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ORIGINAL RESEARCH ARTICLE

Clinical Pharmacokinetics of Dulaglutide in Patients with Type 2 Diabetes: Analyses of Data from Clinical Trials

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Abstract

Background and Objective Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist administered as once-weekly subcutaneous injections for the treatment of type 2 diabetes (T2D). The clinical pharmacokinetics of dulaglutide were characterized in patients with T2D and healthy subjects.

Methods The pharmacokinetics of dulaglutide were assessed throughout clinical development, including conventional pharmacokinetic analysis in clinical pharmacology studies and population pharmacokinetic analyses of data from combined phase 2 and phase 3 studies in patients with T2D. The effects of potential covariates on dulaglutide population pharmacokinetics were evaluated using nonlinear mixed-effects models.

Results Dulaglutide gradually reached the maximum concentration in 48 h and had a terminal elimination half-life of 5 days. Steady state was achieved between the second and fourth doses. The accumulation ratio was 1.56 for the 1.5 mg dose. Intra-individual variability estimates for the area under the plasma concentration–time curve and the maximum concentration were both <17 % [coefficient of variation (CV)]. There was no difference in pharmacokinetics between injection sites (arm, thigh or abdomen). Dulaglutide pharmacokinetics were well described by a two-compartment model with first-order absorption and elimination. The population clearance was estimated at 0.126 L/h [inter-individual variability (CV) 33.8 %]. Age, body weight, sex, race and ethnicity did not influence dulaglutide pharmacokinetics to any clinically relevant degree.

Conclusion The pharmacokinetics of dulaglutide support once-weekly administration in patients with T2D. The pharmacokinetic findings suggest that dose adjustment is not necessary on the basis of body weight, sex, age, race or ethnicity or site of injection.

Key Points

The sustained concentration–time profile of dulaglutide, with low variability, supports once-weekly dosing in patients with type 2 diabetes.

The pharmacokinetic data suggest that dose adjustment of dulaglutide is not necessary on the basis of age, sex, race, ethnicity, body weight or injection site.

1 Introduction

Dulaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes (T2D) in the USA [1, 2]. Dulaglutide is a large molecule (with a molecular weight of approximately 63 kDa, similar to that of albumin) consisting of two dipeptidyl peptidase-4 (DPP-4)-protected GLP-1 analogues covalently linked to a human immunoglobulin (Ig) G4–fragment crystallizable (Fc) heavy chain [3]. As a result of this engineering, dulaglutide was expected to show a flat prolonged concentration–time

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profile with slow absorption kinetics and slow systemic clearance. The rate of clearance of dulaglutide is decreased via fusion of the GLP-1 analogue to the Fc fragment of IgG4, taking advantage of the known interaction of IgG with the neonatal Fc receptor (FcRn). This interaction with FcRn provides an intracellular salvage pathway leading to extended persistence of IgG in the circulation—a mechanism to extend the half-lives of many drugs [4, 5]. In addition to specific cleavage by DPP-4, dulaglutide is presumably degraded into component peptides and amino acids in lysosomes by general protein catabolism pathways, similar to endogenous immunoglobulins [4, 5].

Dulaglutide has demonstrated sustained glycaemic effects for once-weekly subcutaneous administration and a safety and tolerability profile consistent with those of other long-acting GLP-1 receptor agonists [6–8].

Dulaglutide has been investigated in patients with T2D, special populations and healthy subjects during its clinical development. The pharmacokinetics of dulaglutide were evaluated using data from clinical pharmacology studies, including data from an absolute bioavailability study and a relative bioavailability study of different injection sites in healthy subjects. The population pharmacokinetics and covariate analyses of dulaglutide were conducted using data from the combined phase 2 and phase 3 clinical trials in patients with T2D. The results of these analyses, interpretations and clinical applications are presented here.

2 Methods

2.1 Study Overview

All clinical studies described herein were approved by the appropriate ethics committee, and written informed consent was obtained from each subject prior to their inclusion in the study.

2.1.1 Phase 1 Clinical Studies

The clinical pharmacology programme of dulaglutide evaluated pharmacokinetics after single and multiple doses (once weekly, ranging from 4 to 6 weeks) over a wide dose range (0.05–12 mg) in healthy subjects and patients with T2D. Special population studies included subjects with renal and hepatic impairment, elderly subjects and subjects with hypertension. Dulaglutide concentration data from serial blood sampling in eight studies from the clinical pharmacology programme (studies 1–8 in Table 1), which included the doses selected for evaluation in phase 3 (0.75 and 1.5 mg) in 189 healthy subjects and 73 patients with T2D, were included in the meta-analysis of non-compartmental pharmacokinetic parameters. Of the eight studies, two provided multiple-dose data for the 1.5 mg dose in patients with T2D. Single-dose pharmacokinetic data for the 0.75 mg dose were available from two studies, and multiple-dose data for the 0.75 mg dose were available from one study. The pharmacokinetic dose proportionality of dulaglutide was assessed in the 0.5–1.5 mg dose range. In addition, the similarity in pharmacokinetic parameters between healthy subjects and patients with T2D after administration of single doses of dulaglutide was assessed.

The absolute bioavailability of dulaglutide was evaluated in a randomized, two-period crossover study in which 16 healthy subjects received a subcutaneous dose of dulaglutide 1.5 mg and an intravenous dose of dulaglutide 0.1 mg. In addition, the effect of the injection site on dulaglutide pharmacokinetics was assessed in a randomized, three-period crossover study in which 39 subjects received single subcutaneous injections of dulaglutide 1.5 mg in the arm, thigh and abdomen. For both of these crossover studies, there was a washout period of at least 28 days between doses, and pharmacokinetic sampling was conducted for up to 336 h after each dose.

2.1.2 Phase 2 and Phase 3 Clinical Studies

The population pharmacokinetics of dulaglutide were evaluated in patients with T2D in five phase 2 and three phase 3 trials (studies 9–15 in Table 1). The phase 2 trials evaluated dulaglutide (0.1–3 mg) once weekly for 12–52 weeks. Dulaglutide phase 3 doses were selected on the basis of the safety and efficacy data from the phase 2 dose-finding studies [9] and dose/exposure–response modelling and simulation. The phase 3 trials evaluated dulaglutide 0.75 and 1.5 mg for up to 24 months. The population analyses included data from a total of 2054 patients with T2D: 987 patients from five phase 2 studies and 1067 patients from three phase 3 studies. Each patient contributed between one and seven blood samples, with the majority providing 3–5 samples, using sampling schemes that were prospectively optimized for population-based analyses.

2.2 Dulaglutide Plasma Concentrations

Dulaglutide plasma concentrations were evaluated using a validated radioimmunoassay (RIA) method. This assay involved detection of the GLP-1 analogue portion of dulaglutide in human plasma samples, using a guinea pig anti-GLP-1 active antibody (EMD Millipore, St Charles, MO, USA), which measured both active dulaglutide and native GLP-1. The range of quantification was 5–50 ng/mL. The inter-assay accuracy (percentage relative error) ranged from −6.72 to 2.86 %, and the inter-assay precision (percentage relative standard deviation) ranged from 6.73 to 22.2 %.

Table 1 Clinical studies included in combined pharmacokinetic (PK) analyses

Study	Phase	Description	Population	SC dosing regimen
1	1	Multiple-dose safety, PK, PD	Japanese with T2D	1 or 1.5 mg QW for 5 weeks
2	1	PK/PD in elderly	Elderly (≥65 years of age) with T2D	0.5, 0.75 or 1.5 mg QW for 6 weeks
3	1	PK in renal impairment	Normal or impaired renal function	Single 1.5 mg dose
4	1	PK in hepatic impairment	Normal or impaired hepatic function	Single 1.5 mg dose
5	1	Relative bioavailability by injection site and body mass index	Healthy	Single 1.5 mg dose
6	1	Absolute bioavailability	Healthy	Single 0.75 mg IM and SC doses, or single 1.5 mg SC and 0.1 mg IV doses
7	1	Effect of sitagliptin coadministration	T2D	3 single 1.5 mg doses
8	1	Relative bioavailability by device[a]	Healthy	2 single 1.5 mg doses
9	2	Dose ranging in T2D	Overweight/obese with T2D	0.5–2 mg QW for 16 weeks
10	2	Dose-finding in T2D	T2D	0.1, 0.5, 1, 1.5 mg QW for 12 weeks
11	2	Dose-finding in Japanese with T2D	Japanese with T2D	0.25, 0.5, 0.75 mg QW for 12 weeks
12	2	Haemodynamics in T2D	T2D	0.75 or 1.5 mg QW for 6 months
13	2/3	AWARD-5[b]	T2D	0.25, 0.5, 0.75, 1, 1.5, 2, 3 mg QW for 24 months
14	3	AWARD-1[c]	T2D	0.75 or 1.5 mg QW for 12 months[e]
15	3	AWARD-3[d]	T2D	0.75 or 1.5 mg QW for 12 months[e]

Data from studies 1–8 were included in the phase 1 combined analysis; data from studies 9–13 were included in the phase 2 combined analysis; data from studies 13–15 were included in the phase 3 combined analysis

AWARD Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes, *IM* intramuscular, *IV* intravenous, *PD* pharmacodynamics, *QW* once weekly, *SC* subcutaneous, *T2D* type 2 diabetes

[a] Comparative PK of dulaglutide after prefilled syringe and single-use pen administration

[b] Skrivanek et al. [9] and Nauck et al. [13]

[c] Wysham et al. [14]

[d] Umpierrez et al. [15]

[e] Dosing occurred up to 12 months; the primary endpoint was after 6 months

2.3 Analysis of Phase 1 Pharmacokinetics

The phase 1 meta-analysis was performed using studies that included the doses evaluated in the phase 3 trials (0.75 and 1.5 mg) in the intended market formulations. Dulaglutide pharmacokinetic parameters were estimated using non-compartmental methods, implemented in Pharsight WinNonlin® software (Sunnyvale, CA, USA). A comparison of pharmacokinetic parameters between non-diabetic subjects and patients with T2D was performed to support the extrapolation of pharmacokinetic data from these non-diabetic subjects to T2D patients. The pharmacokinetic parameter estimates and variability following administration of multiple dulaglutide doses of 1.5 and 0.75 mg are presented for patients with T2D. Pharmacokinetic parameters were log transformed prior to the statistical analyses, and a linear mixed-effects model was used, with study and subject nested within study as random effects. Dose proportionality was statistically evaluated for the maximum concentration (C_{max}) and the area under the plasma concentration–time curve (AUC) from time zero to the end of the dosing interval at 168 h (AUC_{τ}), based on single-dose data. A power model with log-transformed C_{max} or AUC_{τ} as the response variable and with log-transformed dose as a continuous covariate was used. Study and subject nested within study were included in the model as random effects. The model was fitted across the dose range of 0.5–1.5 mg, and the ratio of the predicted geometric mean values at 0.75 and 1.5 mg was calculated to evaluate the dose proportionality within the intended therapeutic dose range. Dose proportionality was declared if the 90 % confidence intervals (CIs) for the ratio were entirely contained within the range of 0.7–1.43.

2.4 Population Analyses of Combined Phase 2 and Phase 3 Data

Population pharmacokinetic analyses were conducted for the phase 2 and phase 3 studies in diverse T2D patient populations over a wide range of doses.

Table 2 Patient factors assessed in the population pharmacokinetic (PK) analyses

Covariate	Type	Parameters tested	Reason for evaluation
Dose	Continuous[b]	Ka	Dose proportionality in PK
Age	Continuous	Ka, CL, V	Clinical relevance: elderly with T2D
Body mass index	Continuous	F1, Ka, CL, V	Clinical relevance: obese with T2D
Baseline body weight	Continuous	F1, Ka, CL, V	Clinical relevance: obese with T2D
Creatinine clearance	Continuous	CL	Clinical relevance: renal impairment with T2D
Macroalbuminuria[a]	Continuous	CL	Clinical relevance: renal impairment with T2D
Serum creatinine	Continuous	CL, V[a]	Clinical relevance: renal impairment with T2D
Sex	Categorical	F1,[c] Ka, CL, V	Clinical relevance: sex
Race	Categorical	CL, V	Impact of race difference
DPP-4 inhibitor use	Categorical	Ka,[c] CL, V	Potential drug–drug interaction
Ethnic origin (Hispanic/non-Hispanic)	Categorical	Ka,[c] CL, V	Impact of ethnic difference
Smoking status	Categorical	F1,[c] Ka,[c] CL, V	Impact of habits

CL clearance, *DPP-4* dipeptidyl peptidase-4, *F1* relative bioavailability, *Ka* absorption rate constant, *T2D* type 2 diabetes, *V* volume of distribution in the central compartment

[a] Phase 3 only (studies 13–15 in Table 1)

[b] Continuous for phase 2; categorical for phase 3

[c] Phase 2 only (studies 9–13 in Table 1)

The objectives of the population pharmacokinetic analyses were to characterize the pharmacokinetics of dulaglutide and estimate the associated variability in the target patient population, and to evaluate potential intrinsic and extrinsic factors that may significantly influence dulaglutide pharmacokinetics.

These analyses were conducted using nonlinear mixed-effects modelling techniques, implemented in NONMEM® version 7.2 software (ICON Development Solutions). First-order conditional estimation with interaction was used as the estimation method.

The analysis included estimation of inter-individual variability, covariance and the residual error structure. Informative priors were used for the structural parameters of the final population model on the basis of intravenous data from the absolute bioavailability study.

2.4.1 Covariate Analyses

Upon establishment of a satisfactory base model, covariates were evaluated individually for significance (a decrease of $\geq$6.635 points for a χ^2 distribution; $p < 0.01$). Individually significant covariates were included in a full model, and each covariate was tested for significance when removed (an increase of $\geq$10.828 points for a χ^2 distribution; $p < 0.001$); only those that were found to be significant were retained in the final model development. Covariates were prospectively selected on the basis of clinical relevance or expert knowledge of drug disposition (Table 2).

2.4.2 Model Evaluation

The criteria used in selecting the most appropriate base and final models were based on the overall goodness of fit, minimum objective function, robustness of parameter estimates, bootstrapped CIs and a visual predictive check.

The simulations of patient populations and a graphical visualization were implemented in R software version 2.15.3. Bootstrap parameter uncertainty was used to generate a forest plot of covariate effects.

3 Results

The demographics of subjects included in the analyses are summarized in Table 3. The distribution of age, body weight and sex are representative of the target patient population.

3.1 Phase 1 Pharmacokinetics

The statistical summary of non-compartmental pharmacokinetic parameters after multiple doses of dulaglutide 1.5 and 0.75 mg is presented in Table 4. After single 1.5 mg dose administration, the dulaglutide intra-individual variability estimates were 11.9 % for AUC_τ and 16.1 % for C_{max}. A less than proportional increase in dulaglutide exposure for each doubling of the dose over the single-dose range of 0.5–1.5 mg was observed for both C_{max} and AUC_τ (Fig. 1).

Table 3 Demographics for pharmacokinetic analyses

Demographics	Phase 1[b] $N = 262$ $n = 432$[c]	Phase 2 $N = 987$ $n = 3515$	Phase 3 $N = 1067$ $n = 3317$
Sex: female (%)	33.2	48	47
Age (years)[a]	52.4 (19–80)	56 (24–87)	55 (20–86)
Body mass index (kg/m^2)[a]	27.9 (19.4–44.7)	32 (19–52)	33 (22–54)
Body weight (kg)[a]			
Diabetic subjects	83.3 (56–128)	90 (45–156)	94 (46–157)
Non-diabetic subjects	81.5 (52.2–123)	NA	NA
Dulaglutide dose (mg)	0.5–1.5	0.1–3.0	0.75, 1.5
Type 2 diabetes (%)	27.9	100	100
Race/ethnicity (%)			
White	79.8	62	53
Hispanic	0	13	22
Black or African American	11.8	6.3	8.2
Asian	6.9	17	4.8
Native American	0	0	11
Multiple	1.5	0	0
Creatinine clearance (mL/min)[a]	102 (7–251)	116 (33–385)	121 (47–297)
Normal: >80 mL/min (%)	75.6	82.9	87.2
Mildly impaired: >50 and ≤80 mL/min (%)	14.5	16.5	12.6
Moderately impaired: ≥30 and ≤50 mL/min (%)	4.2	0.6	0.3
Severely impaired: <30 mL/min (%)	2.7	0	0
End-stage renal disease (%)	3.1	0	0

Values shown are percentages unless otherwise noted. Because of rounding, values may not add up to 100 %

AUC_τ area under the plasma concentration–time curve from time zero to the end of the dosing interval at 168 h, C_{max} maximum concentration, N number of subjects, n overall number of observations in each analysis dataset, *NA* not applicable, *T2D* type 2 diabetes, t_{max} time to reach $C_{\max}$

[a] Mean (range)

[b] 0.5, 0.75, 1 and 1.5 mg doses are included in the combined phase 1 baseline demographic data, with the 1.5 mg dose data constituting approximately 87 % of the total dataset. Patients with T2D constituted 27.9 % of the subjects in the phase 1 studies

[c] Number represents the number of observations for $C_{\max}$ and $t_{\max}$; AUC_τ had a total of 430 observations

The dulaglutide exposure values following subcutaneous injection into the arm, thigh or abdomen were similar. The 90 % CIs for the ratio of the least squares (LS) means for each of the test sites (upper arm/thigh) compared with the reference site (abdomen) fell within the range of 0.80–1.25 for both AUC from time zero to infinity (AUC_∞) and $C_{\max}$ (Table 5).

Following a single subcutaneous administration of dulaglutide 1.5 mg, pharmacokinetic parameter values were similar in healthy subjects and patients with T2D, with geometric LS mean ratios of 0.923 (95 % CI 0.723–1.18) and 0.857 (95 % CI 0.713–1.03) for AUC_∞ and $C_{\max}$, respectively.

A single 0.1 mg intravenous dose of dulaglutide resulted in AUC_∞ of 2350 ng·h/mL [coefficient of variation (CV) 41 %], terminal elimination half-life ($t_{½}$) of 86.6 h (range 37.9–229), total body clearance (CL) of 0.0426 L/h (CV 41 %) and volume of distribution (V_z) of 5.32 L (CV 17 %). The mean absolute bioavailability following a single subcutaneous administration of dulaglutide 1.5 mg in healthy subjects was 47 %.

3.2 Combined Phase 2 and Phase 3 Data Analysis

A two-compartment model with first-order absorption and elimination was identified to best describe the population pharmacokinetics of dulaglutide.

In the analysis of the combined phase 2 data, a maximum-effect ($E_{\max}$) equation was used to model the effect of dose on bioavailability:

$$F1 = F0 - \frac{\text{FMAX} \times \text{DOSE}}{\text{DOSE} + \text{FD}_{50}}$$

Table 4 Dulaglutide steady-state pharmacokinetic parameters in type 2 diabetes (T2D) patients from non-compartmental analysis

Parameter	0.75 mg[b]	1.5 mg[d]
AUC_τ (ng·h/mL)	6730 (32)	14,000 (30)
C_{max} (ng/mL)	51.6 (30)	114 (35)
t_{max} (h)[a]	48 (24–72.5)	48 (24–72)
$t_{½}$ (days)	5.5 (18)[c]	4.7 (14)
CL/*F* (L/h)	0.111 (32)	0.107 (30)
V_z/F (L)	19.2 (19)[c]	17.4 (28)

Data are shown as geometric mean (CV %) unless otherwise noted

AUC_τ area under the plasma concentration–time curve from time zero to the end of the dosing interval at 168 h, *CL/F* apparent total body clearance of drug calculated after extra-vascular administration, *C_{max}* maximum concentration, *CV* coefficient of variation, *N* number of subjects, *$t_{½}$* terminal elimination half-life, *t_{max}* time to reach C_{max}, *V_z/F* apparent volume of distribution during the terminal phase after extra-vascular administration

[a] Median (range)

[b] Data from a single phase 1 study of dulaglutide 0.75 mg in patients with T2D ($N = 11$)

[c] $N = 9$

[d] Combined data from two phase 1 multiple-dose studies of dulaglutide 1.5 mg in patients with T2D ($N = 15$)

where *F*1 is relative bioavailability, *F*0 is the bioavailability without the dose effect, FD_{50} is the dose corresponding to a half-maximum reduction in bioavailability, which was estimated to be 0.19 mg [standard error of the estimate (SEE) 9.46 %], and FMAX is the maximum reduction in bioavailability, which was determined to be 59.7 % on the basis of the FD_{50} estimate and the constraint that the absolute bioavailability of the 1.5 mg dose must be 47 %, as determined in the absolute bioavailability study.

Age, serum creatinine, creatinine clearance, macroalbuminuria, sex, race, ethnic origin, DPP-4 inhibitor use and smoking status did not influence the pharmacokinetics of dulaglutide in either the phase 2 or phase 3 population analyses. Body weight was statistically significant, with similar effects on both clearance and the volume of distribution. Therefore, body weight was included as a covariate on the bioavailability term in both the phase 2 and the phase 3 population models. In addition, Hispanic ethnic origin was retained as a significant covariate on clearance in the phase 2 population analyses; however, its effect was relatively minor and was not considered to be clinically relevant. Hispanic origin was not significant in the combined phase 3 analyses. Furthermore, body weight was selected over body mass index, as these factors are highly correlated.

Parameter estimates for the final phase 3 pharmacokinetic model are listed in Table 6. Body weight, the only significant covariate in the final model, explained less than 6 % of the overall inter-individual variability on clearance. The effect of body weight on pharmacokinetics (Fig. 2) is not expected to translate into a clinically meaningful effect over the variability in pharmacodynamic response in the patient population, thus it is not considered to be clinically relevant.

Figure 3a shows the agreement between model-predicted concentration–time profiles of dulaglutide and the observed concentration data from the phase 3 studies. The goodness of fit of the phase 3 combined model is shown in the weighted residuals plot (Fig. 3b).

3.3 Clinical Applications

The effects of intrinsic factors on the exposure of dulaglutide are illustrated in Fig. 4. The means and CIs for body weight, age, sex and race/ethnicity shown in the figure were derived using a population

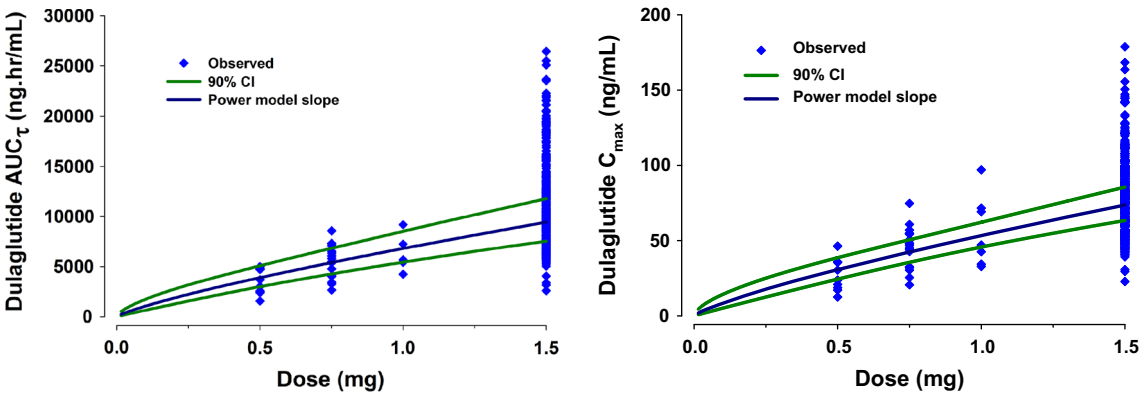

Fig. 1 Dulaglutide dose proportionality for the area under the plasma concentration–time curve from time zero to the end of the dosing interval at 168 h (AUC_τ) and maximum concentration (C_{max}). The *blue diamonds* represent observed data; the *blue solid line* is the model-estimated slope; the *green solid lines* represent the upper and lower limits of the 90 % confidence intervals (CIs)

Table 5 Statistical analysis of key pharmacokinetic parameters by injection site

Parameter and injection site	*N*	Geometric LS mean (90 % CI)	Ratio versus abdomen (90 % CI)
AUC_{∞} (ng·h/mL)			
Abdomen	43	14,959 (14,225–15,730)	–
Upper arm	40	14,557 (13,834–15,319)	0.973 (0.941–1.01)
Thigh	39	14,800 (14,064–15,574)	0.989 (0.956–1.02)
C_{max} (ng/mL)			
Abdomen	43	76.0 (71.8–80.5)	–
Upper arm	40	74.8 (70.5–79.4)	0.984 (0.925–1.05)
Thigh	44	67.7 (63.9–71.6)	0.890 (0.838–0.944)

Subjects received three single SC injections of dulaglutide 1.5 mg—one per injection site

AUC_{∞} area under the plasma concentration–time curve from time zero to infinity, *CI* confidence interval, *C_{max}* maximum concentration, *LS* least squares, *N* number of subjects, *SC* subcutaneous

Table 6 Final population pharmacokinetic (PK) model parameters

Parameter	Population estimate (SEE %)	Inter-individual variability estimate (%)[b] (SEE %)
Relative bioavailability		
Parameter for F1, 1.5 mg dose	0.470 (fixed)	–
Parameter for absorption rate constant (h^{-1})	0.00769 (18.3)	40.5 (20.7)
Parameter for clearance (L/h)	0.0593 (1.74)	33.8 (11.2)
Parameters for compartment volumes of distribution (L)		
Volume of distribution in the central compartment	2.25 (19.2)	55.6 (57.2)
Volume of distribution in the peripheral compartment	3.75 (13.5)	–
Parameter for inter-compartmental clearance (L/h)	0.0201 (38.4)	–
Covariates		
Effect of baseline body weight on F1[a]	−0.00877 (6.61)	–
Covariance between clearance and volume of distribution in the central compartment	0.155 (31.0)	
Residual error: proportional (%)	28.7 (4.97)	

Values shown are for parameters from the analysis of the phase 3 combined dataset. Population PK parameters from the combined phase 2 analyses were consistent with those from the phase 3 analyses; baseline body weight was retained as a significant covariate for bioavailability in the final model in both phase 2 and phase 3 population analyses

CV coefficient of variation, *EXP* exponent, *F1* relative bioavailability, *SEE* standard error of the estimate, *SQRT* square root, *WT* body weight

[a] Described as F1 × EXP ($\theta_{WT,\ F1}$ × (WT − 92.5 kg))

[b] CV % = (SQRT (EXP (OMEGA (variance estimate)) − 1)) × 100 %

pharmacokinetic model. In summary, dulaglutide exposure was not affected to any clinically relevant degree. The impact of these factors on the relative ratios of pharmacokinetic exposures for a typical reference patient indicated that dose adjustment of dulaglutide would not be necessary on the basis of body weight, age, sex, race or ethnicity.

The effect of missed doses on the pharmacokinetics of dulaglutide was simulated using the pharmacokinetic model. The simulation (Fig. 5) assumed that a dose of dulaglutide was omitted on a scheduled dosing day at steady state. The blue line shows the scenario where a dose was taken 3 days before the next scheduled dose, resulting in a transient 20 % higher concentration following the subsequent dose. Thus, if a dose is missed, it should be administered as soon as possible if at least 3 days (72 h) remain until the next scheduled dose. If an interval of less than 3 days remains before the next scheduled dose, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once-weekly dosing schedule. The day of weekly administration can be changed, if necessary, as long as the last dose has been administered at least 3 days earlier.

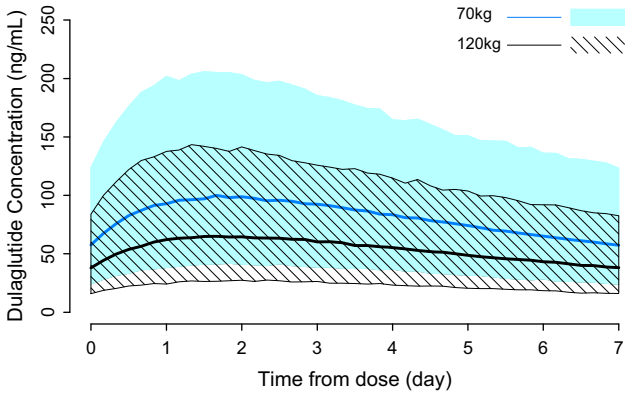

Fig. 2 Effects of body weight on the dulaglutide concentration–time profile at steady state following a 1.5 mg dose in patients with type 2 diabetes. The *blue solid line* and the *blue shaded area* represent the model-predicted median and 90 % prediction intervals for patients with 70 kg body weight. The *black solid line* and the *hatched area* represent the model-predicted median and 90 % prediction intervals for patients with 120 kg body weight

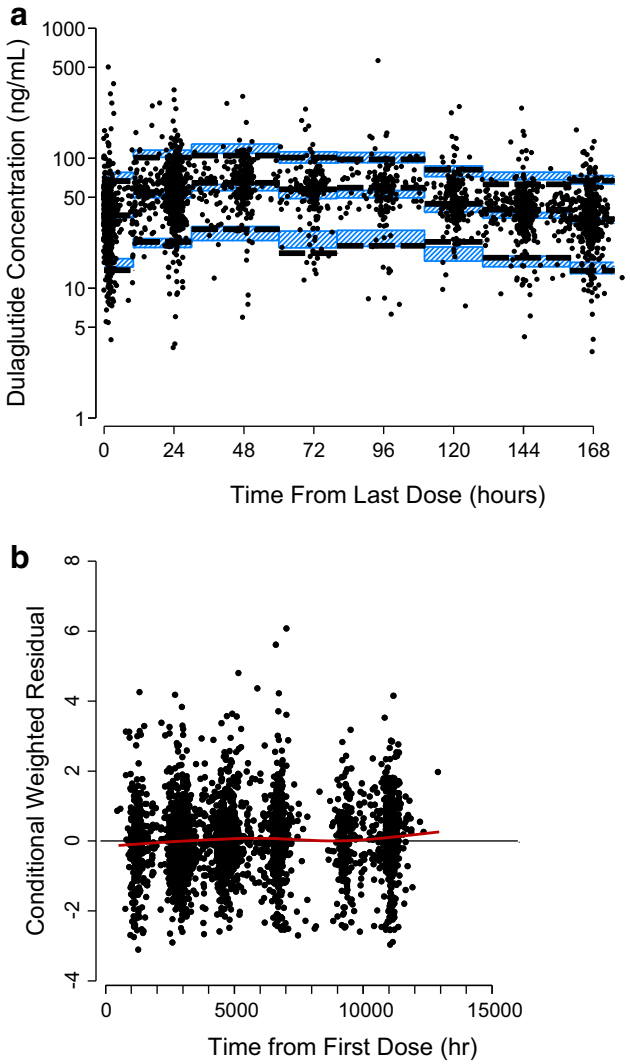

Fig. 3 **a** Visual predictive check of the dulaglutide final population pharmacokinetic model showing predicted and observed dulaglutide concentration–time profiles over a once-weekly dosing interval. The *black dots* represent the observed concentration data from all phase 3 studies; the *black dashed lines* indicate the 5th, 50th and 95th percentiles of the observed data and the *blue hatched areas* represent the 90 % confidence intervals for the 5th, 50th and 95th percentiles of the simulated predictions of the 90 % prediction intervals. **b** Dulaglutide final population pharmacokinetic model goodness of fit: conditional weighted residual versus time. The *solid black line* indicates the reference at zero and the *solid red line* is a locally weighted regression line

4 Discussion

The structure of dulaglutide was engineered to confer increased stability against DPP-4-mediated degradation and to lower its immunogenic potential [3]. This structure, together with the large size of the dulaglutide molecule, results in slow absorption from the subcutaneous site of injection.

Consequently, dulaglutide has been demonstrated to be gradually absorbed and eliminated, resulting in a relatively flat and stable concentration–time profile over a once-weekly dosing interval at steady state. The flat concentration–time profile of dulaglutide, relative to available treatments with once- or twice-daily dosing, is an important attribute that drives the stable glycaemic control of the once-weekly dosing regimen, with acceptable tolerability [10]. Treatments requiring less frequent administration are expected to provide a number of benefits to patients with T2D and may improve patient compliance [11].

Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways and is not anticipated to be eliminated by glomerular filtration or metabolized by cytochrome P450 (CYP) enzymes. Therefore, intrinsic factors associated with either renal or hepatic function are not expected to affect dulaglutide pharmacokinetics.

Dulaglutide showed typical intra-individual and inter-individual variability for a population pharmacokinetic analysis in a large dataset of the target patient population for a biological drug in the incretin class [12]. Dulaglutide has remaining inter-individual pharmacokinetic variability that is not explained by age, sex, race, ethnicity or injection site. A small portion of the variability appears to be explained by body weight; however, this factor is not considered significant in comparison with the overall pharmacokinetic variability. The effect of Hispanic ethnic origin on clearance was retained in the phase 2 model, although the contribution of this covariate was relatively minor. In addition, the effect was not confirmed in the

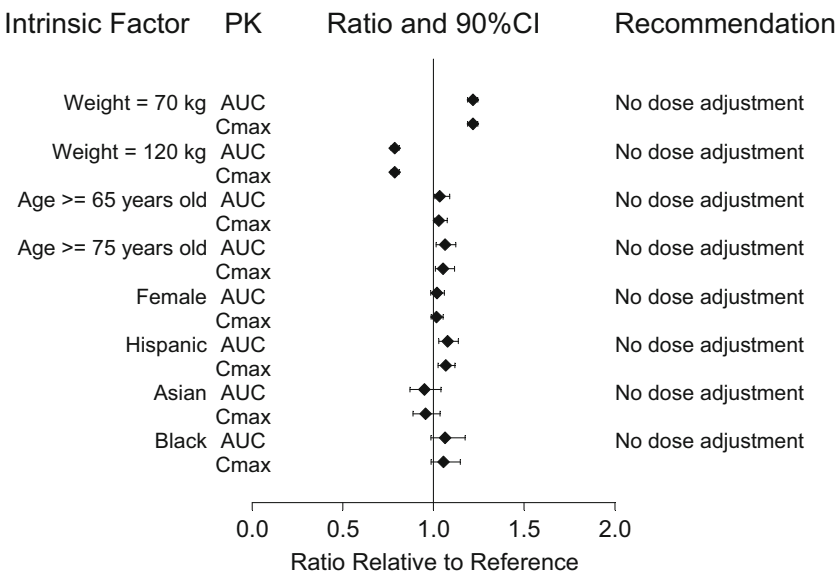

Fig. 4 Effects of intrinsic factors on the pharmacokinetics (PK) of dulaglutide, shown as ratios of the area under the plasma concentration–time curve (AUC) and maximum concentration (C_{max}) values relative to reference values. The reference values for body weight, age, sex and race are 93 kg, 56 years of age, male and white, respectively. The medians and 90 % confidence intervals (CIs) of the ratios are shown

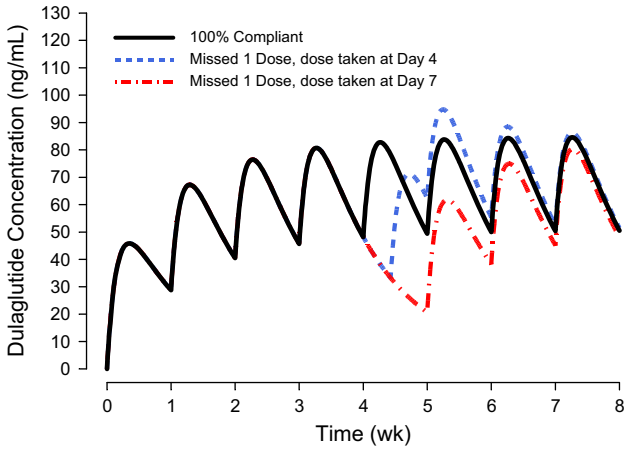

Fig. 5 Effects of missed doses on concentration–time profiles of dulaglutide. The pharmacokinetic model simulated dulaglutide concentration–time profiles following a once-weekly dose of 1.5 mg taken as prescribed (*solid black line*), with a dose being missed at mid-week (*blue dashed line*) or with a dose being skipped (*red dotted–dashed line*)

phase 3 analysis, despite a higher percentage of Hispanic subjects in the phase 3 studies.

Consistent with previous study results, dulaglutide exposure was slightly less than dose proportional. The effect of dose on dulaglutide pharmacokinetics was incorporated into the absorption component of the pharmacokinetic model.

Dulaglutide can be administered once weekly, at any time of day, with or without food, and injected subcutaneously into the abdomen, upper arm or thigh.

In summary, the pharmacokinetic findings suggest that dose adjustment based on demographic factors is not required for dulaglutide.

5 Conclusion

The pharmacokinetics of dulaglutide support a once-weekly dosing regimen in patients with T2D. Dulaglutide can be injected subcutaneously into the arm, thigh or abdomen. Although there is remaining inter-individual pharmacokinetic variability not explained by the factors examined in this study, the pharmacokinetic findings suggest that no dose adjustment of dulaglutide is necessary on the basis of body weight, sex, age, race or ethnicity. Additional assessment of the influence of intrinsic factors on pharmacodynamic measures will be conducted to further confirm this conclusion.

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Compliance with Ethical Standards

Declarations of interest JSG, MAH, XC, JM, CL, JYC and AdlP are employees and shareholders of Eli Lilly and Company.

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Ethical standards All clinical studies described herein were approved by the appropriate ethics committee and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects

gave their informed consent prior to their inclusion in the studies. This manuscript does not contain animal studies or data.

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