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ARTICLE

Population pharmacokinetics of the GIP/GLP receptor agonist tirzepatide

Karen Schneck | **Shweta Urva**

Global PK/PD & Pharmacometrics, Eli Lilly and Company, Indianapolis, Indiana, USA

Correspondence
Karen Schneck, Global PK/PD & Pharmacometrics, Eli Lilly and Company, Indianapolis, IN 46285, USA.
Email: kschneck@lilly.com

Abstract

Tirzepatide is a first-in-class glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved as for the treatment of type 2 diabetes mellitus. A population-based pharmacokinetic (PK) model was developed from 19 pooled studies. Tirzepatide pharmacokinetics were well-described by a two-compartment model with first order absorption and elimination. The tirzepatide population PK model utilized a semimechanistic allometry model to describe the relationship between body size and tirzepatide PK. The half-life of tirzepatide was ~5 days and enabled sustained exposure with once-weekly subcutaneous dosing. The covariate analysis suggested that adjustment of the dose regimen based on demographics or subpopulations was unnecessary. The tirzepatide PK model can be used to predict tirzepatide exposure for various scenarios or populations.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE OF THE TOPIC?

Tirzepatide is a first-in-class glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist once weekly injectable approved for the treatment of type 2 diabetes mellitus and is currently in phase III development for chronic weight management.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study characterizes the pharmacokinetics (PKs) of tirzepatide and investigated the impact of various population characteristics that could affect tirzepatide exposure.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The PKs of tirzepatide and pharmacometric analyses support the approved once weekly subcutaneous dosing of 5, 10, or 15 mg tirzepatide with no dose adjustments necessary for renal impairment, hepatic impairment, body weight, sex, age, race, or ethnicity.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This work demonstrates that population-based analyses and pharmacometrics enable the integration of information across a comprehensive clinical development program to provide a cohesive understanding of tirzepatide PKs and support dosing guidance to healthcare practitioners.

INTRODUCTION

Tirzepatide is a first-in-class glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist injectable approved for the treatment of type 2 diabetes mellitus (T2DM) as a once-weekly (q.w.) subcutaneous (s.c.) injection and is currently in phase III development for chronic weight management. The recommended starting dosage is 2.5 mg s.c. q.w.. After 4 weeks, the dose can be increased to 5 mg s.c. q.w. If additional glycemic control is needed, the dose may be further increased in 2.5 mg increments after at least 4 weeks on a dose. The approved maximum dosage is 15 mg subcutaneously once weekly.[1]

The glucose-lowering effect observed with tirzepatide, attributed to GIP and GLP-1 receptor agonism, may reflect an added benefit of GIP receptor-mediated insulinotropic action and an increase of insulin sensitivity independent of body weight changes.[2,3] The weight loss observed with tirzepatide may be attributed to a combination of the GIP receptor- and GLP-1-receptor-mediated mechanisms regulating satiety and food intake.[2] Significant glycemic and body weight reductions with tirzepatide treatments of 5, 10, or 15 mg once weekly have been consistently observed across a diverse T2DM population across several large clinical trials.[4–10]

The population pharmacokinetic (PK) model was developed based on tirzepatide PK data from 19 studies, which included data from healthy participants in clinical pharmacology studies, participants with renal impairment, hepatic impairment, and data from participants with T2DM in phase I, phase II, and phase III clinical trials. The diverse doses, dosing schemes, and population characteristics of the studies enabled a thorough evaluation of potential influences on tirzepatide PKs.

METHODS

Study overview

All clinical studies (Table 1) included in these analyses were approved by the appropriate ethics committee, and written informed consent was obtained from each participant prior to their inclusion in the study.

PK sampling and bioanalytical assay

Serial PK sampling to determine tirzepatide concentration was implemented in all clinical pharmacology studies. An optimized sparse PK sampling approach was implemented in phase II and phase III studies. In three of the five phase III studies,[4,7,8] trial participants were assigned randomly to the sampling PK time windows of 1–24 h, 24–96 h, or 120–168 h postdose at the protocol-specified visits across the duration of the study. The other phase III studies collected predose samples at the same time as immunogenicity samples and at the follow-up visit. PK samples were collected after single and multiple doses, up to 109 weeks of continuous tirzepatide treatment.

Tirzepatide plasma concentrations were measured using a validated liquid chromatography with mass spectrometry assay, which detected a tirzepatide intact mass, comprising the full-length peptide plus the linker and acyl side chain (Q2 Solutions). The range of quantification was 2–500 ng/mL. Approximately 16% of the total collected tirzepatide concentration samples were below 2 ng/mL, the lower limit of quantitation (LLOQ). Due to the relatively low percentage of samples below the LLOQ in the available data, these samples were excluded from the population PK analysis.

Population modeling approach

Population PK analyses of tirzepatide concentration-time data were performed using the nonlinear mixed-effects modeling program, NONMEM 7.4.2. First order conditional estimation with interaction was used as the estimation method. The mean absolute bioavailability of tirzepatide is ~80% based on i.v. bolus data[1] and was incorporated into the PK model as a fixed value parameter. Because the estimate of bioavailability can potentially be affected by conditions beyond drug property, such as variability of administered dose amount or extent of accurate dose records, the bioavailability of tirzepatide in the pooled datasets was estimated as a fraction relative to the reference fixed value. The relative between-study differences on F were estimated as $F = 0.8 * (1 + \text{Fraction})$ where 0.8 is the absolute bioavailability and the fraction is relative to absolute bioavailability.

TABLE 1 Clinical studies included in tirzepatide population pharmacokinetic analyses.

Study	Phase	Description	Population	S.c. dosing regimen
1[29]	1	Safety, tolerability, PK, PD	Healthy and T2DM	Single dose: 0.25, 0.5, 1, 2.5, 5, and 8 mg Multiple dose: 0.5, 1.5, 4.5, 5, 8, 10, 15 mg q.w. for 4 weeks
2[30]	1	Safety, tolerability, PK, PD	Japanese with T2DM	2.5, 5, 10, 15 mg q.w. for 8 weeks
3[31]	1	Safety, tolerability, PK in renal impairment	Healthy and T2DM	Single dose: 5 mg
4[32]	1	Safety, tolerability, PK in hepatic impairment	Healthy and T2DM	Single dose: 5 mg
5[a]	1	PK, oral contraceptive	Healthy	Single dose: 5 mg
6[a]	1	PK, metabolism	Healthy	Single dose: 4.1 mg
7[a]	1	PK, absolute bioavailability	Healthy	Single dose: 5 mg s.c. and i.v.
8[a]	1	PK, device	Healthy	Single dose: 5 mg
9[a]	1	PK, relative bioavailability by injection site and BMI	Healthy	Single dose: 5 mg in upper arm, thigh, or abdomen
10[33]	1	PK, PD, mechanism of action	T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 28 weeks
11[34]	2	Dose ranging	T2DM	1, 5, 10, 15 mg for 26 weeks
12[35]	2	Dose finding	T2DM	2.5, 4, 5, 8, 10, 15 mg for 12 weeks
13[7]	3	SURPASS-1	T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 40 weeks
14[5]	3	SURPASS-2	T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 40 weeks
15[6]	3	SURPASS-3	T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 52 weeks
16[4]	3	SURPASS-4	T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 104 weeks
17[8]	3	SURPASS-5	T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 40 weeks
18[9]	3	SURPASS J-mono	Japanese with T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 52 weeks
19[10]	3	SURPASS J-combo	Japanese with T2DM	2.5, 5, 7.5, 10, 12.5, 15 mg q.w. for 52 weeks

Abbreviations: BMI, body mass index; PD, pharmacodynamic; PK, pharmacokinetic; T2DM, type 2 diabetes mellitus.

[a]Data on file.

Interindividual variability (IIV) was assessed separately on each of the PK parameters using an exponential error structure which assumes a log-normal distribution of individual parameter values. Covariance between IIV terms was assessed. Proportional, additive, and combined proportional and additive error structures were evaluated for the residual error.

Assessment of the effect of covariates on tirzepatide PK

Population characteristics were prospectively identified and selected to be included in covariate analyses based on clinical relevance or expert knowledge of drug disposition (Table S1).

For continuous covariates, a variety of linear and nonlinear models were tested, such as those shown in Equations 1–3. For categorical covariates, a categorical model was used, such as shown in Equation 4.

$$P = \Theta_1 \times \left(1 + \Theta_2 \bullet COV\right). \quad (1)$$

$$P = \Theta_1 \times \exp\left(\Theta_2 \bullet COV\right). \quad (2)$$

$$P = \Theta_1 \times COV^{\Theta 2}. \quad (3)$$

$$P = \Theta_1 \times \left(1 + \Theta_2 \bullet IND\right). \quad (4)$$

In the Equations 1–4, P is the individual's estimate of the parameter (e.g., clearance [CL] and volume [*V*]), Θ_1 represents the typical value of the parameter, Θ_2

represents the effect of the covariate, COV is the covariate value which was normalized to a relevant centering statistic(e.g., median), and IND is an indicator variable with a value of either 0 or 1 assigned for values of a categorical covariate (e.g., female or male).

Allometric principles were incorporated into the tirzepatide PK base model with body weight-based allometric exponents included as fixed values on CL and volume of distribution (V_d) parameters.[11–13] Because treatment with tirzepatide results in weight reduction over time, the influence of body weight was evaluated as either a baseline covariate or time varying covariate. To describe the influence of body weight on tirzepatide PK more precisely, the relationship between fat mass and CL and V_d was incorporated into the model.[14] Using equations from a semimechanistic model developed in individuals with T2DM and body weights comparable to the tirzepatide-treated population,[15] fat free mass was calculated based on each participant's total body weight, sex, and body mass index (BMI), and subsequently the fat mass was derived (Equations 5–7). The fraction of fat mass that contributed to the relationship between body weight and the PK parameter was estimated (Equation 8).

$$\text{FFM (male)} = 9270 \times \text{BW} / (6680 + 216 \times \text{BMI}). \quad (5)$$

$$\text{FFM (female)} = 9270 \times \text{BW} / (8780 + 244 \times \text{BMI}). \quad (6)$$

$$\text{FM} = \text{BW} - \text{FFM}. \quad (7)$$

$$\text{P} = \text{TVP} \times \left[(\text{FFM} + \text{Frac} \times \text{FM}) / 70\right]^{\text{Eff}}, \quad (8)$$

In Equation 8, P was the individual's estimate of the parameter (e.g., CL and V_d), TVP represented the typical value of the parameter, FFM was the individual's fat-free mass, FM was the individual's fat mass, Frac represented the fraction of fat mass, and Eff represented the allometric exponent. Allometric exponents were included as fixed values on CL, Q, V2, and V3 parameters in the tirzepatide population PK base and final models and the exponent values that were applied were based on publications.[11–14]

Covariates were graphically assessed for their general magnitude of impact on the disposition of tirzepatide and were evaluated individually for statistical significance (a model objective function value decrease of ≥6.635 points for a χ^2 distribution; $p < 0.01$) when added to the base model. Individual covariates identified as statistically significant were included in a full model, and each covariate was tested for statistical significance when removed (a model objective function value increase of ≥10.828 points for a χ^2 distribution; $p < 0.001$). The relative decrease in the variance of the affected parameter and the agreement between predicted and observed concentrations, as assessed by visual inspection, were also taken into consideration when determining the inclusion of a covariate in the model. Only those covariates deemed to be statistically significant and clinically relevant were retained in the final model.

Model evaluation

The PK model was developed according to a workflow described in an analysis plan established prior to commencement of analysis. Key model selection criteria included convergence of the estimation and covariance routines, estimates of parameters and variances reasonably consistent with prior knowledge and expectations (e.g., noncompartmental PK analysis), acceptable precision of the parameter and variance estimates, and graphical evaluation using prediction- or simulation-based metrics to confirm that the model characterized the data with no overt model misspecification or bias.

The final model was evaluated using standard methods, including bootstrap analysis and visual predictive checks, to verify that the model predictions matched the observed data with acceptable precision and accuracy. The bootstrap analysis was performed using PsN version 4.8.1 by sampling from the analysis dataset with replacement to produce resampled datasets with the same number of patients. A total of 1000 bootstrap replicates were assessed and the 95% confidence intervals for each parameter were calculated using the 2.5th and 97.5th percentile values from the distribution of bootstrap parameter values.

Virtual patients simulation

The ordinary differential equations from the tirzepatide final population PK model were implemented in R using the package RxODE.[16] Tirzepatide concentrations and exposure metrics (area under the curve [AUC] and maximum plasma concentration [C_{max}]) were simulated for virtual trial participants using final model estimates for fixed effects and random effects, and observed demographic variables (body weight, BMI, and sex). Virtual patients were generated by resampling the baseline demographics with replacement of the individuals with T2DM in the population PK analyses database. To preserve correlation between baseline demographics, patient factors were randomly selected together as a set of parameters representative of a study population patient.

The tirzepatide exposures in subpopulations of interest were evaluated by simulating tirzepatide concentrations using between-subject variability and residual

error[17] and calculating the mean AUC and C_{max} of 2000 virtual patients relative to the conditions of a reference. The simulations used a steady body weight value with no change over time (such as a baseline value) for each virtual patient. Another simulation examined the behavior of a virtual patient using typical population PK parameter values to illustrate the impact of a delayed or missed dose of tirzepatide.

RESULTS

Population PK modeling

The dataset for tirzepatide PK analysis included 39,644 observations from 5802 participants. The demographics of clinical trial participants included in the analyses are summarized in Table 2.

A two-compartment model with first-order absorption rate constant (k_a) and IIV using a log normal distribution included on k_a, CL, central volume of distribution, and proportional residual error best described the population PKs of tirzepatide. The 95% confidence intervals of PK model parameters derived from bootstrap analysis showed adequate precision in parameter estimation (Table 3). Goodness-of-fit and other diagnostic plots indicated adequate fidelity between model predictions and observed data (Figure 1, Figure S1). Tirzepatide exposure increased proportionally with doses across 0.25–15 mg[29] (Figure 2). Following subcutaneous administration, the time to C_{max} of tirzepatide ranged from 8 to 72 h. Similar exposure was achieved with s.c. administration of tirzepatide in the abdomen, thigh, or upper arm.

Age, serum creatinine, eGFR, aspartate transaminase (AST), alanine aminotransferase (ALT), bilirubin, albumin, anti-tirzepatide antibodies, race, or ethnic origin showed no statistically significant effect on the PKs of tirzepatide.

Body weight incorporated into the model as a time-varying covariate was associated with a statistically significant decrease in model objective function value compared to a model with covariate included as baseline body weight. Tirzepatide CL best correlated with total body weight (fat free mass plus fat mass) because the estimated fractional influence of fat mass approached a value of 1 and no statistical difference was detected when fractional influence of fat mass was estimated or fixed to a value of 1. Tirzepatide V_d correlated with an adjusted total body weight, wherein the fraction of fat mass contributing to the effect was 48% (Equation 4).

Tirzepatide exposure changed by ~1.1% per kg over a body weight range of 70–120 kg. Relative to a typical 90-kg individual, there was approximately a 22% higher and 33% lower difference in exposure for a 70- or 120-kg individual, respectively.

TABLE 2 Demographics for tirzepatide population pharmacokinetic analyses.

	N, Mean ± SD (minimum–maximum)			
Phase	**1**	**1**	**2**	**3**
Population	Healthy	T2DM	T2DM	T2DM
Sex, % female	28	27	44	43
Age (years)	338, 45.5 ± 13.5 (19–84)	183, 58.7 ± 7.74 (31–74)	373, 57 ± 8.77 (31–75)	5354, 58.1 ± 10.5 (18–91)
BMI (kg/m^2)	338, 27.1 ± 4.33 (18.8–44.3)	183, 29.7 ± 4.98 (20.2–45.2)	373, 32.4 ± 5.7 (22.4–51.4)	5354, 32.5 ± 6.39 (21.5–85.6)
Body weight (kg)	338, 79.5 ± 15.6 (50.7–141.2)	183, 86.2 ± 17.2 (56.6–139.6)	373, 91 ± 20.9 (47.7–163)	5354, 90 ± 20.6 (43.1–227)
eGFR (mL/min/1.73 m^2)	337, 95.8 ± 24.2 (6.64–157)	111, 93.7 ± 22.1 (6.25–173)	371, 93.9 ± 16.5 (44.5–130)	5183, 92.4 ± 18.9 (22–151)
Ethnicity, % Hispanic	17	28	49	37
Race/ethnicity (%)				
White	38	64	79	65
Black	22	4	11	3
Asian	39	31	2	24
Native American	0	<1	5	7
Multiple	<1	0	2	<1

Note: The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[36]

Abbreviations: BMI, body mass index; T2DM, type 2 diabetes mellitus.

TABLE 3 Tirzepatide population PK model parameters.

Parameter	Population estimate (95% CI)[a]	Interindividual variability (95% CI)[a]
Bioavailability[b]	0.8 fixed	
Absorption rate constant (1/h)	0.0373 (0.0289, 0.0460)	22.5%[c] (14.9, 28.7)
Clearance (L/h/70 kg)	0.0329 (0.0313, 0.0342)	14.2%[c] (13.7, 14.7)
Intercompartmental clearance (L/h/70 kg)	0.126 (0.101, 0.144)	–
Volume of distribution in central compartment (L/70 kg)t	2.47 (2.05, 2.92)	49.0%[c] (38.3, 62.3)
Volume of distribution in peripheral compartment (L/70 kg)	3.98 (3.56, 4.21)	–
Relative effect on bioavailability between studies[b]	−0.181 (−0.220, −0.147)	–
Allometry exponent for body weight on clearance[13,d]	0.8 fixed	–
Allometry exponent for body weight on volume of distribution[14,e]	1 fixed	–
Fraction of fat mass with effect on volume of distribution[e]	0.482 (0.447, 0.524)	–
Residual error: proportional (%)	20.6 (20.3, 21.0)	58.1% (56.1, 60.0)
Tirzepatide steady-state mean PK parameters in individuals with T2DM[f]		
Half-life (days)	5.4	–
Apparent clearance (L/h)	0.061	–
Apparent volume of distribution (L)	10.3	–

Abbreviations: CI, confidence interval; PK, pharmacokinetic; T2DM, type 2 diabetes mellitus.

[a]The 95% confidence interval derived from bootstrap analysis.

[b]The mean absolute bioavailability (F) of tirzepatide is ~80% based on i.v. bolus data.[1] The relative between-study effect was estimated as $F = 0.8 * (1 + \text{Fraction})$ where 0.8 is the absolute bioavailability and Fraction is the fraction relative to absolute bioavailability.

[c]Shrinkage for the interindividual variability for K_a, CL, and V_c were 57%, 10%, and 21%, respectively.

[d]$\text{iCL} = \text{pCL} \times (\text{BW}/70)^{0.8}$ where iCL is an individual's clearance, pCL is the population clearance, and BW is an individual's body weight. The described structure was applied to clearance and intercompartmental clearance.

[e]$\text{iVd} = \text{pVd} \times (\text{fat free mass} + \text{fat mass}^* \text{Frac}_{FM})/70$ where iVd is an individual's volume of distribution, pVd is the population volume of distribution, and Frac_{FM} is a fraction of fat mass. The described structure was applied to volume of distribution in central and peripheral compartments.

[f]Based on population PK post hoc parameters for individuals with T2DM.

Clinical applications

With a mean half-life of 5.4 days and mean accumulation of 1.7-fold with multiple dosing administration, the PKs of tirzepatide enabled sustained exposure with once-weekly dosing.

A comparison of model predicted AUC and C_{max} for groups representative of select intrinsic factors relative to a reference female individual with T2DM was summarized in a forest plot (Figure 3). Differences in tirzepatide exposure between populations grouped by intrinsic factor were generally within 25% of the reference and were primarily associated with the body weight range of the group. After accounting for body weight, the intrinsic factors (such age, sex, or race) were not associated with any statistically significant differences in tirzepatide PK. Because there is similarity of tirzepatide exposure, comparable tolerability, and robust glycemic and body weight reductions across populations grouped by intrinsic factors, no tirzepatide dose adjustment is recommended.

The scenario where a dose was taken 4 days after the missed schedule dose time, resulting in a transient 20% higher concentration following the subsequent dose that was resumed on the regularly scheduled day was simulated (Figure 4). The simulations assumed that a dose of tirzepatide was omitted on a scheduled dosing day at steady-state, and supported clinical instructions on the latest time to restart dosing. If more than 4 days have passed, it is recommended that the missed dose be skipped and to resume the regular once weekly dosing schedule by

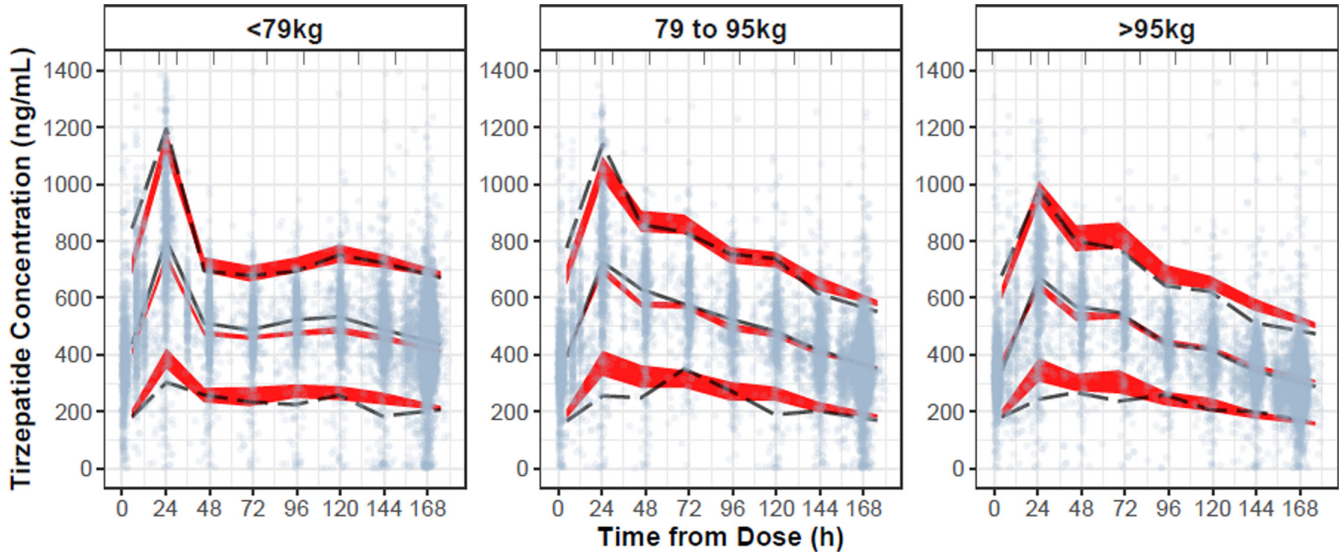


FIGURE 1 Prediction-corrected visual predictive check[37] of the tirzepatide population pharmacokinetic model showing predicted and observed tirzepatide concentration–time profiles over a once-weekly dosing interval stratified by tertiles of baseline body weight in the analysis population. The dots represent the observed concentration data; the black lines indicate the 5th, 50th, and 95th percentiles of the observed data and the shaded areas represent the 95% confidence intervals for the 5th, 50th, and 95th percentiles of the simulated predictions.

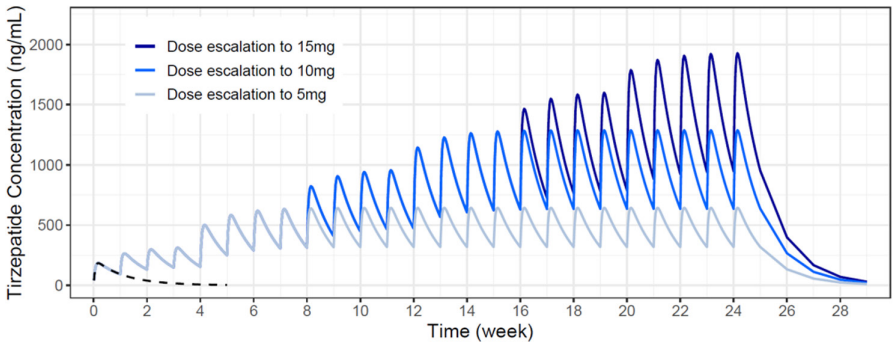


FIGURE 2 Model predicted tirzepatide concentrations over time with dose escalation. Tirzepatide concentrations in a 90-kg individual were simulated using the tirzepatide population pharmacokinetic model. The dashed line denotes a single dose of tirzepatide 2.5 mg. The solid lines denote concentrations following dose escalation up to 5, 10, or 15 mg. Dose escalation started with 2.5 mg subcutaneous once weekly and dose amount was increased by a 2.5-mg increment every 4 weeks.

administering the tirzepatide dose on the next regularly scheduled day. If necessary, the day of weekly administration can be changed if the time between two doses is at least 3 days (≥72 h).[1]

DISCUSSION

Data collected from clinical study participants with characteristics representative of the intended T2DM treatment population enabled the development of a robust, informative population-based model of tirzepatide PKs.

The covariate analyses implemented with the tirzepatide population PK model demonstrated that tirzepatide exposure showed no relationship with markers of renal impairment (serum creatinine, eGFR, and albumin), markers of hepatic impairment (AST, ALT, and bilirubin), or intrinsic factors (age, sex, race, or ethnicity) to any clinically relevant degree that would require a dose adjustment.

Understanding and investigation of the relationship between body size and tirzepatide PK during population model development was motivated by several reasons. The global population is trending toward a greater percentage of individuals with overweight or obesity classification and, subsequently, adequacy of dosing in this group of people is a topic of concern by healthcare practitioners and regulatory agencies.[18,19] Obesity is prevalent in people

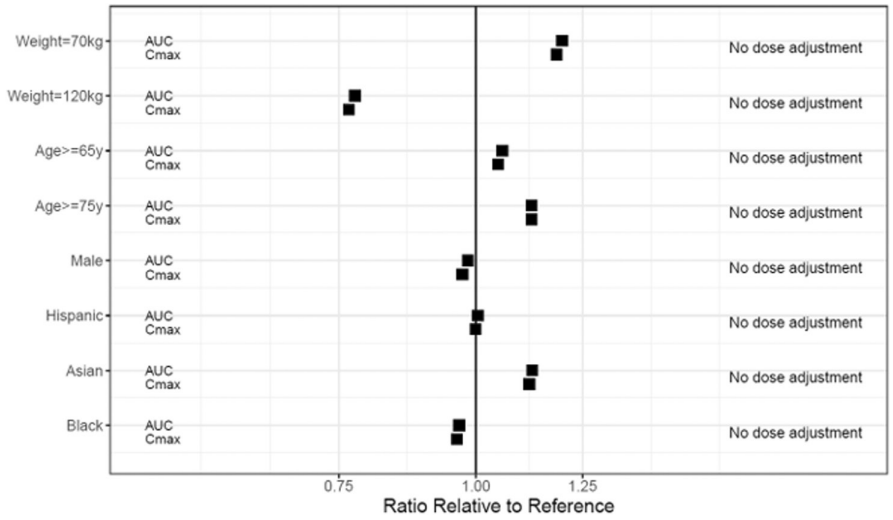
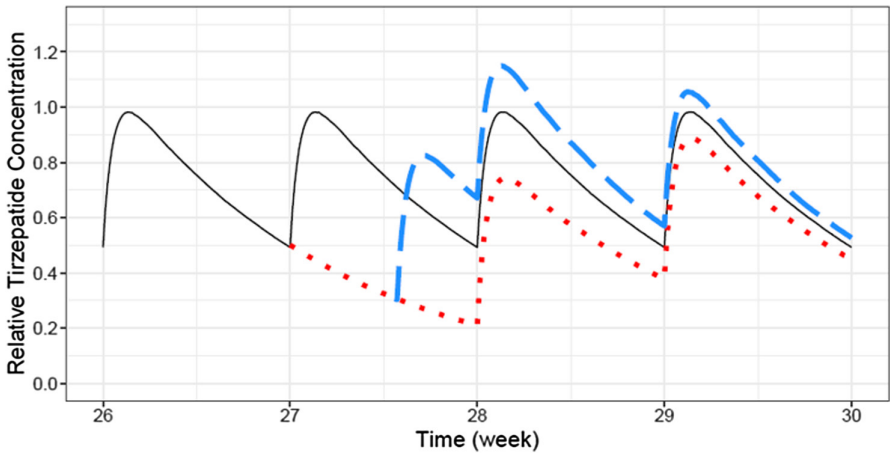


FIGURE 3 Ratios of the area under the plasma concentration–time curve (AUC) and maximum concentration (C_{max}) for subpopulations relative to a reference. The reference values for body weight, age, sex, and race are 88 kg, 55 years old, women, and White, respectively. The body weights 70 and 120 kg were the 10th and 90th percentiles of the population in phase III clinical trials. The median body weight for groups: (age ≥65 years) 82 kg; (age ≥75 years) 76 kg; (male) 89 kg; (Hispanic) 86 kg; (Asian) 76 kg; and (Black) 91 kg. The ratios of the means are shown.

FIGURE 4 Effects of delayed or missed dose on the steady-state concentration–time profile of tirzepatide. The pharmacokinetic model simulated tirzepatide concentration–time profiles following a once-weekly dose taken as prescribed (solid black line), with a dose being delayed until mid-week (blue dashed line) or with a dose being skipped (red dotted line).



with T2DM, the target treatment population for tirzepatide.[20,21] Finally, there is a theoretical "feedback loop" in the framework of PK and pharmacodynamics when considering tirzepatide PK is influenced by body weight and tirzepatide treatment is associated with body weight loss over time.

The approach used in the tirzepatide PK model to describe the relationship between body size and tirzepatide PK was carefully considered. Although many indices of body size have been postulated to correlate with drug dosing in individuals who are obese,[22,23] the work from Janmahasatian et al. describing a semimechanistic model for body composition developed from data with 71% of study participants who were overweight or obese was suitable for the tirzepatide PK analyses.[15] Accounting for body composition did not appear to show an advantage over the use of total body weight in the allometry of tirzepatide CL in this population PK analysis. The commonly used nonlinear relationship expressed as body weight with an exponent ("power") value adequately described the relationship between body weight and tirzepatide CL. As tirzepatide is a therapeutic protein, it was reasonable to expect that tirzepatide distributes mainly in the intravascular space. Incorporating body composition into the allometry of volume of distribution of tirzepatide is consistent with the nonlinear relationship between blood volume and body weight in individuals with obesity. Blood volume will be overestimated in individuals with obesity unless a correction factor is applied to the total body weight.[24,25] Estimating the fraction of fat mass contributing to the allometry of PK is conceptually similar to dosing using the adjusted body weight equation, an approach which has sometimes been used in clinical practice to optimize dosing of i.v. immunoglobulin for individuals with obesity.[26]

Although s.c. GLP-1 receptor agonists have incorporated the impact of body weight on PK,[27,28] the implementation of allometric scaling of PK with time varying body composition described herein for tirzepatide is novel.

In conclusion, the PK of tirzepatide have been systematically investigated using data from a comprehensive clinical development program. The tirzepatide population PK model integrated a novel semimechanistic approach to allometry to better understand the variability of tirzepatide exposure across population groups. The simulation of tirzepatide exposure following tirzepatide treatment in virtual patients enabled and supported clinical dosing guidance. Application of pharmacometrics demonstrated that exposure variability was comparable across age, body weight, sex, race, ethnicity, anti-tirzepatide antibodies, renal impairment, and hepatic impairment, and, hence, no tirzepatide dose adjustment is necessary based on these factors.

AUTHOR CONTRIBUTIONS

K.S. and S.U. wrote the manuscript. K.S. and S.U. designed the research. S.U. performed the research. K.S. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

K.S. and S.U. are employees and shareholders of Eli Lilly and Company.

ORCID

Karen Schneck https://orcid.org/0000-0002-9229-4987
Shweta Urva https://orcid.org/0000-0002-3681-479X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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