanreotide concentrations over time at steady state. The plots were constructed by simulating 1000 profiles (500 males, 500 females, each group of equivalent median weight) and summarizing the results as the 2.5th, 50th, and 97.5th percentiles. Simulations were performed using the population estimates reported for healthy volunteers [3] and those listed in Table 2. The spread of the data appears to be similar between the two populations, but exposure is greater in patients due to the lower rate of elimination. The concentration plateau seen in the profiles representing patients with NETs is due to the zero-order absorption process lasting for 3 days.

None of the covariates tested showed statistically significant effects, with the exception of baseline BW which influenced CL/F and the effects of gender on F_1. The effect of gender on F_1 may be due to differences in the adipose layer at the injection site of in female patients, in addition to differences in perfusion at the subcutaneous level. It is worth noting that gender effects were not identified in the pharmacokinetic analysis performed in healthy volunteers. Gender effects on F_1 should not be interpreted as differences in F between females and males: gender was found to affect F_1, providing estimates of F_1 for males and females of 0.97 and 0.994, respectively. Bioavailability is not modified by gender; differences are in the fractions of the absorbed dose that use the first- or zero-order rate input processes. Our results indicate that in females the contribution of the zero-order process to drug input is lower than

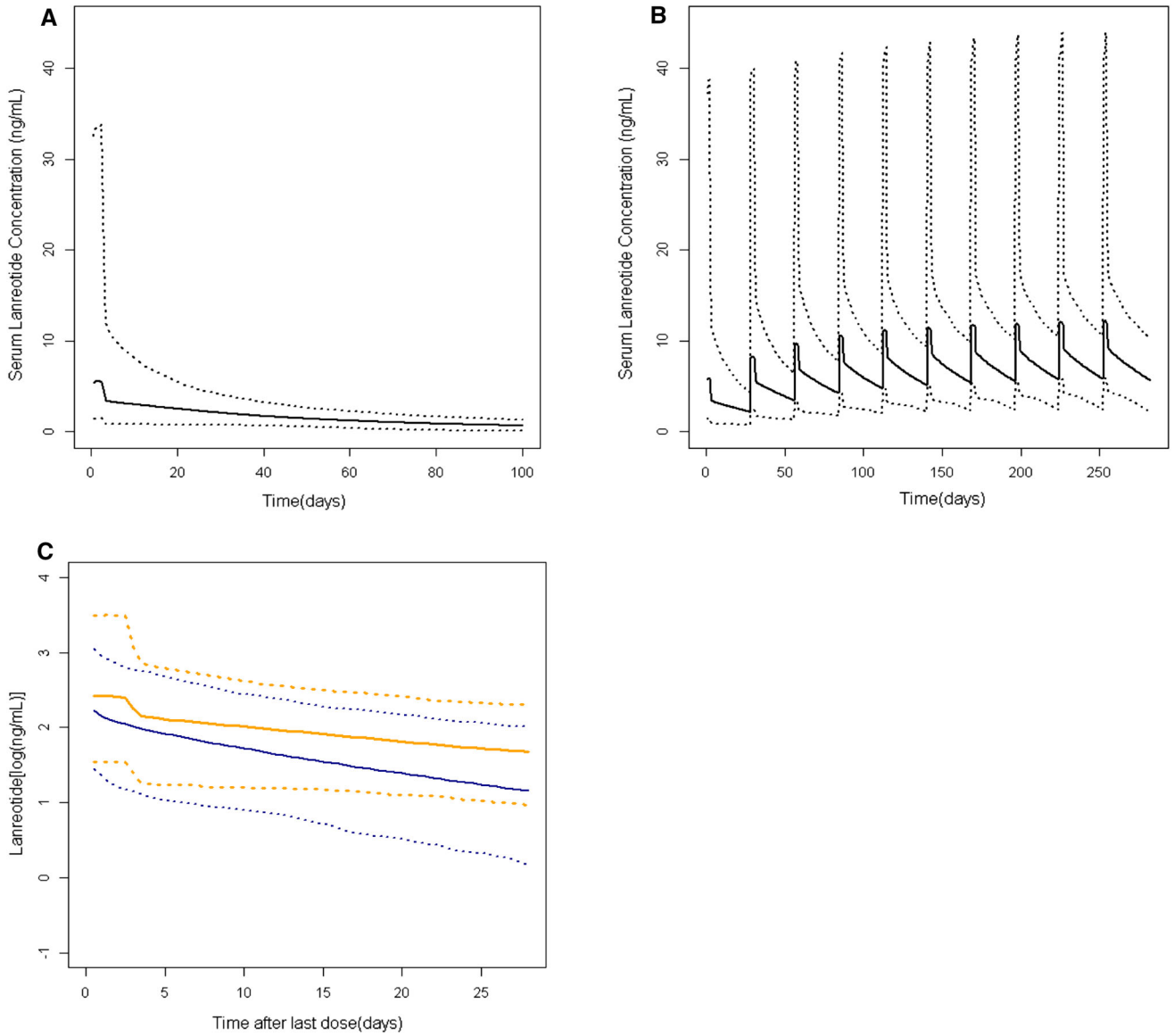

Fig. 6 Median and 95 % prediction intervals of the serum concentration profiles from 1000 simulated patients ($n = 500$ females) after a single dose **a** or assuming 4-weekly subcutaneous **b** administration of lanreotide Autogel® 120 mg. **c** Simulated serum lanreotide concentration profiles in healthy volunteers (*blue*) and in patients with functioning and non-functioning enteropancreatic neuroendocrine tumors (*orange*) at steady state versus time after last administered dose. *Lines* represent the 2.5th (*lower curves*), 50th (*middle curves*), and 97.5th (*upper curves*) percentiles from 1000 simulated patients ($n = 500$ females). The dosing schedule used in the simulation exercise was lanreotide Autogel® 120 mg administered subcutaneously every 4 weeks

in males, explaining the higher maximal predicted concentrations seen in males in the simulated profiles represented in Fig. 4.

An increase in total drug clearance as the result of increasing body weight is a common finding in pharmacokinetics. CL/*F* was found to increase by 30 % for a weight of 104 kg (95th percentile) and to decrease by 23 % for a weight of 51 kg (5th percentile) with respect to median weight of 74 kg. As with the results of the effects of body weight and gender on the pharmacokinetic characteristics of lanreotide Autogel®, the values of AUC and serum concentrations appear to be slightly reduced in the male population as compared with females (Table 3). However, this difference was not considered to be clinically relevant and no dose adjustment of lanreotide Autogel® based on weight is necessary since once the 95 % confidence interval of the AUC_τ values corresponding to patients weighing between 62 and 89 kg (159–346 μg·day/L) was calculated, it was found that the percentages of patients weighing <62 or >89 kg with AUC_τ values greater

Table 3 Summary of pharmacokinetic descriptors

	Whole population	Males	Females	Body weight (kg)[a]		
				≤62	≥70 to ≤77	≥89
C_{min} (ng/mL)	6.23 (0.3–14.7)	5.5 (0.3–14.5)	7 (2–14.7)	7.7 (2–14.7)	6.4 (3.5–12.4)	5.3 (2.8–14.5)
C_{avg} (ng/mL)	8.35 (3.8–18.0)	7.7 (4.5–17.9)	9 (3.8–18)	10.3 (6.3–17.3)	8.3 (5.9–14.6)	6.8 (3.8–17.9)
C_{max} (ng/mL)	12.77 (4.2–63.8)	13.7 (6–63.7)	11.9 (4.2–40.2)	15.3 (7–63.7)	12.2 (6.8–31.8)	10.1 (4.2–23.6)
AUC_{τ} (μg·day/L)	231.5 (103.1–492.0)	216 (124–490)	247 (103–492)	285 (170–489)	228(160–398)	188 (103–490)

Data are given as geometric mean (range)

AUC_{τ} area under the serum concentration–time curve within the dosing interval at steady state, C_{avg} average serum concentration within the dosing interval, C_{max} maximum serum concentration, C_{min} minimum serum concentration

[a] The three categories were chosen since they correspond to the 20th, 50th, and 80th percentiles of the weight distribution in the studied population

than 346 μg·day/L or lower than 159 μg·day/L, respectively was less than 5 %.

Variables that are linked to hepatic function (BIL, ALB, SGOT, SGPT) were part of the covariate analysis and were not found to be significant. However, calculation of the Child-Pugh score was not possible and so we were not able to predict the hepatic impairment status of the patients. For this reason, patients with hepatic impairment were not evaluated in this pooled population pharmacokinetic analysis. Only two patients with severe renal impairment were treated with lanreotide Autogel®.

5 Conclusions

The pharmacokinetics of lanreotide Autogel® were assessed using a population pharmacokinetic analysis of data from 290 patients with functioning/non-functioning GEP-NETs pooled from four clinical trials. Lanreotide Autogel® was administered as multiple deep subcutaneous injections every 4 weeks at a dose of 120 mg in the majority of patients.

The pharmacokinetics of lanreotide Autogel® have been described with a model containing two mechanisms of absorption (first- and zero-order) and one compartment model describing disposition of the drug in the body. The V_d/F was 18.3 L. The CL/F was 513 L/day for a 74 kg patient, representing a substantial difference in clearance in this population of patients with respect to healthy volunteers that could not be explained by any of the covariates tested. The remaining IPV (not explained by covariates effects) was 27 % for CL/F, 150 % for V_d/F, 61 % for k_a, and 1 % for F_1.

Body weight had a moderate effect on the pharmacokinetic profile of lanreotide. Lanreotide CL/F was found to increase by 30 % for a weight of 104 kg (95th percentile) and to decrease by 23 % for a weight of 51 kg (5th percentile), suggesting that evaluation of additional dosing schedules such as lanreotide Autogel® 120 mg every 2 weeks may be justified.

Pharmacokinetic parameters for the whole GEP-NET population could be described and no impact on the lanreotide pharmacokinetic profile could be identified in terms of renal impairment CL_{CR}, BILI, ALB, SGPT, SGOT, location of primary tumor, age, presence of anti-lanreotide antibodies, and symptomatic/asymptomatic characteristics of the disease.

Compliance with Ethical Standards

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Conflict of interest Núria Buil-Bruna, María Jesús Garrido, and Iñaki F. Trocóniz have received research funding from Ipsen Pharma. Marion Dehez, Amandine Manon, Thi Xuan Quyen Nguyen, and Edda L. Gomez-Panzani are employed by Ipsen Pharma.

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