CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215866Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	215866
Link to EDR	\\CDSESUB1\evsprod\NDA215866
Submission Date	09/15/2021
Submission Type	Priority review
Brand Name	Mounjaro
Generic Name	Tirzepatide
Dosage Form and Strength	Solution for injection as pre-filled single-dose pen. Strengths: 2.5mg/0.5mL, 5mg/0.5mL, 7.5mg/0.5mL, 10 mg/0.5mL, 12.5 mg/mL, 15mg/0.5mL
Route of Administration	Subcutaneous Injection
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant	Eli Lilly and Company
Associated IND	128801
OCP Review Team	Division of Cardiometabolic and Endocrine Pharmacology (DCEP): Mohamad Kronfol, Ph.D.; Jayabharathi Vaidyanathan, Ph.D. Pharmacometrics: Elyes Dahmane Ph.D.; Justin Earp Ph.D. PBPK: Yuching Yang Ph.D.; Manuela Grimstein Ph.D.
OCP Final Signatory	Shirley Seo Ph.D.

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1. EXECUTIVE SUMMARY

The Applicant, Eli Lilly and Company, submitted NDA 215866 on September 15, 2021, seeking approval of tirzepatide (Mounjaro) as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus (T2DM).

Tirzepatide is an agonist at the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors developed for the once-weekly treatment of adults with T2DM. Tirzepatide is a 39 amino acid synthetic peptide engineered from the GIP sequence and includes a C20 fatty diacid moiety. Based on known physiology and pharmacology of GIP and GLP-1, dual signaling is proposed to result in improved control of carbohydrate and lipid metabolism and body weight in patients with T2DM.

The to-be-marketed tirzepatide (Mounjaro) is a solution for injection as pre-filled single-dose pen (SDP). The development program consists of pharmacokinetics (PK), pharmacodynamics (PD), tolerability, and pivotal efficacy and safety trials in adult patients.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/ DCEP) reviewed the clinical pharmacology data submitted in NDA 215866 and found it acceptable. The application is approvable from a clinical pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Five pivotal trials GPGK, GPGL, GPGH, GPGM, and GPGI provide primary evidence of tirzepatide effectiveness and safety for adult patients with T2DM either as monotherapy or in combination with other anti-diabetic agents. Patients with T2DM treated with tirzepatide as monotherapy showed significant -1.7% to -1.8% reductions from baseline in HbA1c compared to -0.1% in those taking placebo.
General dosing instructions	• Start at 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly • If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg • Administer once weekly at any time of day, with or without meals • If a dose is missed administer within 4 days of missed dose • Inject subcutaneously in the abdomen, thigh, or upper arm
Dosing in patient subgroups (intrinsic and extrinsic factors)	None of the patient subgroups based on intrinsic factors like age, gender, race, ethnicity, body weight, renal impairment, or hepatic impairment have specific dosing recommendations. Tirzepatide delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications.
Labeling	Refer to Section 2.4.

Bridge between the to-be-marketed and clinical trial formulations	The relative bioavailability (BA) of the single-dose pen (SDP) presentation (to-be-marketed presentation) used in the phase 3 trials was assessed in a dedicated study GPGS and showed comparable BA with the prefilled syringe (PFS) presentation used in the phase 3 study GPGM

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Tirzepatide is a peptide with agonist activity at the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Tirzepatide has high affinity to both the GIP and GLP-1 receptors. The agonism is expected to result in control of HbA1c and body weight. Tirzepatide increases insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner. Tirzepatide slows gastric emptying and this effect diminishes over time. General Clinical Pharmacokinetics is summarized in Table 1

Table 1 General Clinical Pharmacokinetics of tirzepatide

Absorption	• PK is dose proportional in the dose ranging from 0.25-15 mg based on population PK (popPK) analysis • The time to reach maximum plasma concentration (t_{max}) ranges from 8 to 72 hours • Absolute bioavailability is approximately 80%
Distribution	• Plasma Protein Binding is 99% • Apparent Volume of Distribution at steady state (Vd_{ss}) is 10.3 L • Steady State is reached at 4 weeks after once-weekly administration
Metabolism	• Proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis
Elimination	• Plasma Clearance (CL) is 0.061 L/h • Terminal half-life ($t_{1/2}$) is approximately 5 days • Renal excretion is the primary route of elimination. Intact parent is not detected in urine or feces. Approximately 70% of radiolabeled dose recovered as metabolites in urine (50%) and feces (20%)

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Start at 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg. Administer once weekly at any time of day, with or without meals. If a dose is missed administer within 4 days of missed dose. Inject subcutaneously in the abdomen, thigh, or upper arm.

2.2.2 Therapeutic individualization

No dose adjustment is necessary for age, gender, body weight, race, renal or hepatic impairment, and drug interaction.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling comments.

Label Section	Recommendation
7.2 Oral Medications	Added monitoring text for narrow therapeutic index when administered concomitantly with tirzepatide. Added text to inform risk of interaction with Oral Contraceptive.
12.1 Mechanism of action	Removed text (b) (4)
12.2 Pharmacodynamics	Consistent with labeling of approved GLP-1RA, and to prevent promotional language, (b) (4)
12.3 Pharmacokinetics	The Applicant is recommended to include the observed Drug-Drug Interaction (DDI) study results with acetaminophen as well as oral contraceptive under Drug Interaction Studies subheading and removing Figure 3 forest plot of DDI from PBPK simulations.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The Applicant is developing tirzepatide for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The regulatory background pertaining to Clinical Pharmacology included Type B End-of-Phase2 and Pre-NDA meetings as well as Type C written response with key discussion point including adequacy of Clinical Pharmacology studies, PBPK modeling for DDI, PopPK and Exposure-Response (E-R) analysis, and adequacy the Oral Contraceptive (OC) DDI study (see Table 11 in Appendix 4.1). The studies conducted under the

Clinical Pharmacology part of the program included Relative Bioavailability (BA), Single- and Multiple-Ascending Dose (SAD/MAD), Disposition of radioactivity, hepatic and renal impairment, DDI, and Pharmacodynamic (PD) studies, as well as PopPK and E-R reports (See Table 12 in the Appendix 4.1). The intended commercial SDP presentation was used in all phase 3 trials except one (18F-MC-GPGM used the PFS) and the Applicant conducted a relative BA study 18F-MC-GPGS to bridge the PFS to the SDP presentation.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Tirzepatide is a synthetic 39 amino acid single peptide with agonist activity at the GIP and GLP-1 receptors. Tirzepatide has high affinity to both the GIP and GLP-1 receptors. The activity of tirzepatide on the GIP receptor is similar to native GIP hormone. The activity of tirzepatide on the GLP-1 receptor is lower compared to native GLP-1 hormone. At the GLP-1 receptor, tirzepatide is a biased agonist with preferential signaling towards the activation of adenylyl cyclase as opposed to the recruitment of β-arrestin. Tirzepatide is expected to result in control of HbA1c and body weight. Tirzepatide increases first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner. In patients with T2DM, tirzepatide improves insulin sensitivity. Tirzepatide slows gastric emptying and this effect diminishes over time. Tirzepatide decreases food intake.

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with T2DM based on population PK analysis after taking body weight into account. Steady state plasma tirzepatide concentrations are achieved following 4 weeks of once weekly administration.

Absorption

The mean absolute bioavailability of tirzepatide following subcutaneous (SC) administration when compared to IV bolus is 80.9% (Study GPGE, Part D).

In Study GPGA, following multiple SC administration for 4 weeks of 0.5 mg (QW), 5 mg (QW), 5/5/10/10 mg, and 5/5/10/15 mg to patients with T2DM, t_{max} ranges from 24 to 72 hours. Mean (CV%) C_{max} ranges from 54.6 (28) to 1250 (20) ng/mL. Mean (CV%) $AUC_{0\text{-}tau}$ ranged from 7200 (30) to 164000 (14) h*ng/mL. Mean $t_{1/2}$ in patients with T2DM was approximately 5 days, supporting a QW dosing regimen. Multiple QW doses over a 4-week duration resulted in an accumulation ratio of 1.6 in patients with T2DM, based on $AUC_{0\text{-}tau}$.

Population PK analysis included PK data from phase 1, 2, and 3 studies and shows that tirzepatide exposure increased dose-proportionally over the dose range of 0.25 to 15 mg. Following multiple dose administration of tirzepatide 5, 10, and 15 mg, the mean (CV%) steady state peak plasma concentration ($C_{max,ss}$) was 664 (22.4), 1340 (22.8), and 1990 (22) ng/mL, while average systemic exposure ($C_{avg,ss}$) of tirzepatide was 495 (22.7), 998 (23), and 1480 (22.2) ng/mL, respectively. Following multiple dose administration of tirzepatide 5, 10, and 15 mg, the mean (CV%) AUC was 83300 (22.7), 168000 (23), 250000 (22.2) ng*h/mL Accumulation ratio based on $C_{avg,ss}$ was approximately 1.7.

Distribution

The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with T2DM is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Metabolism

Tirzepatide is primarily metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis. In Study GPHX, tirzepatide was the largest component in plasma accounting for approximately 80% of the circulating radioactivity. The 4 minor metabolites in plasma resulting from proteolytic cleavage of the peptide backbone each individually accounted for less than 5.7% of total circulating radioactivity.

Elimination

The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing.

Tirzepatide is eliminated by metabolism. The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces. In Study GPHX, the mean total recovery of administered radioactivity was approximately 70%, from which approximately 50% of the administered radioactivity was excreted in urine and approximately 20% was excreted in feces.

Specific Populations

The intrinsic factors of age, gender, race, ethnicity, body weight, or renal or hepatic impairment do not have a clinically relevant effect on the PK of tirzepatide.

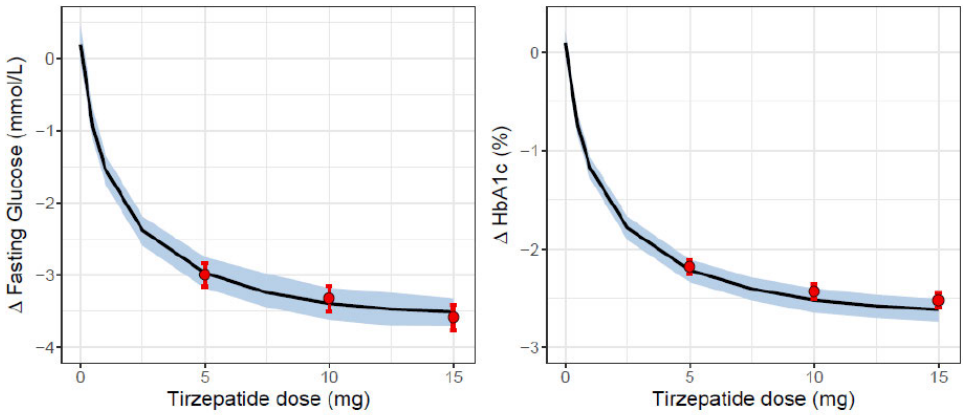
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The Clinical Pharmacology data provide supportive evidence of effectiveness for tirzepatide as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Refer to Table 12 in Appendix 4.1, for the list of clinical studies conducted. In the Pharmacodynamic (PD) Study GPGT, tirzepatide 15 mg enhanced the first- and second-phase insulin secretion rate, reduced fasting and postprandial glucagon secretion, fasting glucose, and food intake (see Appendix 4.1). Fasting Glucose (FG) and HbA1c, and body weight data from multiple studies (seven phase 3 and two phase 2 studies, up to a duration of 104 weeks – see Appendix 4.4) were used to characterize the PK/PD relationship. The population FG-HbA1c model developed for phase 2 Studies GPGB and GPGF in patients with T2DM adequately described FG and HbA1c time course for phase 3 studies. The population PK/PD model was used to predict the dose-response relationship after 52 weeks of treatment. The dose-response relationship shows that the effect of tirzepatide on FG and HbA1c (Figure 1) and body weight (Figure 2) increased with increasing tirzepatide doses of 5, 10, and 15

mg QW (See details of PK/PD modeling in Appendix 4.4). The implementation of stepwise dose-escalation scheme starting at 2.5-mg dose for 4 weeks, followed by increases in doses by 2.5-mg increments every 4 weeks to attain maintenance dose levels of 5, 10, and 15 mg in phase 3 studies, appears to have mitigated the incidence of GI AEs. This resulted in fewer discontinuations due to GI AEs in the phase 3 program, especially at the 10- and 15-mg doses, that were noted in phase 2 Study GPGB.

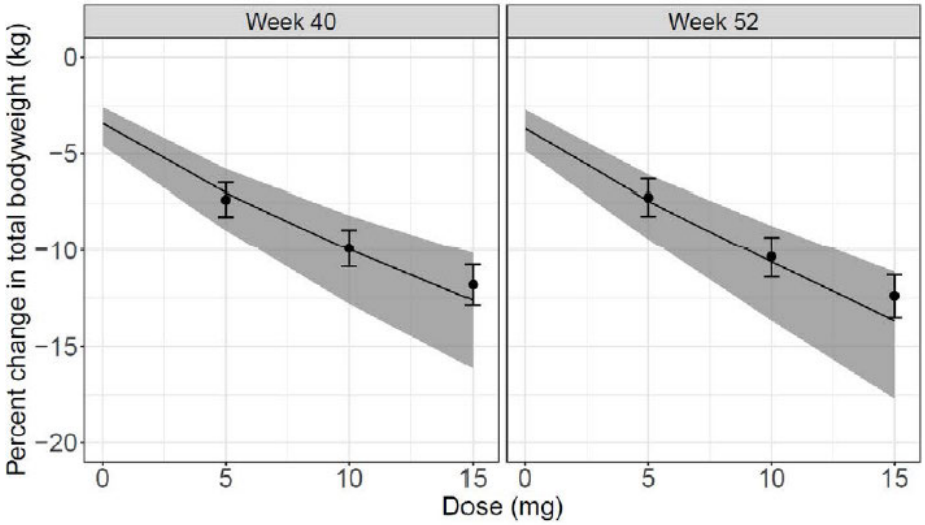
Figure 1 Change from Baseline in Fasting Glucose and Hb1Ac at Week 52, Across Tirzepatide Doses of 5, 10 and 15 mg



Abbreviations: Δ = change from baseline; HbA1c = hemoglobin A1c.
Note: Solid black lines denote the simulation median and the shaded areas denote the 90% confidence interval. Red circles and error bars denote the mean and 95% confidence interval of observed data.

(Source: Applicant's Population PK/D Report, Figure 10.8, page 129)

Figure 2 Change from Baseline in Total Body Weight, Across Tirzepatide Doses of 5, 10 and 15 mg



The continuous line is the median prediction. The shaded area is the 95% confidence interval of the prediction. The points and error bars are the observed mean and 95% confidence interval respectively.

(Source: Applicant's Population PK/D Report, Figure 10.11, page 133)

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the proposed indication. The dosing regimen is to start at 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg. Administer once weekly at any time of day, with or without meals. If a dose is missed administer within 4 days of missed dose. Inject subcutaneously in the abdomen, thigh, or upper arm.

The results of the phase 2 Study GPGB suggested that while promising efficacy (up to 2.4% HbA1c lowering and up to 11.3-kg body weight loss) was noted in the dose range of 5 to 15 mg, the escalation steps to attain 10- and 15-mg doses were not optimal and resulted in several discontinuations attributed to GI tolerability events. Therefore, an additional 12-week Study GPGF was implemented to investigate alternate less intensive dose-escalation schemes, starting at doses as low as 2.5 mg and attaining 12 or 15 mg within 12 weeks. The results of the phase 2 Study GPGF suggested that although robust efficacy results (up to 2% HbA1c lowering and 5.7-kg body weight loss) was attained, starting treatment on lower doses and escalating dose levels in smaller increments may reduce discontinuations due to GI events. This study, together with Study GPGB, provided data to support the final dose selection and dose-escalation regimen for phase 3 development.

The phase 3 studies demonstrated effectiveness of tirzepatide when given as monotherapy and in combination with background metformin, oral antidiabetic medication, or insulin. Dose-dependent changes in HbA1c and body weight were observed. For final efficacy and safety conclusions on the pivotal phase 3 studies refer to Clinical review in DARRTS.

The Exposure-Response analysis for safety characterized the effect of tirzepatide on the probability of occurrence of nausea, vomiting or diarrhea adverse events (AEs). The PK/PD model was reasonable to describe the occurrence of nausea, vomiting, and diarrhea and the development of tolerance over time during chronic treatment. According to the phase 3 studies data, no alternative dose titration appeared to be required based on specific demographics. In addition, the current dosing regimen appears to have mitigated the incidence of gastrointestinal AEs. The majority of nausea, vomiting, and diarrhea AEs were reported during the dose-escalation phase, and their incidence decreased with time with a prevalence <10% once steady-state concentrations for the maintenance doses were attained (See Appendix 4.4).

No dedicated tQT study was conducted, in part due to challenges with the long half-life of tirzepatide and titration schedule to achieve steady-state concentrations associated with the highest dose. The submitted non-clinical and clinical data (concentration-QT analysis using ECG readings from Phase 1 and 2 Studies GPGA, GPGB, & GPGF, and Phase 3 studies) do not indicate any unexpected or important effects of tirzepatide on the QTc interval at clinically relevant exposures associated with the proposed dose (i.e., up to 15 mg once weekly). See review by QT-IRT review team dated 02/16/2022 in DARRTS.

Across seven phase 3 clinical studies, 51.1% of evaluable treated patients developed TE ADA during the planned treatment period. Approximately 66% and 27% of ADA+ patients showed cross-reactivity with native GIP (nGIP) and native GLP-1 (nGLP-1). The development of antidrug antibody was not associated with an altered PK profile or an impact on efficacy or safety of the drug (Refer to Immunogenicity review on 2/15/22 in DARRTS). The population PK analysis showed no statistically significant relationship between ADA and CL.

The handling of missed dose was assessed in the population PK analysis. Administration of tirzepatide dose within 4 days of the missed dose resulted in <20% increase in C_{max} associated with the subsequent scheduled dose. If more than 4 days have passed, it is recommended that the missed dose be skipped and to resume the regular weekly (QW) dosing schedule by administering tirzepatide on the next regularly scheduled day. The Applicant's proposal to administer tirzepatide as soon as possible within 4 days (96 hours) of a missed dose, otherwise to skip the dose (if more than 4 days has passed) before resuming the regular weekly regimen is acceptable.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No dose adjustment is necessary for age, gender, body weight, race, renal or hepatic impairment, and drug interaction.

Renal Impairment (RI)

The effect of renal impairment on the PK of tirzepatide was assessed in a dedicated Study GPGG. Participants were assigned to the control group, or a RI group based on estimated glomerular filtration rate (eGFR) values calculated using the modification of diet in renal disease abbreviated equation. No clinically relevant effects on the PK were observed based on AUC, C_{max}, and $t_{1/2}$ of a single SC dose of 5 mg tirzepatide for participants with mild, moderate, or severe RI or end stage renal disease (ESRD) when compared to participants with normal renal function.

In addition, phase 3 trials included subjects with different degrees of renal impairment (mild, moderate, severe, and ESRD) and based on population PK analysis, no effect of renal impairment on tirzepatide PK was observed. Coupled with the dedicated RI trial, no dose adjustment is warranted in patients with renal impairment.

Hepatic Impairment (HI)

The effect of hepatic impairment on the PK of tirzepatide was assessed in a dedicated Study GPGQ. Participants were assigned to the control group, or a HI group Child-Pugh (CP) classification, with mild (CP-A), moderate (CP-B), and severe (CP-C) hepatic impairment. No clinically relevant effects on the PK were observed based on AUC, C_{max}, and t_{max} of a single SC dose of 5 mg tirzepatide for participants with mild, moderate, or severe HI when compared to participants with normal hepatic function.

Effect of Body Mass Index (BMI) and Injection site on PK

No dose adjustments are warranted based on differences in BMI and no specific recommendations are needed based on different injection sites. The effect of BMI and injection site on the PK of tirzepatide was assessed in a dedicated Study GPHI. PK in participants with a high BMI (27.1 to 45.0 kg/m^2; N = 27) were compared to participants with a low BMI (18.5 to 27.0 kg/m^2; N = 27). Participants in each BMI group were randomized to 1 of 3 injection site sequences and received 3 single 5 mg SC injections of tirzepatide into the upper arm (test 1), the thigh (test 2), and the abdomen (reference). No clinically relevant effects on the PK were observed based on AUC and C_{max}.

The overall systemic exposure to tirzepatide $AUC_{0-\infty}$ was similar across all 3 injection sites. The overall systemic exposure to tirzepatide $AUC_{0-\infty}$ across all 3 injection sites was 19% to 25% higher in participants with low BMI compared with participants with high BMI. The overall C_{max}, irrespective of injection site, was comparable between the low and high BMI groups, with a geometric LS means ratio of 1.11 and the 90% CI falling within the 0.80 to 1.25 range. BMI had no apparent effect on the rates of tirzepatide absorption and elimination, with median t_{max} and mean $t_{1/2}$ observed at similar times across all administration sites for both BMI groups.

Effect of other covariates from population PK analysis

According to the population PK analysis, the body weight covariate affected tirzepatide exposure. Relative to a 90 kg subject, tirzepatide exposure (C_{max} and AUC) are expected to be 23% higher and 21% lower in a 70 kg and 120 kg subject, respectively. However, because these differences in exposures are not expected to be clinically impactful, no dose adjustment is required based on body weight. The effect of age, sex, ethnicity, renal and hepatic impairment, as well as ADA were not found to have a statistically significant effect on the PK of tirzepatide.

Japanese patients from the Phase 3 studies have about 17% higher tirzepatide exposure and $C_{max,ss}$ compared to non-Japanese patients due to lower body weight, (median weight is 90 kg in non-Japanese compared to a 76 kg in the Japanese). The review team assessed the effect of tirzepatide on the increase in Heart Rate (HR). Under similar exposure, Japanese patients had higher mean increase in HR compared to non-Japanese (Refer to Appendix section 4.4). Therefore, Japanese patients may need to be closely monitored for HR increase and potential cardiovascular events given the higher sensitivity to HR increase compared to non-Japanese. However, given the proposed gradual titration of tirzepatide treatment that will allow to control for potential adverse events, no dose adjustment is likely required in the Japanese population. Refer to Clinical review team in DARRTS for final recommendation.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

In Vitro Assessment of DDI potential

The potential of tirzepatide to directly inhibit or induce cytochromes P450 (CYPs) (CYP3A, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, and CYP1A2) was evaluated. In vitro data indicate

low clinical risk as a result of potential DDI(s) involving inhibition or induction of CYP enzymes by tirzepatide. The potential for tirzepatide to inhibit renal and hepatic transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT2, MATE1, and MATE2-K) was assessed. The in vitro data indicate low clinical risk as a result of potential DDI(s) involving human membrane hepatic or renal transporters with tirzepatide.

Gastric Emptying Delay

Tirzepatide delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. This effect is consistent with the known effect of GLP-1 RAs including other approved once-weekly GLP-1 RA drugs.

In Study GPGA, tirzepatide delayed gastric emptying (GE) at doses ≥1.5 mg QW. A delay was observed in acetaminophen t_{max} of approximately 1 hour and a maximum decrease in C_{max} of approximately 50% after the first 5 mg dose with no clinically relevant impact on AUC. This delay in gastric emptying (GE) was greatest following the first tirzepatide dose and appeared to show tachyphylaxis, and hence the delay in GE was less evident following repeated tirzepatide doses within the 4-week duration.

To further evaluate the potential impact of delayed GE, a semi-mechanistic PK model was used to estimate the magnitude of delayed GE on PK of atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin. The Applicant's PBPK analysis provided a mechanistic interpretation of the effect of tirzepatide-induced GE delay. This modeling approach has been applied to one other GLP-1RA (dulaglutide). The PBPK reviewer considered the analysis adequate to provide a qualitative assessment in terms of PK changes for the test drugs taking into consideration the clinical experience with other GLP-1RAs, and current understanding of the GE delay mechanism and possible impact on drug PK parameters (See Appendix 4.5). Therefore, the totality of evidence suggested that no clinically meaningful effect would be expected, and no dose modification would be needed for the tested drug(s) when concomitantly administered with tirzepatide.

Effect on PK of Oral Contraceptive (OC)

The Applicant assessed the effect of single dose 5 mg tirzepatide on PK of OC in healthy female subjects in Study GPGR. The Applicant concludes that the AUC of norelgestromin and ethinyl estradiol was reduced by 16% to 23% when the OC was administered in the presence of single 5 mg tirzepatide compared to dosing with OC alone (Table 2). The $AUC_{0\text{-}tau}$ of norelgestromin component was reduced by about 28.8% (lower 90CI% for geometric mean ratio of $AUC_{0\text{-}tau}$ is 0.71). Ethinyl estradiol also showed a similar decrease in $AUC_{0\text{-}tau}$ of about 27% (lower 90CI% for geometric mean ratio of $AUC_{0\text{-}tau}$ is 0.73). The C_{max} of norelgestromin and ethinyl estradiol was reduced by 55% to 59% when the OC was administered in the presence of 5 mg tirzepatide compared to dosing with OC alone. Delays in t_{max} of 2.5 to 4.5 hours were observed when the OC was administered in the presence of 5 mg tirzepatide.

The Applicant concludes the reduction in C_{max} is of limited clinical relevance while AUC drives contraception efficacy. Therefore, with the intended clinical dosing scheme of tirzepatide 2.5

mg starting dose followed by gradual stepwise dose escalation, the impact of tirzepatide on the exposure of norelgestromin and ethinyl estradiol is expected to be reduced, as the tirzepatide starting dose is 2.5 mg and repeated dosing is associated with a diminishing gastric emptying effect.

However, the Clinical Pharmacology team determined that the reduction in $AUC_{0\text{-}tau}$ and C_{max} of the progestin component (norelgestromin) could pose a clinically significant risk of loss of efficacy of orally administered hormonal contraceptives. The estrogen component (ethinyl estradiol) exhibited similar reductions. Although the starting dose is 2.5 mg once weekly, the proposed clinical doses can be up-titrated to 7.5, 10, 12.5, and 15 mg, the risk of which is unknown. The clinical pharmacology team considered dose separation of oral contraceptives used in the case of exenatide and found dose separation not an adequate solution for tirzepatide due to the once weekly dosing interval. Therefore, patients using oral hormonal contraceptives should use an alternative non-oral contraceptive method or add a barrier method of contraception during treatment with tirzepatide. Since delayed gastric emptying is the expected mechanism of interaction of oral contraceptives and tirzepatide, delayed gastric emptying is not expected to impact hormonal contraceptives that are not administered orally. The effect on gastric emptying is presented in the labeling under section 7 (b) (4) and 12.3.

Table 2 Geometric Mean Ratios of PK Parameter of Oral Contraceptive with and without tirzepatide in Study GPGR

		Ethinyl Estradiol			Norelgestromin		
Parameter	**Treatment**	**Geometric Mean (N)**	**Ratio of Geometric Means (OC+TZP: OC)**	**90% CI for Ratio (Lower, Upper)**	**Geometric Mean (N)**	**Ratio of Geometric Means (OC+TZP: OC)**	**90% CI for Ratio (Lower, Upper)**
$AUC_{0\text{-}tau}$ (pg.h/mL)	OC + TZP	811 (21)	0.788	(0.730, 0.850)	16008 (25)	0.775	(0.712, 0.843)
	OC	1029 (21)			20659 (25)		
$AUC_{0\text{-}t_{last}}$ (pg.h/mL)	OC + TZP	912 (23)	0.800	(0.722, 0.888)	25994 (25)	0.838	(0.771, 0.912)
	OC	1139 (23)			31005 (25)		
C_{max} (pg/mL	OC + TZP	49.6 (24)	0.410	(0.355, 0.473)	983 (25)	0.451	(0.402, 0.505)
	OC	121 (24)			2181 (25)		
		Ethinyl Estradiol			**Norelgestromin**		
Parameter	**Treatment**	**Median (N)**	**Median of differences (OC + TZP – OC)**	**Approximat 90% CI for differences (Lower, Upper)**	**Median (N)**	**Median of differences (OC + TZP – OC)**	**Approximate 90% CI for differences (Lower, Upper)**
t_{max} (hour)	OC + TZP	5.99 (24)	4.23	(1.50, 6.50)	6 (25)	4.50	(1.50, 5)
	OC	1 (24)			1.50 (25)		

Abbreviations. OC = oral contraceptive (21 days of active tablets [0.035 mg ethinyl estradiol and 0.25 mg norgestimate] and 7 days of nonactive tablets); TZP = tirzepatide 5 mg administered subcutaneously.
(Source: page 59 Table 2.7.2.13 of Summary of Clinical Pharmacology)

3.3.5. Is the Clinical Phase 3 trial formulation of tirzepatide bioequivalent to the to-be-marketed formulation?

Yes. The Applicant conducted Study GPGS, a relative bioavailability (BA) study that demonstrated the comparability of 5 mg tirzepatide injections of the solution formulation administered subcutaneously via the prefilled syringe (PFS) and the single-dose pen (SDP). Study GPGM was the only phase 3 study to use the PFS. The to-be-marketed formulation (SDP) was used in all other phase 3 studies. The relative BA of tirzepatide from the SDP presentation used in the phase 3 studies was comparable with the PFS presentation used in the phase 3 study GPGM. The geometric means ratios (90% CIs) of $AUC_{0-\infty}$ and C_{max} are 0.979 (0.962, 0.997) and 0.955 (0.905, 1.01) respectively.

4. APPENDICES

4.1. Clinical PK and/or PD Assessments

Study GPGA: A Single- and Multiple-Ascending Dose Study in Healthy Subjects to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TIRZEPATIDE and Multiple Doses in Patients with Type 2 Diabetes Mellitus

The Applicant conducted Study GPGA, a phase 1, patient-/subject- and investigator-blind, randomized, placebo controlled study to assess the safety, tolerability, PK, and PD of tirzepatide after (1) single-ascending dose (SAD) (Part A) in healthy participants, (2) 4-week multiple-ascending dose (MAD) (Part B) in healthy participants, and (3) 4-week multiple dose evaluation in patients with T2DM (Part C).

One-hundred and nine participants were dosed in randomized order with tirzepatide (42 in Part A, 25 in Part B, and 42 in Part C). The 6 SAD levels in Part A were 0.25, 0.5, 1, 2.5, 5, and 8 mg. The 4 MAD levels in Part B were 0.5 mg QW, 1.5 mg QW, 4.5 mg QW, and 5/5/8/10 mg QW titration over 4 weeks. The 4 multiple dose levels in Part C were 0.5 mg QW, 5 mg QW, 5/5/10/10 mg, and 5/5/10/15 mg QW titration over 4 weeks. In Parts B and C, gastric emptying was assessed by measuring acetaminophen PK following administration of 1g at the time of expected C_{max} of tirzepatide. Blood was collected to assess tirzepatide PK before and up to 672 hours (Part A) and 840 hours (Part B and C) after the dose. Tirzepatide PK parameters were calculated using noncompartmental analysis and included C_{max}, $AUC_{0-\infty}$, t_{max}, and $t_{1/2}$.

Following single SC administration of 0.25, 0.5, 1, 2.5, 5, and 8 mg in healthy adults (Part A) the median time to maximum plasma concentration (t_{max}) ranges from 8 to 96 hours (Table 3). Mean (CV%) maximum plasma concentration (C_{max}) ranges from 26 (29) to 874 (19) ng/mL. Mean (CV%) area under the concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$) ranges from 5760 (22) to 169000 (8) h*ng/mL (Table 3 and Figure 3).

Following multiple SC administration of 0.5 mg (QW), 1.5 mg (QW), 4.5 mg (QW), and 5.0/5.0/8.0/10.0 mg to healthy adults (Part B), t_{max} ranges from 8 to 72 hours. Mean (CV%) C_{max} ranges from 77.8 (35) to 1510 (10) ng/mL. Mean (CV%) area under the concentration versus time

curve during 1 dosing interval ($AUC_{0\text{-}tau}$) ranged from 10600 (34) to 198000 (6) h*ng/mL (Table 4 and Figure 4).

Following multiple SC administration for 4 weeks of 0.5 mg (QW), 5 mg (QW), 5/5/10/10 mg, and 5/5/10/15 mg to patients with T2DM (Part C), t_{max} ranges from 24 to 72 hours. Mean (CV%) C_{max} ranges from 54.6 (28) to 1250 (20) ng/mL. Mean (CV%) $AUC_{0\text{-}tau}$ ranged from 7200 (30) to 164000 (14) h*ng/mL. Mean $t_{1/2}$ in patients with T2DM was approximately 5 days, supporting a QW dosing regimen. Multiple QW doses over a 4-week duration resulted in an accumulation ratio of 1.6 in patients with T2DM, based on $AUC_{0\text{-}tau}$ (Table 5, Figure 5).

The Applicant concludes that GI adverse events (AEs; nausea, vomiting, diarrhea, decreased appetite, abdominal distension) were the most commonly reported by healthy participants and patients with T2DM and the GI AEs were dose related. During titration regimen of 5/5/10/15 mg, patients with T2DM reported the highest incidence of GI AEs, and the highest number of increased severity (moderate) but there were no reports of severe or SAEs. t_{max} was within 24 to 48 hours after dosing. PK parameters were similar when comparing healthy participants versus patients with T2DM (See section 3.2).

Weekly doses of tirzepatide for 4 weeks were associated with reductions in fasting plasma glucose and body weight for patients with T2DM. After 4 weeks of tirzepatide treatment with either 5/5/10/10 mg or 5/5/10/15 mg QW titration in patients with T2DM, there was a significant reduction in the fasting plasma glucose compared to placebo. Fasting plasma glucose decreased from baseline with tirzepatide versus placebo with the ratio of the least squares (LS) means (95% CI) to placebo was up to 0.68 (0.56-0.83). Body weight reductions were observed with LS mean (95% CI) decreases from baseline versus placebo at 4 weeks of up to 2.62 kg (1.45 to 3.79).

In Study GPGA, dose proportionality analysis using power model over the single dose range of 0.25 to 8 mg resulted in a ratio of dose-normalized geometric means (90%CI) in $AUC_{0\text{-}\infty}$ and C_{max} of about 0.8 (0.7, 0.9) and 0.85 (0.68, 1.0), while analyses based on multiple-dose data in healthy participants resulted in a ratio of dose-normalized geometric means (90%CI) in $AUC_{0\text{-}tau}$ and C_{max} of 1.1 (0.83, 1.53) and 1.3 (0.95, 1.8). In addition, dose proportionality over the proposed clinical dose was inferred from the population PK analysis.

Immunogenicity results for healthy subjects from phase 1 Study GPGA show that following multiple administration for 4 weeks, one subject in the of 5/5/8/10 mg QW titration group (Part B) had treatment-emergent (TE) Anti-Drug Antibody (ADA). The subject had negative ADA baseline assessment, and at Days 15 and 22, anti-LY3298176 titers were 1:20 but increased at Days 29, 36, and 57 to 1:40. This subject had 2 study treatment AEs that resolved within 1 to3 days. In the phase 3 studies, the incidence of ADA+ patients increased in a dose dependent manner from 5mg, 10mg and 15mg as well as with the length of the treatment.

Tirzepatide delayed gastric emptying (GE) at doses ≥1.5 mg QW. This was supported by an observed delay in acetaminophen t_{max} of approximately 1 hour and a maximum decrease in C_{max} of approximately 50 % after the first 5 mg dose with no clinically relevant impact on AUC. This delay in gastric emptying (GE) was greatest following the first tirzepatide dose and appeared to show

tachyphylaxis, and hence the delay in GE was less evident following repeated tirzepatide doses within the 4-week duration. The maximum effect of tirzepatide on GE was studied under conservative clinical conditions, i.e., this approach was conservative or a worst-case scenario, because it evaluated maximum possible effect of tirzepatide on GE. These conditions included escalation to tirzepatide doses of 10 and 15 mg within 4 weeks via 5/5/10/15mg scheme, thereby attaining the highest doses within 3 to 4 weeks, which is significantly faster than the time required to attain these doses in the phase 3 and the proposed clinical dosing scheme of stepwise escalation starting from a 2.5- mg dose for 4 weeks, with 2.5-mg dose increments every 4 weeks to attain 10- or 15-mg dose levels. However, the effect of the proposed clinical dosage regimen of 7.5, 10, 12.5, and 15 mg QW on gastric emptying is unknown.

The reviewer's conclusion agrees with that of the Applicant. In patients with T2DM, tirzepatide QW dosing is consistent with GLP-1 pharmacology. Safety, tolerability, and PK/PD profile of tirzepatide in this study supported further development of tirzepatide in patients with T2DM suggesting a slower dose up titration may be warranted.

Table 3 Tirzepatide PK Parameters on Day 1 in Study GPGA Part A Single Ascending Dose

	Geometric Mean (Geometric CV%)					
Dose mg (N)	**0.25**	**0.5**	**1.0**	**2.5**	**5.0**	**8.0**
N	6	12	5	6	5	7
$AUC_{0-\infty}$ (h*ng/mL)	5760 (22)	12000 (24)	22600 (14)	53200 (36)	90500 (15)	169000 (8)
C_{max} (ng/mL)	26.0 (29)	57.7 (37)	108 (14)	231 (40)	397 (23)	874 (19)
t_{max} [a] (h)	48 (48, 48)	48 (24, 96)	24 (8, 48)	24 (24, 96)	24.05 (24, 72)	48 (24, 72.02)
$t_{1/2}$ [b] (h)	116 (94.6, 132)	124 (94.4, 163)	106 (92.9, 117)	120 (102, 137)	123 (99.9, 147)	111 (99.6, 121)

[a] Median (minimum, maximum). [b] Geometric mean (minimum, maximum).

(Source: page 31, Table GPGA.7.1, Study GPGA Report)

Table 4 Tirzepatide PK Parameters on Day 22 in Study GPGA Part B Multiple Ascending Dose

	Geometric Mean (Geometric CV%)			
Dose	**0.5 mg (QW)**	**1.5 mg (QW)**	**4.5 mg (QW)**	**5.0/5.0/8.0/10.0 mg**
N	4	5	6	4
AUC_{0-tau} [a] (h*ng/mL)	10600 (34)	24800 (15)	103000 (23)	198000 (6)
C_{max} (ng/mL)	77.8 (35)	198 (13)	884 (27)	1510 (10)
t_{max} [b] (h)	23.83 (23.83, 72.08)	23.83 (23.65, 24.37)	24.17 (24.17, 24.17)	24.17 (8, 72)
$t_{1/2}$ [c] (h)	152 (149, 154)[d]	113 (91.9, 124)	132 (108, 157)	126 (114, 134)
CL/F (L/h)	0.0472 (34)	0.0604 (15)	0.0436 (23)	0.0505 (6)
Vz/F (L)	8.99 (22)d	9.83 (11)	8.32 (19)	9.18 (7)
RA	1.84 (8)	1.52 (11)	1.94 (11)	-

Abbreviations: CL/F = apparent total body clearance of drug calculated after extra-vascular administration; CV = coefficient of variation; N = number of subjects; QW = once weekly; RA = accumulation ratio based on AUC(0-tau); Vz/F = apparent volume of distribution during the terminal phase after extra-vascular administration. [a] tau = 168 h. [b] Median (minimum, maximum). [c] Geometric mean (minimum, maximum). [d] Parameters ($t_{1/2}$ and Vz/F) at the 0.5-mg QW dose level are based on n=3.

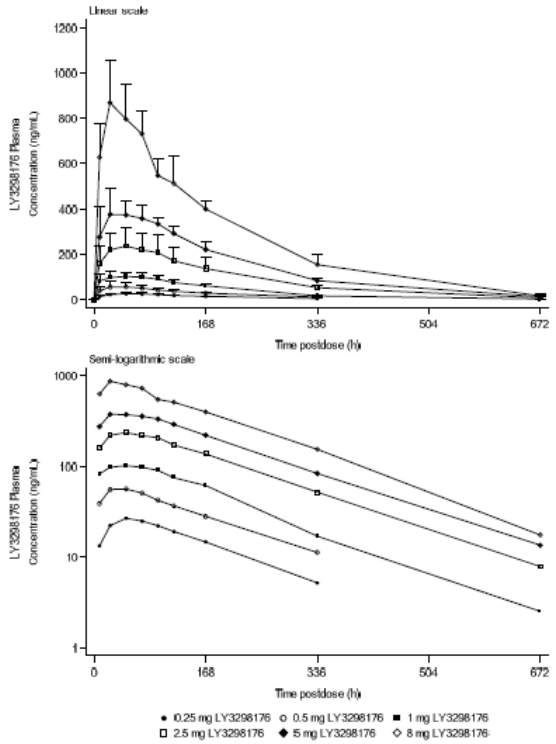
(Source: page 37, Table GPGA.7.5, Study GPGA Report)

Table 5 Tirzepatide PK Parameters of on Day 22 in Study GPGA Part C Multiple Dose

	Geometric Mean (Geometric CV%)			
Dose	0.5 mg (QW)	5.0 mg (QW)	5.0/5.0/10.0/10.0 mg	5.0/5.0/10.0/15.0 mg
N	9	6	12	10
$AUC_{0\text{-}tau}$[a] (h*ng/mL)	7200 (30)	81900 (18)	131000 (26)	164000 (14)
C_{max} (ng/mL)	54.6 (28)	614 (16)	1030 (32)	1250 (20)
t_{max} [b] (h)	24.25 (24.25, 72.62)	24.25 (24.17, 24.25)	24.25 (24.17, 72)	24.25 (24.25, 72)
$t_{1/2}$[c](h)	120 (107, 148)[d]	114 (103, 132)	115 (95.7, 142)	104 (92.7, 120)
CL/F (L/h)	0.0694 (30)	0.0611 (18)	0.0762 (26)	0.0913 (14)
Vz/F (L)	10.4 (31)d	10.0 (23)	12.6 (28)	13.8 (19)
RA	1.51 (24)	1.67 (11)	-	-

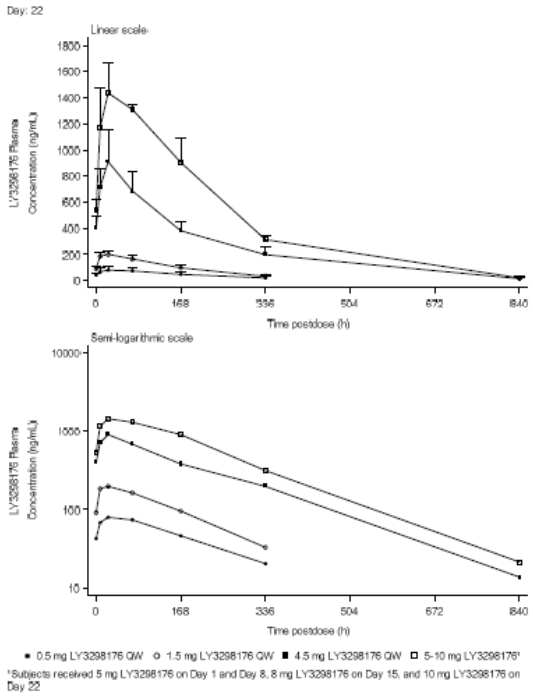
[a] tau = 168 h. [b] Median (minimum, maximum). [c] Median (minimum, maximum). Parameters ($t_{1/2}$ and Vz/F) at the 0.5-mg QW dose level are based on n=5.
(Source: Table GPGA.7.9 Study GPGA Report)

Figure 3 Mean tirzepatide plasma concentration-time profiles following SC administration on a linear and semi-log scale – Part A Study GPGA



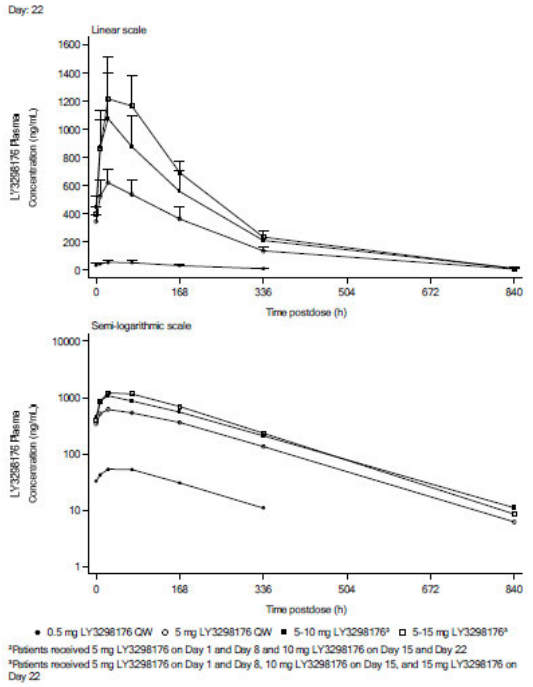
(Source: page 32, Figure GPGA.7.1. of Study GPGA Report)

Figure 4 Mean tirzepatide plasma concentration-time profiles following SC administration on a linear and semi-log scale for Day 22 – Part B Study GPGA



(Source: page 39, Figure GPGA.7.4. of Study GPGA Report)

Figure 5 Mean tirzepatide plasma concentration-time profiles following last SC administration on Day 22 in patients with T2DM on a linear and semi-log scale - Part C Study GPGA



(Source: page 45, Figure GPGA.7.6. of Study GPGA Report)

Study GPHI: Effect of Injection Site on the Relative Bioavailability of a Single Dose of Tirzepatide in Subjects with Low and High Body Mass Indices

GPHI was a phase 1, open-label study conducted in 54 healthy participants to determine the bioavailability of tirzepatide injections into the thigh and upper arm relative to the abdomen. The bioavailability of tirzepatide in participants with a high body mass index (BMI) (27.1 to 45.0 kg/m2; N = 27) relative to participants with a low BMI (18.5 to 27.0 kg/m2; N = 27) was also assessed. Fifty four participants, 37 males and 17 females, aged 24 to 70 years inclusive, participated in the study with 27 in the low BMI group with (average BMI=24.57 kg/m2), and the remaining 27 were in the high BMI group (average BMI=32.93 kg/m2).

Participants in each BMI group were randomized to 1 of 3 injection site sequences and received 3 single 5-mg SC injections of tirzepatide via an SDP into the upper arm (test 1), the thigh (test 2), and the abdomen (reference). At least 35 days separated each injection to allow sufficient time for complete drug washout. Blood was collected to assess tirzepatide PK before and up to 840 hours after the dose.

The Applicant concludes that the site of administration and BMI had no statistically significant effect on the exposure of 5 mg tirzepatide. Following a single SC injection of 5 mg tirzepatide, $AUC_{0-\infty}$ and C_{max} was not different between injection to the thigh and upper arm as compared with the abdomen with 90% CIs for the ratios of the LS geometric means contained within 0.8 and 1.25. Median t_{max} occurred at 24 hours postdose at each injection site . Data from this study indicate that tirzepatide can be administered SC in the abdomen, upper arm, and thigh without adjusting the dose. C_{max} of tirzepatide at the upper arm and thigh injection sites were comparable between the low and high BMI groups, while C_{max} at the abdomen injection site was approximately 23% higher in the low BMI group compared with the high BMI group. See section 3.3.3 for full PK results.

The reviewer's conclusion agrees with that with the Applicant. Tirzepatide may be administered at any of the 3 injection sites tested. Together with population PK/PD analyses of clinical data, tirzepatide administered to patients with the tested range of body weights may not necessitate dose adjustment.

Study GPGC: A Multiple-Ascending Dose Study in Japanese Patients with T2DM to Investigate the Safety, Tolerability, PK, and PD of TIRZEPATIDE

GPGC was a phase 1, multicenter, patient-/investigator-blind, placebo-controlled, randomized, parallel-dose group, 8-week MAD study conducted in Japanese patients with T2DM to investigate the safety, tolerability, PK, and PD of tirzepatide. Forty eight, 47 males and 1 female, aged between 31 and 70 years participated in this study. The dose groups and dose-escalation regimens were 5 mg (5 mg tirzepatide Weeks 1 to 8), 10 mg (2.5 mg tirzepatide Weeks 1 to 2; 5 mg Weeks 3 to 4; 10 mg Weeks 5 to 8), and 15 mg (5 mg tirzepatide Weeks 1 to 2; 10 mg Weeks 3 to 6; 15 mg Weeks 7 to 8).

The Applicant concludes that the most frequently reported treatment-emergent adverse events (TEAEs) were decreased appetite and GI AEs, which were dose dependent and mild severity.

At Day 50, following multiple SC administration of 5 mg, 2.5/5/10 mg (2.5 mg tirzepatide Weeks 1 to 2; 5 mg Weeks 3 to 4; 10 mg Weeks 5 to 8), and 5/10/15 mg (5 mg tirzepatide Weeks 1 to 2; 10 mg Weeks 3 to 6; 15 mg Weeks 7 to 8) to Japanese patients with T2DM, t_{max} ranges from 24 to 48 hours (Table 6 and Figure 6). Mean (CV%) C_{max} ranges from 838 (22) to 2270 (17) ng/mL. Mean (CV%) $AUC_{0\text{-}tau}$ ranged from 104000 (19) to 285000 (15) h*ng/mL (Table 6). Accumulation ratio ranged from 1.94-2.14. Fasting plasma glucose decreased from baseline with tirzepatide. LS mean (95% CI) decreases compared with placebo were up to 69.08 mg/dL (52.30 to 85.85). LS mean (95% CI) body weight reductions from baseline versus placebo at 8 weeks were up to 6.59 kg (5.26 to 7.92).

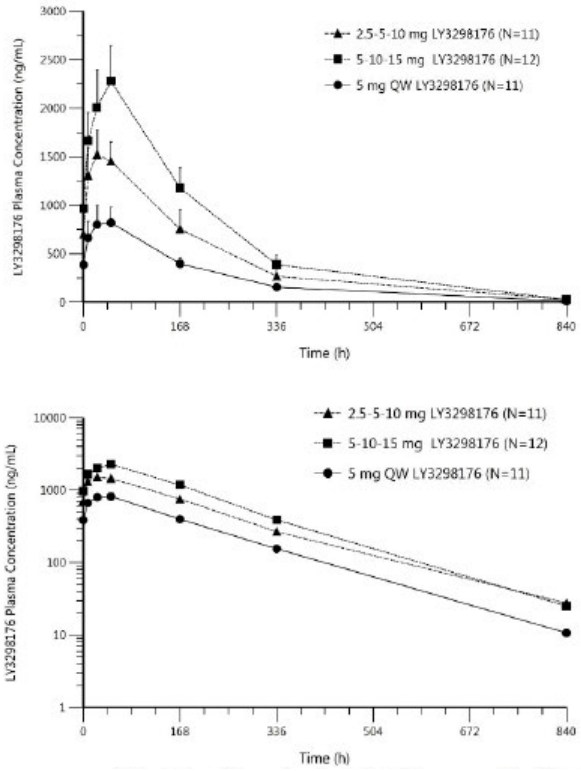
The reviewer's conclusion agrees with that of the Applicant. The PK/PD profiles based on this Study GPGC were similar to those expected based on phase 1 Study GPGA when accounting for differences in day of assessment of PK and respective accumulation ratios.

Table 6 Tirzepatide PK Parameters on Day 50 in Study GPGC

	Geometric Mean (Geometric CV%)		
Dose	**2.5/5/10 mg**	**5/10/15 mg**	**5 mg (QW)**
N	11[a]	12[b]	11
$AUC_{0\text{-}tau}$[c] (ng*h/mL)	192000 (16)	285000 (15)	104000 (19)
C_{max} (ng/mL)	1520 (15)	2270 (17)	838 (22)
t_{max}[d] (h)	24.00 (24.00, 48.00)	48.00 (24.00, 48.05)	48.00 (23.83, 48.00)
$t_{1/2}$[e] (h)	135 (105, 186)	121 (94.4, 138)	127 (112, 144)
CL/F (L/h)	0.0311 (25)	0.0321 (17)	0.0288 (21)
Vz/F (L)	6.04 (14)	5.61 (13)	5.27 (15)
RA	-	-	2.12 (14)
Peak to trough	2.07 (19)	1.94 (21)[f]	2.14 (12)

2.5/5/10 refers to titrated doses over 8 weeks where 2.5 mg was given QW for 2 weeks followed by 5 mg for 2 weeks and 10 mg for 4 weeks. 5/10/15 refers to titrated doses over 8 weeks where 5.0 mg was given QW for 2 weeks followed by 10 mg for 4 weeks and 15 mg for 2 weeks. [a] One patient in the 2.5/5/10 mg QW titration group discontinued after receiving 1 dose of LY3298176 (2.5 mg) due to patient decision (concern about study procedures/perceived risks). [b] One patient in the 5/10/15 mg QW titration group discontinued after receiving 4 doses of LY3298176 (5, 5, 10, 10 mg) due to an AE (decreased appetite). One patient skipped dosing on Day 43 due to an AE (not related to study treatment) and was not up titrated to 15 mg. Two patients were not up-titrated to 15 mg by the investigator's decision considering the patients overall condition, including AEs. [c] τ = 168 h. [d] Median (minimum, maximum).[e] Geometric mean (minimum, maximum).[f] N = 10.
(Source: page 24 Table GPGC.7.2 of Study GPGC report)

Figure 6 Mean tirzepatide plasma concentration time profiles following SC administration on Day 50 on a linear and semi-log scale in Study GPGC



(Source: page 27 Figure GPGC 7.2 of Study GPGC study report)

Study GPGS: A Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by an Autoinjector versus Prefilled Syringe in Healthy Subjects

GPGS was a phase 1, open-label, randomized, 2-period, 2-sequence, crossover study in 45 healthy participants to establish comparability between the SDP (also called Auto-Injector (AI)) and a prefilled syringe (PFS). Participants were randomly assigned to 1 of 2 sequences and received 2 single 5 mg/0.5 mL SC tirzepatide injections, one with the SDP and one with the prefilled syringe, with at least 35 days between tirzepatide doses. Blood samples were collected to assess tirzepatide PK before and up to 840 hours after dosing .

The Applicant concludes that the PK of tirzepatide was similar following administration of 5 mg tirzepatide via an SDP or PFS with the 90% CIs for the ratios of geometric LS means of $AUC_{0-\infty}$ and C_{max} contained within 0.8 to 1.25. Both devices were used in phase 3 studies whereas the SDP is planned for commercial use. The reviewer's conclusion agrees with that of the Applicant.

Study GPGE : Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of Tirzepatide in Healthy Subjects

GPGE was a phase 1, single-center, 4-part study, conducted in 52 healthy participants to establish the bioavailability of tirzepatide as a solution formulation. The 4 parts, Parts A through D, of Study GPGE are summarized in Table 7.

Table 7 Description of Study GPGE Parts A through D

	Design	Objective	Dosing	N	PK Sampling
Part A	Randomized, 2-period, 2-treatment, crossover study	To evaluate the PK of a single SC dose of tirzepatide, administered as solution formulation versus lyophilized formulation in healthy participants.	5-mg SC dose as a solution formulation versus a lyophilized formulation. The washout period between the 2 doses was at least 35 days.	20	For each period: predose and up to 37 days postdose
Part B	Fixed, single-arm study	To evaluate the PK of a single IV dose of tirzepatide, solution formulation, in healthy participants.	Single 0.5-mg IV ~10 minute infusion	8	Predose and up to at least 70 days postdose
Part C	Randomized, placebo-controlled, 4-week titration study	To primarily evaluate the safety and tolerability of tirzepatide following multiple SC weekly doses of a solution formulation in healthy participants. Secondary objective was to evaluate the PK of tirzepatide, administered as a solution formulation.	Solution formulation SC at a dose of • 5 mg on Days 1 (Week 1) and 8 (Week 2) • 7.5 mg on Day 15 (Week 3), and • 10 mg on Day 22 (Week 4).	16	For each of the 4 doses: predose and samples up to 72 hours postdose. An additional sample at 57 days after the first dose
Part D	Fixed, single-arm study	To evaluate the PK of a single bolus IV dose of tirzepatide, lyophilized formulation, in healthy participants.	Single 0.5-mg IV dose, bolus.	8	Predose and up to at least 70 days postdose

Abbreviations: IV = intravenous; N = number of participants enrolled; PK = pharmacokinetics; SC = subcutaneous.

(Source: page 13 Table 2.7.1.4. of Summary of Biopharmaceutics)

The Applicant concludes from Part A that the PK of tirzepatide was similar following administration of 5 mg tirzepatide as a lyophilized or solution formulation with the 90% confidence intervals (CIs) contained within 0.8 to 1.25 for the ratio of geometric least square (LS) means of $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} (Table 8).

In Part C, PK of tirzepatide following administration of 5/5/7.5/10 mg (5-mg dose at Weeks 1 and 2, 7.5 mg at Week 3, and 10 mg at Week 4) regimen, 5-, 7.5-, and 10-mg doses was evaluated. PK results are summarized in Table 9. One subject in Part C had nausea after receiving tirzepatide 7.5 mg SC on Day 15, elected not to receive study treatment, and discontinued the study. All TEAEs were mild in severity. Injection site reactions (ISR) were the most frequently reported TEAEs followed by gastrointestinal-related TEAEs including nausea, abdominal pain, diarrhea, and decreased appetite.

The Applicant concludes that in Part B, IV infusion data were intended to calculate the absolute bioavailability of tirzepatide. The PK evaluation following IV administration in Part B led to inconclusive results. As Part B led to inconclusive results, Part D was added to evaluate PK following administration of an IV bolus dose and to estimate the absolute bioavailability of tirzepatide using a lyophilized formulation. Absolute bioavailability of 5 mg SC lyophilized formulation of tirzepatide used in Part A of the study was computed to be approximately 80%, using IV bolus data from Part D (Table 10). The terminal half-life following IV bolus dose was approximately 100 hours, which compares well to the approximately 5 day half-life that is observed following SC administration. The reviewer's conclusion agrees with that of the Applicant.

Table 8 PK Parameters of tirzepatide following single 5 mg SC Administration as lyophilized or solution formulation in Study GPGE Part A

Parameter	SC 5 mg tirzepatide	n	Geometric least squares mean	Ratio of geometric least squares mean (Solution : Lyophilized) (90% CI)
$AUC_{0-\infty}$ (ng* h/mL)	Lyophilized	19	112737	0.966 (0.943, 0.99)
	Solution	20	108919	
$AUC_{0-tlast}$ (ng* h/mL)	Lyophilized	19	111539	0.964 (0.94, 0.988)
	Solution	20	107473	
C_{max} (ng/mL)	Lyophilized	20	524	1.1 (1.03, 1.17)
	Solution	20	575	
t_{max} (h)*	Lyophilized	20	24	
	Solution	20	23.99	

*median
(Source: page 15 Table 2.7.1.5 and 2.7.1.6 of Summary of Biopharmaceutics)

Table 9 PK Parameters of tirzepatide following SC Administration 5/5/7.5/10 mg in Study GPGE Part C

Parameter Geometric mean (CV%)	5 mg TIRZEPATIDE SC[a] (Day 1) (N=12)	7.5 mg TIRZEPATIDE SC[a] (Day 15) (N=12)	10 mg TIRZEPATIDE SC[a] (Day 22) (N=11)
C_{max} (ng/mL)	663 (23)	1270 (24)	1900 (24)
t_{max} (h)[b]	24 (8-71.83)	24 (8-48)	24.18 (8-48)
AUC_{0-tau} (ng h/mL)	68900 (19%)	149000 (26%)	Not reported [c]

[a] Participants received tirzepatide as a 5-mg dose on Days 1 and 8, a 7.5-mg dose on Day 15, and a 10-mg dose on Day 22. [b] Median (range). [c] Not reported for 10-mg dose as serial samples were collected up to 72 h postdose, and no sample was collected at 168 hours postdose after 10-mg dose
(Source: page 16 Table 2.7.1.8 of Summary of Biopharmaceutics)

Table 10 PK Parameters of Tirzepatide and absolute bioavailability Following Intravenous Administration in Study GPGE Part D

Parameter	0.5 mg tirzepatide bolus IV (N=8)	
	Geometric Mean (CV%)	Bioavailability (F)
$AUC_{0-\infty}$ (ng h/mL)	14000 (16%)	0.809
C_{max} (ng/mL)	206 (19%)	
t_{max} (h)*	0.17 (0.10-2)	

*median (min, max), F = absolute bioavailability based upon geometric mean (Part A SC [lyophilized] vs Part D IV);
(Source: page 16 Table 2.7.1.7 of Summary of Biopharmaceutics)

Study GPGG: Pharmacokinetics of TIRZEPATIDE Following Administration to Subjects with Impaired Renal Function

GPGG was a multicenter, parallel, single-dose, open-label study in participants with normal renal function and in participants with mild, moderate, or severe renal impairment (RI) or end stage renal disease (ESRD) on dialysis. Participants were assigned to the control group, or a RI group based on estimated glomerular filtration rate (eGFR) values calculated using the modification of diet in renal disease abbreviated equation.

Categories of healthy control participants and RI groups are detailed as follows:

- Healthy: ≥90 mL/min/1.73 m^2
- Mild RI: 60 to 89 mL/min/1.73 m^2
- Moderate RI: 30 to 59 mL/min/1.73 m^2
- Severe RI: <30 mL/min/1.73m2 but not on dialysis
- ESRD: requires dialysis

A total of 45 participants, 30 males and 15 females, aged 40 to 84 years, inclusive, 8 with mild, 8 with moderate, 7 with severe RI, 8 with ESRD on dialysis and 14 age-, gender-, and weight matched healthy individuals with normal renal function, participated in this study. Of the 45 participants, 6 had T2DM (n=2 each in the mild and severe RI groups, and n=1 each in the moderate and ESRD groups). All participants received a single SC dose of tirzepatide 5 mg. The primary PK parameters were $AUC_{0-\infty}$ and C_{max}.

The Applicant concludes that the overall exposure to tirzepatide, based on AUC and C_{max}, and the elimination kinetics as assessed using geometric mean $t_{1/2}$ was similar across the control and RI groups . No clinically relevant effects on the PK of a single SC dose of 5 mg tirzepatide were observed for participants with mild, moderate, or severe RI or ESRD when compared to participants with normal renal function .

The reviewer's conclusion agrees with that of the Applicant. There were no clinically relevant effects of RI on PK of tirzepatide. Adjustment to the dose of tirzepatide may not be required in patients with RI or in patients undergoing dialysis.

Study GPGQ: A Single Dose Pharmacokinetic Study of Tirzepatide in Subjects with Varying Degrees of Hepatic Impairment

Study GPGQ was a multicenter, parallel, single-dose, open-label, single-period study of tirzepatide in participants with normal hepatic function and participants with hepatic impairment based on Child-Pugh (CP) classification, with mild (CP-A), moderate (CP-B), and severe (CP-C) hepatic impairment. The PK of tirzepatide in participants with hepatic impairment was compared to healthy control participants (matched for age, gender, and body weight) to investigate the impact of varying degrees of hepatic impairment.

A total of 32 participants, 24 males and 8 females, aged 27 to 72 years, inclusive, 13 with normal hepatic function, 6 with mild, 6 with moderate, and 7 with severe hepatic impairment participated in this study. Of the 32 participants, 3 had T2DM (mild hepatic impairment group). A total of 31 participants completed the study as 1 participant from the severe hepatic impairment group was lost to follow-up. All participants received a single SC dose of tirzepatide 5 mg. The primary PK parameters of $AUC_{0-\infty}$ and C_{max} were evaluated.

The Applicant concludes that the overall exposure to tirzepatide, based on $AUC_{0-\infty}$ and C_{max} and t_{max} , was similar across the control and hepatic impairment groups. Geometric mean ratio (90%CI) showed no clinically meaningful difference in C_{max} or $AUC_{0-\infty}$ between participants in the

control group and the hepatic impairment groups. There was no significant relationship between the exposure of tirzepatide and CP score.

The reviewer's conclusion agrees with that of the Applicant. There were no clinically relevant effects of hepatic impairment on PK of tirzepatide. Adjustment to the dose of tirzepatide, based on PK, may not be required in patients with hepatic impairment.

Study GPGT: The Effect of Tirzepatide on Insulin and Glucagon Secretion in Patients with Type 2 Diabetes Mellitus in clamp procedure

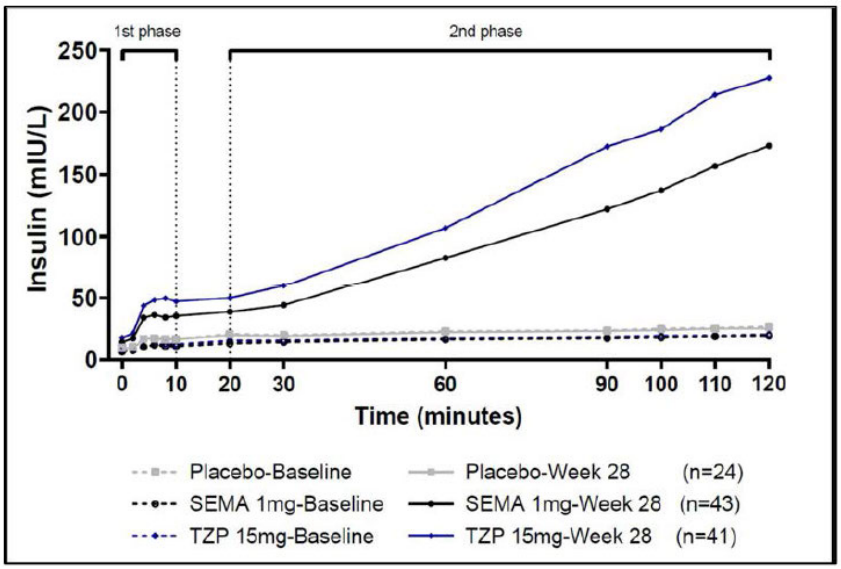
GPGT was a phase 1, multicenter, randomized, sponsor, investigator- and patient-blind, parallel-arm study to compare the effect of tirzepatide, semaglutide, and placebo on insulin, glucose, and glucagon secretion in 117 patients with T2DM treated with diet and exercise and stable dose of metformin. The 15 mg tirzepatide dose was attained via the same stepwise escalation used in phase 3 studies.

The Applicant concludes that the estimated difference (95% CI) in change from baseline in the total insulin secretion rate from hyperglycemic clamp ($ISR_{0\text{-}120min}$) for comparisons between tirzepatide and placebo was 381.23 pmol/min/m^2 (339.29, 423.17). Results for assessment of first- and second-phase ISRs were consistent with the results for the total $ISR_{0\text{-}120min}$. At week 28 tirzepatide enhanced the first- ($ISR_{0\text{-}8min}$) and second-phase ($ISR_{20\text{-}120min}$) insulin secretion rate by approximately 225.7 pmol/min/m^2 (165.8, 285.7) and 411.69 pmol/min/m^2 (366.99, 456.39) from baseline vs placebo, respectively. Insulin concentration over time is presented in Figure 7.

At week 28 tirzepatide lowered Fasting Glucose by -2.61 mmol/L (95%CI -3.03, -2.19) from baseline vs placebo. In addition, tirzepatide lowered the total post-meal blood glucose $AUC_{0\text{-}240\ min}$ by -992.1 mmol*min/L (95%CI -1123.5, -860.8) from baseline at week 28 (Figure 8). Tirzepatide reduced fasting glucagon concentration at week 28 by -4.5 pmol/L (-6.3, -2.6), and total post-meal glucagon $AUC_{0\text{-}240min}$ by -1787.5 pmol*min/L (-2249.0, -1325.9) from baseline vs placebo (Figure 9). At week 28 tirzepatide lowered food intake by -309.8 kcal (95%CI -423.0, -196.6) from baseline vs placebo. At week 28 tirzepatide improved M-value by 19.8 µmol/min/kg (95%CI, 13.4, 26.1) from baseline vs placebo. The Applicant states that the M-value from hyperinsulinemic euglycemic clamp is the measure of insulin sensitivity; M-value is defined as the glucose infusion rate (GIR) over the last 30 minutes of the clamp (+150 to +180 minutes) minus a correction factor for non-constant glucose level divided by body weight (DeFronzo et al. 1979). No other approved GLP1-RA has description of M-value in labeling.

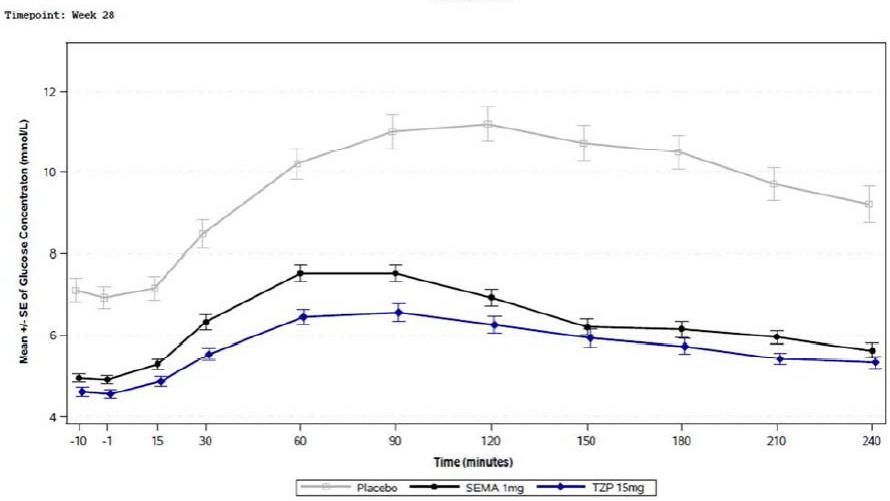
The reviewer's conclusion agrees with that of the Applicant. This study demonstrated improvements in measures of glucose concentration and insulin and glucagon secretion with tirzepatide compared to placebo and semaglutide.

Figure 7 Mean insulin concentration 0-120 minutes during hyperglycemic clamp at baseline and Week 28 in Study GPGT



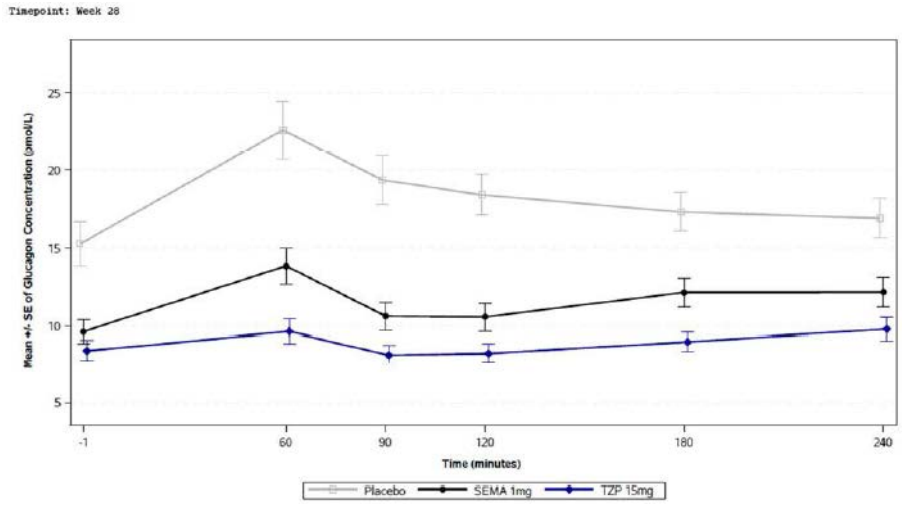
(Source: page 63 Figure 2.7.2.12. of Summary of Clinical Pharmacology)

Figure 8 Mean Blood glucose concentrations (± SE) during standardized mixed-meal tolerance test in Study GPGT



(Source: page 67 Figure 5.8 of Study GPGT report)

Figure 9 Mean Glucagon concentration (± SE) during standardized mixed-meal tolerance test in Study GPGT



(Source: page 84 Figure 5.11 of Study GPGT report)

Study GPGR: Effect of Tirzepatide on Oral Contraceptive (OC) PK in Healthy Female Subjects

GPGR was a phase 1, single-center, open-label, 2-period, fixed sequence study with a lead-in period, in healthy female participants conducted to evaluate the effects of single SC dose of tirzepatide 5 mg on OC PK. Each OC cycle consisted of 21 days of active combination tablet (ethinyl estradiol 0.035 mg and norgestimate 0.25 mg) followed by 7 days of placebo. Each enrolled participant completed 3 OC cycles; (1) Cycle 1: Lead-in period, (2) Cycle 2: OC alone in Period 1(OC PK samples were collected over 48 hours after OC dosing on Day 21), (3) Cycle 3: OC + tirzepatide 5 mg in Period 2.

Single dose of tirzepatide 5 mg was administered SC on Day 20. OC dosing on Day 21 occurred approximately 24 hours after tirzepatide dosing to correspond with the predicted peak exposure (tirzepatide t_{max} approximately 24 hours) of tirzepatide. This permitted the study of the influence of tirzepatide at its highest exposure and greatest impact on gastric emptying, on OC PK. OC PK samples were collected over 48 hours after OC dosing on Day 21.

The Applicant concludes that the AUC of norelgestromin and ethinyl estradiol was reduced by 16% to 23% when the OC was administered in the presence of 5 mg tirzepatide compared to dosing with OC alone (Table 2, Section 3.3.4). The $AUC_{0\text{-}tau}$ of norelgestromin component was reduced by about 30% (lower 90CI% for geometric mean ratio of $AUC_{0\text{-}tau}$ is 0.71). Ethinyl estradiol also showed a similar decrease in $AUC_{0\text{-}tau}$ of about 27% (lower 90CI% for geometric mean ratio of AUC0-tau is 0.73). C_{max} of norelgestromin and ethinyl estradiol was reduced by 55% to 59% when the OC was administered in the presence of 5 mg tirzepatide compared to dosing with OC alone. Norgestimate (parent of norelgestromin) C_{max} and AUC was reduced by 66% (ratio of geometric mean (90%CI) 0.345 (0.274, 0.436) and 20% (ratio of geometric mean (90%CI) 0.792 (0.614, 1.02). Delays in t_{max} of 2.5 to 4.5 hours were observed when the OC was administered in the presence of 5 mg tirzepatide.

The Applicant concludes the reduction in C_{max} is of limited clinical relevance while AUC drives contraception efficacy. Therefore, with the intended clinical dosing scheme of tirzepatide 2.5-mg starting dose followed by gradual stepwise dose escalation, the impact of tirzepatide on OC PK is expected to be minimal, as the tirzepatide starting dose is low and repeated dosing is associated with a diminishing gastric emptying effect.

However, the clinical pharmacology team determined that the reduction in $AUC_{0\text{-}tau}$ and C_{max} of the progestin component (norelgestromin) poses a clinically significant risk of loss of efficacy and subsequent failure of oral contraceptive that is highly dependent on the progestin component. The estrogen component (ethinyl estradiol) showed similar reductions. Although starting doses are 2.5 mg once weekly, the proposed clinical doses can be up-titrated to 7.5, 10, 12.5, and 15 mg, the risk of which is unknown. The clinical pharmacology team considered dose separation of oral contraceptive used in the case of exenatide and found dose separation not adequate solution for tirzepatide due to the once weekly dosing interval of tirzepatide. The delayed gastric emptying is the expected mechanism of interaction of oral contraceptives and tirzepatide and hence, delayed gastric emptying is not expected to impact hormonal contraceptives that are not administered orally. In addition, patients using oral hormonal contraceptives should use an alternative non-oral contraceptive method or add a barrier method of contraception during treatment with tirzepatide. The effect on gastric emptying is presented in the labeling under section 7 (b) (4) and 12.3.

Study GPHX: Disposition of [^{14}C]-Tirzepatide Following Subcutaneous Administration in Healthy Male Subjects

GPHX was a single-center, single-dose, open-label study of tirzepatide, conducted to determine the disposition of radioactivity and PK of tirzepatide in healthy male participants following a single SC injection of approximately 4.1 mg tirzepatide containing approximately 100 µCi [^{14}C]-tirzepatide.

Six healthy male participants aged between 30 and 56 years, participated and completed the study. Participants remained resident in the clinical research unit until Day 15. If participants had not met release criteria by Day 15, they were required to return to the clinical research unit for up to seven 48-hour residential inpatient follow-up visits. Sequential blood samples were obtained predose and after dose administration to quantify the PK of the total radioactivity in whole blood and plasma, and tirzepatide in plasma. Sequential urine and fecal samples were obtained to determine the mass balance of tirzepatide by quantification of radioactivity and to identify metabolites. Participants were required to attend all follow-up visits as scheduled until such time that the release criterion (<1.0% total radioactivity in excreta) was met or up to Day 64, whichever occurred first.

The Applicant concludes that the mean percent (SD) total recovery of administered radioactivity was approximately 70% (1.98) of the administered radiolabeled dose, from which approximately 50% (2.58) of the administered radioactivity was excreted in urine and approximately 20% (2.05) was excreted in feces. Radioactivity was not detected in expired air. The Applicant extrapolation of the data between the collection intervals of the sparse sampling resulted in an estimated overall recovery of 99% with 66% renally eliminated and 33% recovered in feces.

Four minor metabolites (M1, M3, M4, M13) resulting from proteolytic cleavage of the peptide backbone were identified in plasma. Metabolites M1 + M3 (coeluting), M4 and M13 accounted for means of 5.5%, 5.7% and 1.3% of the total circulating radioactivity, respectively. Tirzepatide was the largest circulating component in plasma accounting for approximately 80% of the circulating radioactivity. Six metabolites were identified in urine. The 2 prominent metabolites, M5 and M7, in urine, represented approximately 21% and 9% of the dose. Four minor metabolites in urine (M8, M11, M17, and M18) each represented less than 3% of the dose. All metabolites in urine were formed by proteolytic cleavage of the peptide backbone and β-oxidation of the C20 fatty acid, with 2 metabolites, M11 and M17, showing amide hydrolysis in the linker region. Six metabolites were identified in feces. The 6 metabolites (M12, M5, M19, M7, M11, and M8) identified accounted for a total of 6.8%, 3.3%, 2.9%, 1.0%, 0.6%, and 0.5% of the dose. All metabolites in feces were formed by proteolytic cleavage of the peptide backbone and β-oxidation of the C20 fatty acid, with 2 metabolites, M12 and M19, showing additional amide hydrolysis in the linker region.

Following t_{max}, concentrations declined in a monophasic manner and geometric mean $t_{1/2}$ was similar for total radioactivity in plasma and whole blood at approximately 180 hours. The geometric mean ratio of whole blood total radioactivity to plasma total radioactivity was 0.500 for $AUC_{0-\infty}$, suggesting that tirzepatide does not preferentially bind to red blood cells. Tirzepatide was eliminated by metabolism with no intact tirzepatide observed in urine or feces.

The reviewer's conclusion agrees with that of the Applicant and notes that based on the observed data, approximately 30% of radioactivity might not have been recovered.

Additional Tables

Table 11 Regulatory background pertaining to Clinical Pharmacology

Date	**Meeting or Communication – key discussion points**
03/29/2016	Under IND 128801, the Applicant submitted protocol for Study GPGA: a SAD/MAD study in healthy volunteers with part C MAD in T2DM
09/06/2018	Type B End-of-Phase 2 meeting –adequacy of Clinical Pharmacology studies, utilization of PBPK modeling for DDI, evaluating potential QTc prolongation, use of phase 1 to 3 data in the population PK analysis, and adequacy of the 5 mg in the OC DDI study
07/11/2019	Response to request for comment on PBPK and OC DDI
08/27/2020	Type C Written Response – Population PK/PD, Integrated Summary of Efficacy, Program Safety Analysis Plan, Immunogenicity, intercurrent events
06/24/2021	Type B Pre-NDA meeting – Population PK analysis report, dose in registration trial, Exposure-Response relationship, Immunogenicity, validation report of Norgestimate and Ethinyl estradiol, PBPK model and validation
09/15/2021	NDA 215866 submitted

Table 12 Index of Studies and Analyses in the Clinical Pharmacology Program

Study	Description	Population	SC Dosing Regimen
Disposition and Metabolism Study			
GPHX	Disposition of radioactivity and PK	Healthy males	Single 2.9-mg dose a [^{14}C-TZP 100 µCi]
Healthy Participant PK, PD, and Tolerability			
GPGA	Single- and multiple-dose safety, PK, and PD	Healthy participants	[A] SAD: 0.25, 0.5, 1, 2.5, 5.0, and 8 mg TZP or placebo [B] MAD total dosing duration 4 weeks TZP QW [1] 0.5 mg [2] 1.5 mg [3] 4.5 mg TZP QW dose escalation: [4] 5/5/8/10 mg each dose for 1 week or Dulaglutide: 1.5 mg QW or Placebo
PK and/or PD in Patients with T2DM, and Tolerability			
GPGA	Multiple-dose safety, PK, and PD	T2DM [diet/exercise control or using single OAM (metformin or SU)]	Total dosing duration: 4 weeks TZP QW: [1] 0.5 mg [2] 5 mg TZP QW dose escalation: [3] 5/5/10/10 mg each dose for 1 week TZP QW dose escalation: [4] 5/5/10/15 mg each dose for 1 week or Placebo
GPGC	Multiple-dose safety, PK, PD	Japanese T2DM (diet/exercise control or using single OAM [metformin or DPP-IV inhibitor])	Total dosing duration: 8 weeks TZP QW dose range: 2.5 to 15 mg [1] 2.5 mg (2 weeks), 5 mg (2 weeks), 10 mg (4 weeks) [2] 5 mg (2 weeks), 10 mg (4 weeks), 15 mg (2 weeks) [3] 5 mg for 8 weeks or Placebo
Effect of Injection Delivery Device on PK			
GPGS	Effect of injection device	Healthy Participants	Single 5-mg dose TZP delivered through prefilled syringe vs single-dose pen (autoinjector) (cross-over study)
Effect of Intrinsic Factors			
GPHI	Effect of BMI	Healthy participants; low and high BMI	Single 5 mg TZP
GPGG	Effect of renal impairment	Normal or impaired renal function	Single 5 mg TZP
GPGQ	Effect of hepatic impairment	Normal or impaired hepatic function	Single 5 mg TZP
Effect of tirzepatide on PK and/or PD of other drugs			
GPGR	Effect on combined OC	Healthy women eligible to use OC	Single 5 mg TZP
Mechanistic Pharmacodynamic Study			
GPGT	Effect on pancreatic α and β cell function and insulin sensitivity	T2DM [diet/ exercise control and metformin ± 1 other OAM (SU or DPP-IV inhibitors or SGLT-2i or a-GI)]	Total dosing duration: 28 weeks Dose-escalation scheme: TZP QW: 2.5 mg (4 weeks), 5 mg (4 weeks), 7.5 mg (4 weeks), 10 mg (4 weeks), 12.5 mg (4 weeks), 15 mg (8 weeks) or Semaglutide 1 mg [b] or Placebo
Studies Providing Population PK/PD Information			
GPGB	Phase 2	T2DM (diet/ exercise control ± metformin)	Total dosing duration: 26 weeks TZP QW dose range: 1 to 15 mg [1] 1 mg [2] 5 mg [3] 5 mg (2 weeks) and then 10 mg for remainder of study [4] 5 mg (2 weeks), 10 mg (4 weeks) and then

			15 mg for remainder of study or Dulaglutide: 1.5 mg QW or Placebo
GPGF	Phase 2	T2DM (diet/ exercise control ± metformin)	Total dosing duration: 12 weeks TZP QW dose range: 2.5 to 15 mg [1] 2.5 mg (2 weeks), 5 mg (2 weeks), 10 mg (4 weeks), 15 mg (4 weeks) [2] 2.5 mg (4 weeks), 7.5 mg (4 weeks), 15 mg (4 weeks) [3] 4 mg (4 weeks), 8 mg (4 weeks), 12 mg (4 weeks) or Placebo
GPGH	Phase 3	T2DM diet/ exercise control and metformin ± SGLT-2i)	TZP QW: 5, 10, and 15 mg QW[c] for 52 weeks or insulin degludec
GPGI	Phase 3	T2DM on metformin and insulin glargine	TZP QW: 5, 10, and 15 mg QW[c] for 40 weeks or placebo
GPGK	Phase 3	T2DM (diet/ exercise)	TZP QW: 5, 10, and 15 mg QW[c] for 40 weeks or placebo
GPGL	Phase 3	T2DM diet/ exercise control and metformin)	TZP QW: 5, 10, and 15 mg QW[c] for 40 weeks or semaglutide 1 mg
GPGM	Phase 3	T2DM with increased CV risk; on 1 to 3 OAMs	TZP QW: 5, 10, and 15 mg QW[c] for up to 104 weeks or insulin glargine
GPGO	Phase 3	Japanese T2DM (diet/exercise)	TZP QW: 5, 10, or 15 mg QW[c] for 52 weeks or dulaglutide 0.75 mg QW for 52 weeks
GPGP	Phase 3	Japanese T2DM (diet/exercise and 1 OAM)	TZP QW: 5, 10, or 15 mg QW[c] for 52 weeks on background OAMs [d]

Abbreviations: a-GI = alpha-glycosidase inhibitors; CV = cardiovascular; BMI = body mass index; DPP-IV = dipeptidyl peptidase-4; MAD = multiple ascending dose; OC = oral contraceptive; OAM = oral antihyperglycemic medication; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; SAD = single-ascending dose; SC = subcutaneous; SGLT-2i = sodium-glucose cotransporter type 2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; TZP = tirzepatide administered SC. a Planned dose 4.1 mg; actual dose 2.9 mg; however, 100 µCi 14C was administered per plan. b Semaglutide dose-escalation scheme: Per Ozempic label, i.e., starting dose is 0.25 mg QW for 4 weeks, followed by an increase to 0.5 mg QW for the next 4 weeks, followed by an increase to 1 mg QW for the duration of the study. c Tirzepatide dose-escalation scheme for all Phase 3 studies: Starting dose is 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study in the 5-mg group. For the 10-mg group, the starting dose is 2.5 mg QW for 4 weeks, followed by dose increases of 2.5 mg every 4 weeks (2.5 to 5 mg to 7.5 to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg group, the starting dose is 2.5 mg QW for 4 weeks, followed by dose increases of 2.5 mg every 4 weeks (2.5 to 5 mg to 7.5 to 10 mg to 12.5 to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study. d OAMs: SUs, biguanides, a-GIs, TZD, glinides, or SGLT-2i's. (Source: page 17 Table 2.7.2.1 of Summary of Clinical Pharmacology)

4.2 In Vitro Studies

Six in vitro studies with human biomaterials were conducted to determine protein binding and the potential for tirzepatide to inhibit and/or induce CYP enzymes and transporters was investigated as follows.

Study LY3298176-fu assessed the in vitro plasma protein binding of tirzepatide in rat, monkey, and human plasma by a florescence polarization (fp) method. In the presence of a fixed 0.05 µM concentration of the fluorescent ligand, binding was measured over a range of protein concentrations (0.01 to 250 µM) for the following matrices: human serum albumin (HSA), human α1-acid glycoprotein, and human plasma. Fluorescent-labeled tirzepatide bound to albumin, but not α1-acid glycoprotein. Consequently, the protein binding of fluorescent-labeled tirzepatide in plasma was attributed to albumin. The protein binding of fluorescent-labeled tirzepatide in plasma was calculated from the dissociation constant (Kd) related to albumin and its measured concentration in plasma to determine fraction unbound in 6 replicates of human plasma. Tirzepatide was highly bound in human plasma with a mean percent bound of 99.06%.

Study XT195111 assessed the in vitro inhibitory potential of tirzepatide on CYP3A, 2D6, 2C19, 2C9, 2C8, 2B6, and 1A2 in human hepatic microsomes. Following 5-minute incubations of enzyme substrate with tirzepatide concentrations up to 100 µM, samples were analyzed for formation of the specific marker metabolite. At concentrations up to 100 µM, 309x higher than the 0.324 µM C_{max} for tirzepatide 15 mg dose, none of the evaluated CYPs were sufficiently inhibited by tirzepatide to determine a half-maximal inhibitory concentration (IC_{50}) value. In addition, there was no evidence of time-dependent inhibition (NADPH-independent) of any CYP enzymes examined (Table 13). These results suggest that tirzepatide would not be expected to cause clinically relevant inhibition of the clearance of other drugs metabolized by these CYP enzymes.

Table 13 Summary In vitro evaluation of tirzepatide as an inhibitor of human CYP enzymes

Enzyme	Substrate	Direct inhibition		Time-dependent (NADPH-independent) inhibition [c]		Time- plus NADPH-dependent inhibition [c]	
		0-min preincubation		30-min preincubation without NADPH		30-min preincubation with NADPH	
		IC50 (µM)[a]	Maximum inhibition observed (%)[b]	IC50 (µM)[a]	Maximum inhibition observed (%)[b]	IC50 (µM)[a]	Maximum inhibition observed (%)[b]
CYP3A	Testosterone		14.5		11.2		18.6
CYP3A	Midazolam	> 100	18.9	> 100	21.4	> 100	23.8
CYP2D6	Dextromethorphan		9.4		3.1		4.3
CYP2C19	S-Mephenytoin		9.1		4.5		12.3
CYP2C9	Diclofenac		8.7		7.2		8.7
CYP2C8	Amodiaquine		11		8.2		18.1
CYP2B6	Efavirenz		5.3		NA		4.4
CYP1A2	Phenacetin		2.4		NA		2.0

NA Not applicable. No value was obtained as the rates at all concentrations of TIRZEPATIDE evaluated were higher than the control rates. [a] Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC50 values. [b] Maximum inhibition observed (%) is calculated with the following formula: Maximum inhibition observed (%) = 100% − the minimum percent solvent control for any test article concentration. [c] When an IC50 value was calculated, time-dependent (i.e., NADPH-independent) inhibition and metabolism-dependent (i.e., time- plus NADPH- dependent) inhibition were determined by comparison of IC50 values with and without preincubation and NADPH and by visual inspection of the IC50.

(Source: Table 4, page 28 of Study XT195111 report)

Study XT193106 evaluated the potential of tirzepatide to induce CYP1A2, 2B6, 2C8, 2C9, C19, 2D6, 3A4, and 3A5 in cultured human hepatocytes from 3 separate donors using quantitative reverse transcription-polymerase chain reaction. An enzyme activity assessment was also conducted via LC-MS/MS analysis of marker substrates for each enzyme. Clinically relevant CYP inducers were included as positive controls, specifically, omeprazole (CYP1A2 inducer), CITCO (CYP2B6 inducer), phenobarbital (CYP2B6 inducer and CYP3A5 mRNA), rosiglitazone (a weak inducer of CYP3A4/5), pioglitazone (a moderate inducer of CYP3A4/5) and rifampin (moderate inducer of CYP2C8, CYP2C9, CYP2C19, CYP3A5 and strong inducer of CYP3A4). Tirzepatide was not found an inducer of the mRNA expression or activity level of these CYPs at concentration ranging from 0.1 to 100 µM because it did not demonstrate concentration-dependent increases in mRNA expression resulting in fold change ≥ 2 and response ≥ 20% of the positive control response. These results suggest that the potential for tirzepatide to cause clinically relevant drug interactions via induction of these drug-metabolizing CYP enzymes is low.

Study TIRZEPATIDE MATE1 and 2K Inh assessed the in vitro inhibitory potential of tirzepatide on MATE1 and MATE2-K at concentrations range 0.01 to 200 µM using [^{14}C] metformin (20 µM) as substrate. Neither of the transporters were sufficiently inhibited by tirzepatide to determine a half-maximal inhibitory concentration (IC50) value. Hence, no inhibition of MATE1 or MATE2-K was

observed in the tirzepatide concentration range tested. These in vitro data suggest that the potential for tirzepatide to cause clinically relevant drug interactions via MATE1 or MATE2-K is low.

Study TIRZEPATIDE-2020TP-SLC-Inh assessed the in vitro inhibitory potential of tirzepatide concentrations of up to 200 µM on OCT1, OCT2, OAT1, or OAT3 or up to 250 µM OATP1B1 or OATP1B3 transporters. OATP1B1-mediated transport of [^{3}H] rosuvastatin was inhibited by TIRZEPATIDE with the average IC_{50} value of 15.65 µM in 0.1% fatty acid-free human serum albumin (HSA-faf), but no inhibition was observed in physiologically relevant concentration of albumin of 4% HSA-faf. OATP1B3-mediated transport of [^{3}H] atorvastatin with the average IC_{50} value of 2.81 µM in 0.1% HSA-faf and 129.65 µM in 4% HSA-faf. The remaining SLC transporters were challenged with TIRZEPATIDE in the presence of 0.1% HSA-faf. OCT1 and OCT2-mediated uptake of [^{14}C] metformin, OAT1-mediated uptake of [^{14}C] p-aminohippuric acid, and OAT3-mediated uptake of [^{3}H] estrone 3-sulfate were not inhibited by tirzepatide in a concentration-dependent manner. These suggest that the potential for tirzepatide to cause clinically relevant drug interactions via OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 is low.

Study TIRZEPATIDE-2020TP-BCRP-Pgp-In was an in vitro assessment of TIRZEPATIDE for Breast Cancer Resistance Protein (BCRP) and P-glycoprotein (P-gp) inhibition potential over the concentration range 0.091 to 200µM. [^{3}H]-vinblastine and [^{3}H]-rosuvastatin were the P-gp and BCRP substrates used respectively. At the highest tirzepatide concentration tested of 200 µM, the observed range of inhibition of P-gp was 47.6-50.1% and BCRP was 15.5-27.8%. These in vitro data suggest that the potential for tirzepatide to cause clinically relevant drug interactions via BCRP and P-gp is low.

4.3 Summary of Bioanalytical Method Validation and Performance

The Applicant used the same validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay developed and validated by (b) (4) method over the course of clinical development to determine tirzepatide concentration in human serum. Table 14 lists the method validation summaries used.

Briefly, the LC/MS method involved extraction of tirzepatide from human plasma using immunoaffinity capture in a 96-well format and LSN3316897 [Stable isotope-labeled TIRZEPATIDE] as the internal standard. The tirzepatide and internal standard were identified and quantified using Q Exactive or Q Exactive Plus quadrupole-orbitrap mass spectrometer equipped with Heated Electrospray Ionization™ (HESI) and High Mass Resolution, Accurate Mass Monitoring (HRAM) detection. Liquid chromatography was performed with an LC/MS system consisting of a Supelco Discovery BioWide Pore C5-3 (5.0 x 0.1 cm, 3 µm) chromatography column and Dionex UltiMate 3000 with gradient elution using Mobile Phase A: 5:95 Formic Acid/Water and Mobile Phase B: 5:95 Formic Acid/Acetonitrile in 50:50 Water/Methanol. The detection was monitored at mass (amu) of 1204.140/1204.391 for tirzepatide and a mass (amu) of 1206.395 for the internal standard. The concentrations were calculated using peak area ratios, and the linearity of the calibration curve was determined using linear regression analysis employing a 1/x2 weighting. The standard curve range was 2 ng/mL to 500 ng/mL. The lower limit of quantitation was 2 ng/mL, and

the upper limit of quantitation was 500 ng/mL. The inter-assay accuracy (%RE) during validation ranged from - 0.5% to 10.9%. The inter-assay precision (%CV) during validation was ≤12.2%. Quality control samples across the standard curve range were included in each sample analysis batch. Plasma samples with concentrations of tirzepatide above the upper limit of quantitation were determined by up to a 100-fold dilution. Incurred sample reanalysis was conducted for all clinical studies and the results indicated that the assay method performed according to established ISR acceptance criteria with a (b) (4) % passing rate.

Table 14 Bioanalytical method validation summary

Bioanalytical method validation report name, amendments, and hyperlinks	Report 151682VKM_EII_R1		
Method description	Method Validation for the Quantitation of Tirzepatide (LY3298176) in Human Plasma by HRAM LC/MS		
Materials used for standard calibration curve and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BE03437-014-737 Citrate buffer solution		
Validated assay range	2.00 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BE03437-014-737 Dry powder		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents (LBA)	Not applicable		
Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	151682VKM_EII_R1 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-2.4 to 4.0%	151682VKM_EII_R1 Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	≤13.6%	151682VKM_EII_R1 Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs: Tirzepatide	2.8 to 10.9%	151682VKM_EII_R1 Section 5.3.1.4
	Inter-batch %CV QCs: Tirzepatide	≤9.7%	151682VKM_EII_R1 Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤6.4% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was 0.0% of LLOQ.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was 0.0% of LLOQ.
Dilution linearity & hook effect	100-fold dilution validated. Hook effect not applicable.		
Bench-top/process stability	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature		
Freeze-Thaw stability	5 freeze/thaw cycles at -20 and -70°C		
Long-term storage	378 days at -20 and -70°C		
Parallelism	Not applicable		
Carry over	There was no significant carryover.		

Bioanalytical method validation report name, amendments, and hyperlinks	Report 151682VKM_EII_R2
Method description	Method Validation for the Quantitation of Tirzepatide (LY3298176) in Human Plasma by HRAM LC/MS

Materials used for standard calibration curve and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BE03437-014-737 Citrate buffer solution		
Validated assay range	2.00 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BE03437-014-737 Dry powder		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents (LBA)	Not applicable		
Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	151682VKM_EII_R2 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-2.4 to 4.0%	151682VKM_EII_R2 Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	≤13.6%	151682VKM_EII_R2 Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs: Tirzepatide	2.8 to 10.9%	151682VKM_EII_R2 Section 5.3.1.4
	Inter-batch %CV QCs: Tirzepatide	≤9.7%	151682VKM_EII_R2 Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤6.4% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was -20.5% of LLOQ.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was -13.5% of LLOQ.
Dilution linearity & hook effect	100-fold dilution validated. Hook effect not applicable.		
Bench-top/process stability	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature		
Freeze-Thaw stability	5 freeze/thaw cycles at -20 and -70°C		
Long-term storage	378 days at -20 and -70°C		
Parallelism	Not applicable		
Carry over	There was no significant carryover.		

Bioanalytical method validation report name, amendments, and hyperlinks	Report 191444PVDJS_EII
Method description	Partial Method Validation for the Quantitation of Tirzepatide (LY3298176) in Human Plasma by HRAM LC/MS
Materials used for standard calibration curve and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Dry powder
Validated assay range	2.00 to 500 ng/mL
Material used for quality controls (QCs) and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Dry powder
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents (LBA)	Not applicable

Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	191444PVDJS_EII Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-2.8 to 4.8%	191444PVDJS_EII Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	≤4.8%	191444PVDJS_EII Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs QCs: Tirzepatide	-2.1 to 2.8%	191444PVDJS_EII Section 5.3.1.4
	Inter-batch %CV QCs: Tirzepatide	≤12.9%	191444PVDJS_EII Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤12.3% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was 6.9% of LLOQ.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was 7.3% of LLOQ.
Dilution linearity & hook effect	100-fold dilution validated. Hook effect not applicable.		
Bench-top/process stability[a]	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature		
Freeze-Thaw stability[a]	5 freeze/thaw cycles at -20 and -70°C		
Long-term storage[a]	378 days at -20 and -70°C		
Parallelism	Not applicable		
Carry over	There was no significant carryover.		

Bioanalytical method validation report name, amendments, and hyperlinks	Report 191444PVDJS_EII_R1		
Method description	Partial Method Validation for the Quantitation of Tirzepatide (LY3298176) in Human Plasma by HRAM LC/MS		
Materials used for standard calibration curve and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Citrate buffer solution		
Validated assay range	2.00 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Dry powder		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents (LBA)	Not applicable		
Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	191444PVDJS_EII_R1 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-2.8 to 4.8%	191444PVDJS_EII_R1 Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	≤4.8%	191444PVDJS_EII_R1 Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs QCs: Tirzepatide	-2.1 to 2.8%	191444PVDJS_EII_R1 Section 5.3.1.4
	Inter-batch %CV QCs: Tirzepatide	≤12.9%	191444PVDJS_EII_R1 Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤12.3% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was 6.9% of LLOQ.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was 7.3% of LLOQ.

Dilution linearity & hook effect	100-fold dilution validated. Hook effect not applicable.	
Bench-top/process stability[a]	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature	
Freeze-Thaw stability[a]	5 freeze/thaw cycles at -20 and -70°C	
Long-term storage[ab]	680 days at -20 and -70°C	
Parallelism	Not applicable	
Carry over	There was no significant carryover.	

Bioanalytical method validation report name, amendments, and hyperlinks	Report 202444PVDJS_EII
Method description	Partial Method Validation for the Quantitation of Tirzepatide (LY3298176) in Human Plasma by HRAM LC/MS

Materials used for standard calibration curve and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Citrate buffer solution		
Validated assay range	2.00 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Dry powder		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents (LBA)	Not applicable		
Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	202444PVDJS_EII Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-4.0 to 4.5%	202444PVDJS_EII Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	NA	202444PVDJS_EII Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs QCs: Tirzepatide	-4.3 to 4.0%	202444PVDJS_EII Section 5.3.1.4
	Intra-batch[a] %CV QCs: Tirzepatide	≤6.8%	202444PVDJS_EII Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤2.4% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Dilution linearity & hook effect	10-fold dilution validated. Hook effect not applicable.		
Bench-top/process stability[a]	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature		
Freeze-Thaw stability[a]	5 freeze/thaw cycles at -20 and -70°C		
Long-term storage[a]	378 days at -20 and 522 days at -70°C		
Parallelism	Not applicable		
Carry over	There was no significant carryover.		

Bioanalytical method validation report name, amendments, and hyperlinks	Report 202160PVDJS_EII		
Method description	Partial Method Validation for the Quantitation of Tirzepatide (LY3298176) (Supplied as a 1:1 Mixture of $^{14}C_4$-LY3298176/^{12}C-LY3298176) in Human Plasma by LC/HRMS		
Materials used for standard calibration curve and concentration	$^{14}C_4$-LY3298176/^{12}C-LY3298176 (supplied as a 1:1 mixture in control plasma) Internal standard (IS): LSN3479389 lot ALE-BE06321-058 Dry powder		
Validated assay range	3.12 to 390 ng/mL		
Material used for quality controls (QCs) and concentration	$^{14}C_4$-LY3298176/^{12}C-LY3298176 (supplied as a 1:1 mixture in control plasma) Internal standard (IS): LSN3479389 lot ALE-BE06321-058 Dry powder		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents (LBA)	Not applicable		
Regression model and weighting	Weighted 1/x^2 quadratic regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	202160PVDJS_EII Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-8.2 to 5.9%	202160PVDJS_EII Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	≤5.7%	202160PVDJS_EII Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs: Tirzepatide	2.9 to 8.2%	202160PVDJS_EII Section 5.3.1.4
	Inter-batch %CV QCs: Tirzepatide	≤9.2%	202160PVDJS_EII Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤20.0% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤5.0% of LLOQ.
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was 0.0% of LLOQ.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was 15.3% of LLOQ.
Dilution linearity & hook effect	10-fold dilution validated. Hook effect not applicable.		
Bench-top/process stability[a]	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature		
Freeze-Thaw stability[a]	5 freeze/thaw cycles at -20 and -70°C		
Long-term storage[a]	378 days at -20 and 522 days at -70°C		
Parallelism	Not applicable		
Carry over	There was no significant carryover.		

Bioanalytical method validation report name, amendments, and hyperlinks	Report 8226219		
Method description	Validation of a Method for the Determination of Acetaminophen in Human Plasma using Liquid Chromatography with Tandem Mass Spectrometric Detection		
Materials used for standard calibration curve and concentration	Acetaminophen lots 088K0040, K0I244, 096K0072 and P500005 Internal standard (IS): Acetaminophen-d4 lot 14SSR-11-1, 11-GHZ-105-1 and 11-ABY-24-1 Dry powder		
Validated assay range	50.0 to 50000 ng/mL		
Material used for quality controls (QCs) and concentration	Acetaminophen lots 088K0040, K0I244, 096K0072 and P500005 Internal standard (IS): Acetaminophen-d4 lot 14SSR-11-1, 11-GHZ-105-1 and 11-ABY-24-1 Dry powder		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents (LBA)	Not applicable		
Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	8226219 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Acetaminophen	-3.3 to 2.8%	8226219 Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Acetaminophen	≤4.6%	8226219 Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs QCs: Acetaminophen	2.1 to 8.7%	8226219 Section 5.3.1.4
	Inter-batch %CV QCs: Acetaminophen	≤5.1%	8226219 Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤5.3% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was within 2.7% of the theoretical value.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was within 18.7% of the theoretical value.
Dilution linearity & hook effect	10-fold dilution validated. Hook effect not applicable.		

Bench-top/process stability	Plasma: 24 hours at room temperature Extracted plasma: 75 hours at 4°C	
Freeze-Thaw stability	5 freeze/thaw cycles at -20 and -70°C	
Long-term storage	646 days at -20°C and 638 days at -70°C	
Parallelism	Not applicable	
Carry over	There was no significant carryover.	

Bioanalytical method validation report name, amendments, and hyperlinks	Report 8416335	
Method description	Validation of a Method for the Determination of Norgestimate, Norelgestromin and Ethinyl Estradiol in Human Plasma by HPLC with MS/MS Detection	
Materials used for standard calibration curve and concentration	Norgestimate lot G1J236 Norelgestromin lot F010T0 Ethinyl Estradiol lot R0M195 Internal standard (IS): Norgestimate-d6 lot 048, Norelgestromin-d6 lot Z-432, Ethinyl Estradiol-d4 lot 1-MIT-149-1 Dry powder	
Validated assay range	Norgestimate 5.00 to 500 pg/mL Norelgestromin 25.0 to 2500 pg/mL Ethinyl Estradiol 10.0 to 1000 pg/mL	
Material used for quality controls (QCs) and concentration	Norgestimate lot G1J236 Norelgestromin lot F010T0 Ethinyl Estradiol lot R0M195 Internal standard (IS): Norgestimate-d6 lot 048, Norelgestromin-d6 lot Z-432, Ethinyl Estradiol-d4 lot 1-MIT-149-1 Dry powder	
Minimum required dilutions (MRDs)	Not applicable	
Source and lot of reagents (LBA)	Not applicable	
Regression model and weighting	Weighted $1/x^2$ least squares linear regression	
Validation parameters	**Method validation summary**	**Source location**

Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	8416335 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Norgestimate Norelgestromin Ethinyl Estradiol	 -2.8 to 2.4% -3.0 to 4.8% -1.5 to 1.0%	8416335 Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Norgestimate Norelgestromin Ethinyl Estradiol	 ≤5.9% ≤10.4% ≤8.3%	8416335 Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs: Norgestimate Norelgestromin Ethinyl Estradiol	 -3.0 to -1.3% -0.1 to 4.8% -4.0 to 0.1%	8416335 Section 5.3.1.4
	Inter-batch %CV QCs: Norgestimate Norelgestromin Ethinyl Estradiol	 ≤6.1% ≤7.6% ≤3.3%	8416335 Section 5.3.1.4
	Total Error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤20% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was 15% of theoretical value.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was 15% of theoretical value.
Dilution linearity & hook effect	50-fold dilution validated for all analytes. Hook effect not applicable.		
Bench-top/process stability	Norgestimate: Plasma: 26 hours at room temperature Extracted plasma: 27 hours at 4°C Norelgestromin: Plasma: 26 hours at room temperature Extracted plasma: 44 hours at 4°C Ethinyl estradiol: Plasma: 26 hours at room temperature Extracted plasma: 44 hours at 4°C		
Freeze-Thaw stability	Norgestimate, norelgestromin, ethinyl estradiol: 5 freeze/thaw cycles at -20 and -70°C		

Long-term storage	Norgestimate and norelgestromin: 433 days at -20°C and -70°C Ethinyl estradiol: 407 days at -20°C and -70°C	
Parallelism	Not applicable	
Carry over	There was no significant carryover.	

(Source: Table APP.2.7.1.4.1 of Appendix of the Summary of Biopharmaceutic Studies and Associated Analytical Methods)

4.4 Pharmacometrics Review

In general, the Applicant's population PK and PK-PD analyses are considered acceptable for descriptive labeling purposes and for capturing tirzepatide PK-PD. More specifically, the developed population PK (popPK) model was utilized to support the current submission as outlined below:

Table 1. Utility of the Population PK-PD Modeling

Utility of the final model		**Reviewer's Comments**
Derive exposure metrics and PK parameters	• The popPK was used to assess the adequacy of the proposed dosing in all adult patients, identify and quantify the effect of various covariates on tirzepatide exposure and assess the need for dose adjustment. • The popPK model was used to predict tirzepatide concentrations, C_{max} and the area under the concentration-time curve over the weekly dosing interval (AUCtau) at each dose level, as well as predict tirzepatide half-life and justify handling missed dose. • The popPK model was used to predict the individual PK parameters used in the sequential PK-PD modeling.	• Body weight was the only statistically significant and relevant covariate on tirzepatide clearance and volume of distribution parameters. However, no dose adjustment is required based on body weight due to the moderate effect on exposure in the context of the gradual titration of tirzepatide treatment. • Age, sex, ethnicity, renal and hepatic impairment as well as ADA status and titers were not found to have a statistically significant effect on the PK of tirzepatide, and no dose adjustment is necessary based on these covariates. • The Applicant's proposal to administer tirzepatide as soon as possible within 4 days (96 hours) of a missed dose, otherwise to skip the dose (if more than 4 days has passed) before resuming the regular weekly regimen is acceptable.
Derive exposure metrics for Exposure-response analyses	• The final PK model was used to predict the individual PK parameters used in the sequential PK-PD modeling for the following models: the fasting Glucose and HbA1c model, the body weight loss model and the nausea-vomiting and diarrhea Markov models.	• The developed PK-PD models adequately described the effect of tirzepatide regimen on lowering fasting Glucose and HbA1c, lowering body weight, and the development of tolerance to nausea-vomiting and diarrhea.

1. Population Pharmacokinetic Analysis

The population PK (popPK) analysis was based on PK data from 19 studies (Table 2): ten Phase 1 studies in healthy subjects and subjects with type 2 diabetes (T2DM), two Phase 2 studies, and seven Phase 3 studies in patients withT2DM.

Tirzepatide was administered subcutaneously (SC) as a single or repeated weekly dose of 0.25 to 15 mg up to 104 weeks (Table 2). In one Phase 1 study (GPGE, Part D), tirzepatide was administered as single dose (0.5 mg) intravenous (IV) bolus. The analysis dataset was comprised of 39644 PK observations from 5811 subjects, after exclusion of 7670 BLQ (below limit of quantification of 2 ng/mL) concentrations, that represented a small fraction (16%) of the PK data. In the Phase 1 studies, PK samples were collected between 0 and 864 hours post-dose, with 10 to 15 samples per study participant. In the Phase 2 GPGB study, sparse PK sampling was collected at time windows of 1 to 48 hours, 48 to 72 hours, and 96 to 168 hours. In three Phase 3 studies (GPGK, GPGM, GPGI), PK sample collection was performed either at pre-dose or scheduled at randomly assigned PK window of 1 to 24 hours, 24 to 96 hours, or 120 to 168 hours post-dose (at protocol-specified 3 or 4 visits). In the Phase 2 GPGF study and in four Phase 3 studies (GPGL, GPGH, GPGO, GPGP), PK samples were collected pre-dose at the same time as immunogenicity samples at 5 to 6 visits across the duration of the studies and at the follow-up visit.

The summary statistics for the baseline continuous and categorical demographic characteristics stratified by study phase and health status are presented in Table 3. About 95% of participants were patients with T2DM. A majority of the participants were white, non-Hispanic males. The average age and body weight at baseline were 57 years and 89 kg, respectively.

Table 2. Tirzepatide Clinical Studies Used for the Population Pharmacokinetic and Exposure-Response Analyses

Study Alias and Treatment Duration	Study Description	Participant Type (N)	Treatment Regimen/ Formulation	Analysis Population
Phase 1 / Clinical Pharmacology Studies				
GPGA Parts A & B (4 weeks)	A SAD and 4-week MAD study in healthy subjects to investigate the safety, tolerability, PK, and PD of tirzepatide and a 4-week MD study in patients with T2DM.	Healthy participants (89)	Part A: Tirzepatide SC single dose 0.25, 0.5, 1, 2.5, 5, and 8 mg Part B: Tirzepatide SC QW Cohort 1: 0.5 mg Cohort 2: 1.5 mg Cohort 3: 4.5 mg Cohort 4: 5/5/8/10 mg All with lyophilized formulation	PopPK
GPGA Part C (4 weeks)	A SAD and 4-week MAD study in healthy subjects to investigate the safety, tolerability, PK and PD of tirzepatide and a 4-week MD study in patients with T2DM.	T2DM (53)	Tirzepatide SC QW Cohort 1: 0.5 mg Cohort 2: 5 mg Cohort 3: 5/5/10/10 mg Cohort 4: 5/5/10/15 mg All arms with lyophilized formulation	PopPK
GPGC (8 weeks)	An 8-week MAD evaluation in Japanese patients with T2DM.	T2DM - Japan (48)	Cohort 1: 10mg Tirzepatide SC QW • Weeks 1 to 2: 2.5 mg • Weeks 3 to 4: 5 mg • Weeks 5 to 8: 10 mg Cohort 2: 15 mg Tirzepatide SC QW • Weeks 1 to 2: 5 mg • Weeks 3 to 6: 10 mg • Weeks 7 to 8: 15 mg Cohort 3: 5 mgTirzepatide SC QW • Weeks 1 to 8: 5 mg All arms with lyophilized formulation	PopPK
GPGG (single)	A parallel-design, open-label, multicenter, single-dose study to assess PK and tolerability of a single dose of tirzepatide in subjects with mild, moderate, or severe renal impairment, or ESRD, and control subjects with normal renal function.	Control: Healthy participants (14) Treatment: Renal impairment with or without T2DM (31)	Tirzepatide SC single dose 5 mg lyophilized formulation	PopPK

Source: Applicant's Population PK/PD Report, pages 23-29. (continued on next page)

GPGQ (single)	A multicenter, parallel, single-dose, open-label, single-period study of tirzepatide in subjects with normal hepatic function and subjects with mild, moderate, and severe hepatic impairment. Subjects who have a concomitant T2DM diagnosis were not specifically excluded.	Control: Healthy participants (13) Treatment: Renal impairment with or without T2DM (19)	Tirzepatide SC single dose 5 mg with solution in PFS	PopPK
GPGR (single)	A single-center, open-label, 2-period, fixed sequence study with a lead-in period, to assess the effect of tirzepatide on the PK of an oral contraceptive.	Healthy female participants (40)	Tirzepatide SC single dose 5 mg with solution in PFS	PopPK
GPGT (28 weeks)	A Phase 1, multicenter, randomized, sponsor-, investigator- and patient-blind, parallel-arm study to study the effect of tirzepatide 15-mg dose and placebo on total clamp disposition index and to study the effects on α and β cell function, insulin sensitivity, glucose and lipid metabolism, and energy balance in patients with T2DM.	T2DM (108)	15mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 28: 15 mg All with lyophilized formulation	PopPK
GPHX (single)	An open-label, single-center study following a single dose of approximately 4.1 mg tirzepatide containing approximately 100 μCi of [^{14}C]-tirzepatide administered as an SC injection.	Healthy male participants (6)	Tirzepatide SC single dose 4.1 mg with solution formulation	PopPK
Biopharmaceutic Studies				
GPGE (single and 4 weeks)	A single-center study: • Part A: Relative bioavailability of solution versus lyophilized formulation following single dose • Part C: A 4-week multiple-dose evaluation of solution formulation • Part D: Single dose of IV bolus.	Healthy participants (Part A: 20, Part C: 16, Part D: 8)	Part A: Crossover, tirzepatide SC 5 mg lyophilized vs tirzepatide SC 5-mg solution Part C: 10 mg Tirzepatide SC QW • Weeks 1 to 2: 5 mg • Week 3: 7.5 mg • Week 4: 10 mg Part D: Tirzepatide IV 0.5-mg single dose bolus with lyophilized formulation	PopPK
GPGS (single)	A single-center, open-label, randomized, 2-period, 2-sequence, crossover study to compare the PK of	Healthy participants (45)	Tirzepatide SC single dose 5 mg with solution in PFS vs tirzepatide SC single dose 5 mg with solution in AI	PopPK

Source: Applicant's Population PK/PD Report, Table7.1, pages 23-29. (continued on next page)

	tirzepatideadministered SC by an AI versus a prefilled syringe.			
GPHI (single)	A single-center, open-label, 3-period, 3-sequence, randomized, crossover study conducted in overtly healthy male and female subjects in 2 BMI groups (low and high). • Low BMI: 18.5 to 27.0 kg/m^2 • High BMI: 27.1 to 45.0 kg/m^2.	Healthy participants (54)	Tirzepatide SC single dose 5 mg in the upper arm, thigh, or abdomen with solution in AI	PopPK
Phase 2 Studies				
GPGB (26 weeks)	A multicenter, randomized, double-blind, parallel, placebo- and active comparator-controlled 26-week study with tirzepatide compared with dulaglutide 1.5 mg or placebo in patients with T2DM.	T2DM (316)	Cohort 1: 1 mg Tirzepatide SC QW • Weeks 1 to 26: 1 mg Cohort 2: 5 mg Tirzepatide SC QW • Weeks 1 to 26: 5 mg Cohort 3: 10 mg Tirzepatide SC QW • Weeks 1 to 2: 5 mg • Weeks 3 to 26: 10 mg Cohort 4: 15 mg Tirzepatide SC QW • Weeks 1 to 2: 5 mg • Weeks 3 to 6: 10 mg • Weeks 7 to 26: 15 mg All with lyophilized formulation	PopPK & Exp-Resp
GPGF (12 weeks)	A multicenter, randomized, double-blind, parallel, placebo-controlled, 12-week titration study in patients with T2DM.	T2DM (111)	Cohort 1: 15 mg-1 Tirzepatide SC QW • Weeks 1 to 2: 2.5 mg • Weeks 3 to 4: 5 mg • Weeks 5 to 8: 10 mg • Weeks 9 to 12: 15 mg Cohort 2: 15 mg-2 Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 7.5 mg • Weeks 9 to 12: 15 mg Cohort 3: 12 mg Tirzepatide SC QW • Weeks 1 to 4: 4 mg • Weeks 5 to 8: 8 mg • Weeks 9 to 12: 12 mg All with lyophilized formulation	PopPK & Exp-Resp

Source: Applicant's Population PK/PD Report, Table7.1, pages 23-29. (continued on next page)

Global Phase 3 Studies				
GPGK (SURPASS-1) (40 weeks)	A multicenter, randomized, double-blind, parallel, placebo-controlled, 40-week study in patients with T2DM naive to diabetes injectable therapy.	T2DM (478)	Cohort 1: 5 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 40: 5 mg Cohort 2: 10 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 40: 10 mg Cohort 3: 15 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 40: 15 mg All with solution formulation in AI	PopPK & Exp-Resp
GPGL (SURPASS-2) (40 weeks)	A multicenter, randomized, parallel, open-label comparator 40-week study comparing tirzepatide versus semaglutide in patients with T2DM.	T2DM (1878)	Cohort 1: 5 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 40: 5 mg Cohort 2: 10 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 40: 10 mg Cohort 3: 15 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 40: 15 mg All with solution formulation in AI	PopPK & Exp-Resp
GPGH (SURPASS-3) (52 weeks)	A multicenter, randomized, parallel, open-label comparator 52-week study comparing tirzepatide versus insulin degludec in patients with T2DM.	T2DM (1437)	Cohort 1: 5 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 52: 5 mg Cohort 2: 10 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg	PopPK & Exp-Resp

Source: Applicant's Population PK/PD Report, Table7.1, pages 23-29. (continued on next page)

			• Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 52: 10 mg Cohort 3: 15 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 52: 15 mg All with solution formulation in AI	
GPGM (SURPASS-4) (104 weeks)	A multicenter, randomized, parallel, open-label comparator 104-week study comparing tirzepatide versus insulin glargine in patients with T2DM with increased CV risk.	T2DM (1995)	Cohort 1: 5 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 104: 5 mg Cohort 2: 10 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 104: 10 mg Cohort 3: 15 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 104: 15 mg All with solution formulation in PFS	PopPK & Exp-Resp
GPGI (SURPASS-5) (40 weeks)	A multicenter, randomized, double-blind, parallel, multinational, placebo-controlled 40-week study in patients with T2DM receiving titrated basal insulin glargine (with or without metformin).	T2DM (475)	Cohort 1: 5 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 40: 5 mg Cohort 2: 10 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 40: 10 mg Cohort 3: 15 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg	PopPK & Exp-Resp

Source: Applicant's Population PK/PD Report, Table7.1, pages 23-29. (continued on next page)

			• Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 40: 15 mg All with solution formulation in AI	
Regional Phase 3 Studies				
GPGO (SURPASS J-mono) (52 weeks)	A multicenter, randomized, double-blind, parallel, active-controlled, 52-week study of tirzepatide monotherapy in patients with T2DM.who had discontinued OAM monotherapy or were OAM-naïve.	T2DM - Japan (636)	Cohort 1: 5 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 52: 5 mg Cohort 2: 10 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 52: 10 mg Cohort 3: 15 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 52: 15 mg All with solution formulation in AI	PopPK & Exp-Resp
GPGP (SURPASS J-combo) (52 weeks)	A multicenter, randomized, add-on treatment, parallel, 52-week study in patients with T2DM taking OAMs.	T2DM - Japan (443)	Cohort 1: 5 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 52: 5 mg Cohort 2: 10 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 52: 10 mg Cohort 3: 15 mg Tirzepatide SC QW • Weeks 1 to 4: 2.5 mg • Weeks 5 to 8: 5 mg • Weeks 9 to 12: 7.5 mg • Weeks 13 to 16: 10 mg • Weeks 17 to 20: 12.5 mg • Weeks 21 to 52: 15 mg	PopPK & Exp-Resp

Abbreviations: AI = autoinjector; BMI = body mass index; CV = cardiovascular; ESRD = end stage renal disease; Exp-Resp = exposure-response analysis; IV = intravenous; MAD = multiple-ascending dose; MD = multiple dose; N = number of subjects; OAM = oral antihyperglycemic medication; PD = pharmacodynamics; PFS = prefilled syringe; PK = pharmacokinetics; PopPK = population pharmacokinetics; QW = once weekly; SAD = single-ascending dose; SC = subcutaneous; T2DM = type 2 diabetes mellitus.

Source: Applicant's Population PK/PD Report, Table7.1, pages 23-29.

Table 3. Summary of Baseline Demographic Characteristics

	N, Mean ± SD (Minimum – Maximum)				
	Phase 1		Phase 2	Phase 3	Combined
	Not T2DM Participant	T2DM Patient	T2DM Patient		
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)	6248, 57.4 ± 10.9 (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)	6248, 32.1 ± 6.35 (18.8 – 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)	6248, 89.4 ± 20.4 (43.1 – 227)
Fat Body Mass [a] (kg)	338, 23.8 ± 9.99 (8.22 – 72.2)	183, 28.3 ± 11.5 (9.18 – 63.4)	373, 34.3 ± 13 (13.1 – 82.3)	5354, 33.9 ± 13.9 (10.3 – 128)	6248, 33.2 ± 13.8 (8.22 – 128)
Lean Body Mass [b] (kg)	338, 55.7 ± 9.84 (33.5 – 81.7)	183, 57.9 ± 10.4 (34.9 – 82.5)	373, 56.7 ± 12.4 (30.4 – 88.4)	5354, 56.1 ± 11.7 (27.8 – 108)	6248, 56.2 ± 11.6 (27.8 – 108)
T2DM Duration (years)	NA	183, 10.2 ± 5.32 (1.02 – 25)	373, 8.59 ± 6.14 (0.5 – 38.4)	5353, 9.07 ± 6.93 (0.003 – 59.7)	5909, 9.08 ± 6.84 (0.003 – 59.7)
Fasting Glucose (mmol/L)	338, 5.20 ± 0.583 (3.3 – 8.2)	109, 9.62 ± 2.24 (3.7 – 17.5)	373, 9.48 ± 2.92 (4.5 – 23.2)	5330, 9.51 ± 2.75 (2.44 – 28)	6150, 9.27 ± 2.85 (2.44 – 28)
Hemoglobin A1c (%)	NA	174, 8.05 ± 0.764 (6.50 – 10.3)	373, 8.21 ± 1.01 (5.80 – 12.4)	5353, 8.31 ± 0.957 (5.20 – 15.8)	5900, 8.30 ± 0.957 (5.20 – 15.8)
GFR ($mL/min/1.73m^2$)	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)	6002, 92.7 ± 19.2 (6.25 – 173)
AST (IU/L)	337, 21.9 ± 9.8 (9 – 110)	182, 22.8 ± 11.0 (6 – 84)	373, 24.3 ± 28.6 (8 – 534)	5350, 22.9 ± 12.4 (6 – 171)	6242, 22.9 ± 13.7 (6 – 534)
ALT (IU/L)	337, 21.9 ± 11.9 (5 – 83)	182, 30.0 ± 18.2 (7 – 108)	373, 29.4 ± 30.1 (7 – 527)	5349, 28.7 ± 17.7 (5 – 288)	6241, 28.4 ± 18.5 (5 – 527)
Albumin (g/dL)	338, 42.5 ± 3.87 (26 – 51)	182, 42.6 ± 2.75 (35 – 49)	373, 44.3 ± 2.76 (37 – 52)	1915[c], 45.4 ± 2.85 (32 – 55)	2808, 44.7 ± 3.17 (26 – 55)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; BMI = body mass index; BW = body weight; FBM = fat body mass; GFR = glomerular filtration rate; LBM = lean body mass; SD = standard deviation; T2DM = type 2 diabetes mellitus.

[a] FBM = BW – LBM (Janmahasatian et al. 2005).

[b] $LBM_{female} = (9270*BW)/(8780 + 244*BMI)$; $LBM_{male} = (9270*BW)/(6680 + 216*BMI)$ (Janmahasatian et al. 2005).

[c] Albumin was not collected in Phase 3 Studies GPGH and GPGL.

Source: Applicant's Population PK/PD Report, Table7.5, pages 42-43. (continued on next page)

	Percent of Population (%)				
	Phase 1		Phase 2	Phase 3	Combined
	Healthy Participant	T2DM Patient	T2DM Patient		
Concomitant Diabetes Medication					
AGI	NA	0	0	1	1
DPP-4 Inhibitor		3	<1	<1	<1
GLP-1 Analog		0	4	<1	<1
Insulin		<1	1	7	6
Metformin		64	81	47	47
SGLT2 Inhibitor		2	<1	14	12
Sulfonylurea		0	2	10	9
Thiazolidinedione		0	0	1	1
None Reported		30	10	19	23
Ethnicity					
Hispanic	17	28	49	37	36
Not Hispanic	82	72	44	42	45
Not Reported	2	0	7	21	18
Formulation					
Lyophilized Powder	30	95	100	0	10
Solution	70	5	0	100	90
Injection Device					
Auto Injector	22	0	0	81	71
Manual Syringe	54	98	100	0	12
Prefilled Syringe	24	2	0	19	17
Injection Site					
Abdomen	85	100	100 [a]	0	8
Arm	5	0	0	0	<1
Thigh	5	0	0	0	<1
Not Reported	5	0	0	100	92
Race					
American Indian	0	<1	5	7	6
Asian	39	31	2	24	24
Black	22	4	11	3	5
Multi-racial	<1	0	2	<1	<1
Hawaiian/Pacific Islander	0	0	<1	<1	<1
White	38	64	79	65	64
Not Reported	0	0	<1	<1	<1
Sex					
Female	28	27	44	43	42
Male	72	73	56	57	58
Subrace					
Japanese	0	26	0	20	18
Not Japanese	40	44	32	50	48
Not Reported	60	30	68	30	36

Abbreviations: AGI = alpha-glucosidase inhibitor; DPP = dipeptidyl peptidase; GLP-1 = glucagon-like peptide; NA = not applicable; SGLT = sodium glucose co-transporter; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

a Injection site was not collected in the Phase 2 studies. Per the protocols, patients were instructed to inject in the abdomen only

Source: Applicant's Population PK/PD Report, Table7.6, pages 44.

Base PK model

The pharmacokinetics of tirzepatide was best described by a 2-compartment distribution model with linear elimination from the central compartment. The SC absorption of tirzepatide was characterized as first-order process without lag time. The PK model was parameterized in terms of clearance (CL), central and peripheral volumes of distribution (Vc and Vp respectively), intercompartmental clearance (Q), absorption rate constant (Ka) and absolute bioavailability (F1). Interindividual (or between-subject) variability (IIV) was estimated on CL, Vc, Ka and on the proportional residual error. The residual error model consisted of a proportional error model.

Covariates Analysis

Age, sex, total body weight (WT) and fat free mass (FFM, Janmahasatian S, et al. Clin Pharmacokinet. 2005; 44(10): 1051-1065), body mass index (BMI), formulation (lyophilized vs. solution), injection device(syringe vs. autoinjector), race, ethnicity (Hispanic vs. non-Hispanic, Japanese vs. non-Japanese), anti-drug antibodies (ADA), albumin, aspartate and alanine transaminases, eGFR (estimated glomerular filtration using the CKD-EPI formula of the National Institute of Health at https://www.niddk.nih.gov/.../ckd-epi-adults-conventional-units) were the examined covariates during covariate model selection.

The following covariates were retained in the final PK model:

- WT (time varying covariate) on CL and Q, using a power model centered at 70 kg.
- FFM and an estimated fraction of the fat mass (time varying covariates) on Vc and Vp, using a power model centered at 70 kg.
- Formulation (lyophilized) on Ka, using a proportional model.
- Study effect (other than study GPGE) on F1 (F1 fixed to 80% for SC formulations as determined from study GPGE for a 5 mg single SC dose relative to a single 0.5 mg IV bolus dose).

Final model

The parameter estimates from the final popPK model for tirzepatide are listed in Table 4. According to the popPK model, for an average 70 kg individual receiving the SC solution formulation (single dose pen), the population estimates for tirzepatide CL, Vc, Q, Vp, F1 and Ka are 0.0329 L/h (0.79 L/day), 2.47 L, 0.126 L/h, 3.98 L and 66% (absolute bioavailability) and 0. 0373 h^{-1}, respectively.

The estimated interindividual variability (IIV) expressed as coefficient of variation (%CV) were 14.2%, 49% and 22.5% for CL, Vc, and Ka, respectively. The interindividual random effect (ETA) shrinkage from the final popPK model was 10.5%, 21% and 56.9% for CL, Vc and Ka.

Table 4. Parameter Estimates from the Final Population PK Model

Parameter	Base model Estimate Median (95% CI)[a]	Final model Estimate Median (95% CI)[a]
Bioavailability (F, fraction, Θ_1)	0.8 fixed	0.8 fixed
Absorption rate (ka, 1/h, Θ_2)	0.0361 0.0363 (0.0287, 0.0448)	0.0373 0.0370 (0.0289, 0.0460)
Clearance (CL, L/h, Θ_3)	0.0326 0.0326 (0.0311, 0.0341)	0.0329 0.0329 (0.0313, 0.0342)
Intercompartmental clearance (Q, L/h, Θ_5)	0.125 0.126 (0.101, 0.143)	0.126 0.125 (0.101, 0.144)
Central volume of distribution (Vc, L, Θ_4)	2.47 2.48 (2.07, 2.98)	2.47 2.46 (2.05, 2.92)
Peripheral volume of distribution (Vp, L, Θ_6)	3.93 3.91 (3.48, 4.17)	3.98 3.98 (3.56, 4.21)
Covariate Effects		
Covariate effect on F[b] Relative study effect (Θ_{10})	 -0.189 -0.191 (-0.226, -0.153)	 -0.181 -0.181 (-0.220, -0.147)
Covariate effect on CL and Q[c] Body weight (kg)	 0.8 fixed	 0.8 fixed
Covariate effect on Vc and Vp[d] Body weight (kg) Fraction fat mass (Θ_9)	 1 fixed 0.487 0.488 (0.450, 0.530)	 1 fixed 0.482 0.483 (0.447, 0.524)
Covariate effect on ka[e] Lyophilized formulation (Θ_{11})	 NA	 -0.161 -0.161 (-0.207, -0.107)
Interindividual variability CV%		
ka (Ω_2)	25.6% 25.7 (19.4, 31.5)	22.5% 22.1 (14.9, 28.7)
CL (Ω_3)	14.1% 14.1 (13.7, 14.6)	14.2% 14.2 (13.7, 14.7)
Vc (Ω_4)	48.3% 48.0 (37.6, 60.5)	49.0% 49.5 (38.3, 62.3)
Proportional residual (Ω_7)	57.9% 57.9 (56.0, 60.0)	58.1% 58.0 (56.1, 60.0)
Residual variability		
Proportional (%)	20.6% 20.6 (20.2, 20.9)	20.6% 20.6 (20.3, 21.0)

Abbreviations: BW = body weight; CI = bootstrap-derived confidence interval; CL = clearance; CV = coefficient of variation; F = bioavailability; FAT = fat mass (kg); FFM = fat-free mass (kg); ka = absorption rate constant; Q = intercompartmental clearance; Vc = central volume of distribution; Vd = volume of distribution; Vp = peripheral volume of distribution; NA = not applicable.

[a] Median and 95% CI derived from bootstrap analysis (Section 8.3.3.1).

[b] $F = \Theta_1 * (1 + \Theta_{10})$ where Θ_1 is the bioavailability value from Study GPGE and Θ_{10} is the relative fraction.

[c] iCL = pCL * (BW/70)^0.8 where iCL is an individual's CL, pCL is the population CL, and BW is an individual's BW. The described structure was applied to CL and Q.

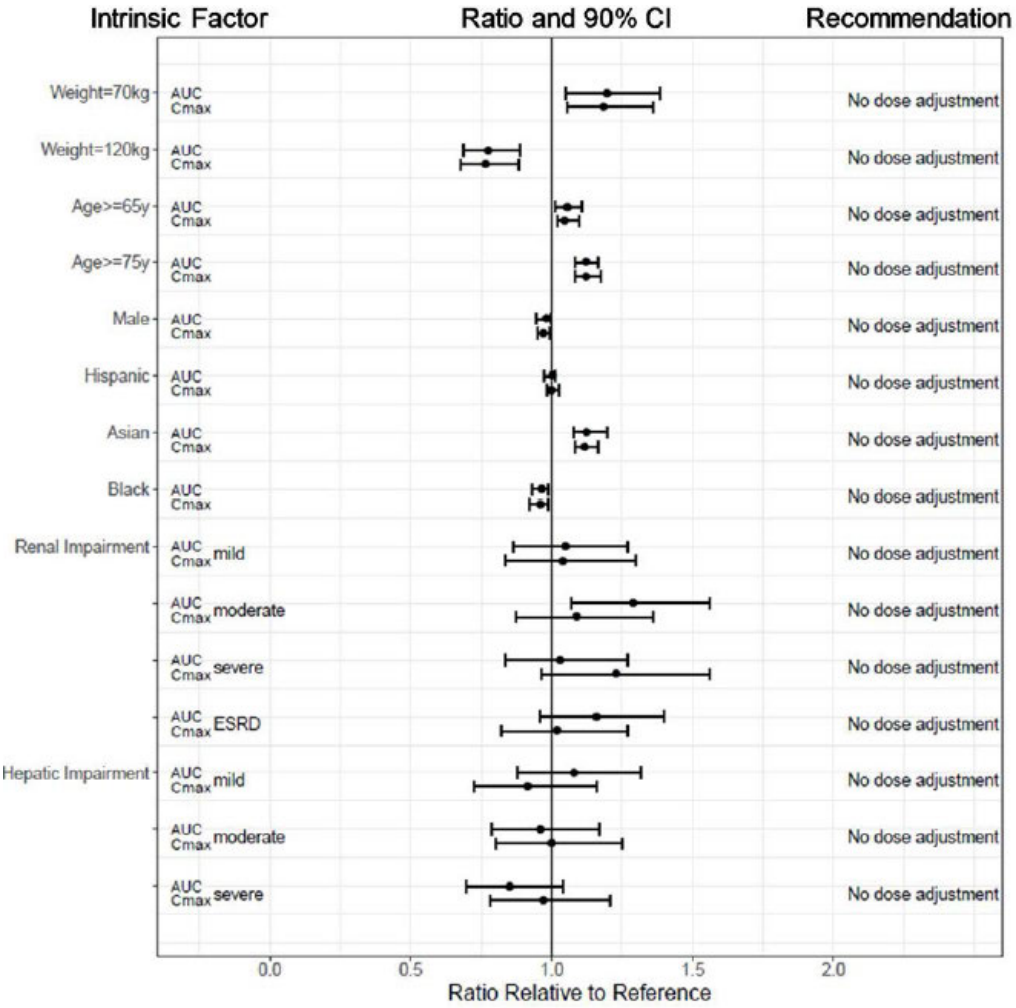
[d] iVd = pVd * [(FFM + FAT* Θ_9)/70]^1 where iVd is an individual's Vd, pVd is the population Vd, FFM is an individual's FFM, FAT is an individual's FAT, and Θ_9 is a fraction. The described structure was applied to Vc and Vp.

[e] ika = pka * (1 + Θ_{11}) where ika is an individual's ka, pka is the population ka, and Θ_{11} is a fraction.

Source: Applicant's Population PK/PD Report, Table 9.2, page 68.

Body weight was the only statistically and clinically relevant covariate driving the differences in tirzepatide exposure. According to the Applicant's PK model and simulations, relative to a 90 kg subject, tirzepatide exposure (C_{max} and AUC) are expected to be 23% higher and 21% lower in a 70 kg and 120 kg subject, respectively (Figure 1). However, based on the moderate differences (about 30%) in exposure, no dose adjustment is required based on body weight. The effect of age, sex, ethnicity, organ impairment as well as ADA were not found to have a statistically significant effect on the PK of tirzepatide.

Figure 1. Forest Plot for the Effect of Intrinsic Covariates on Tirzepatide exposure



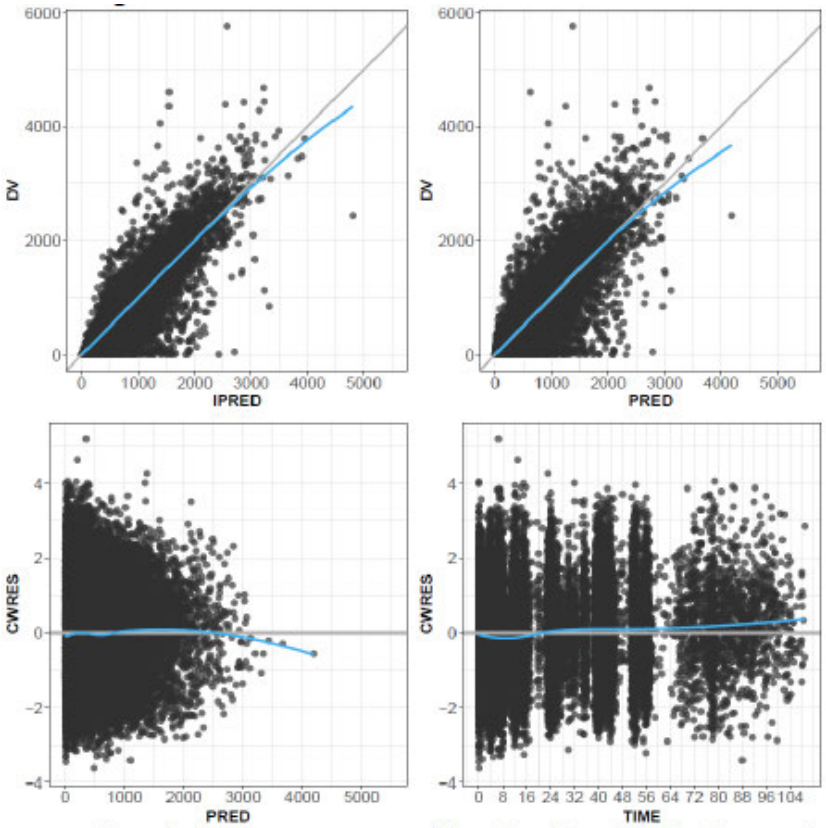
Abbreviations: AUC = area under the concentration versus time curve; CI = confidence interval; Cmax = maximum observed drug concentration; ESRD = end stage renal disease.

Note: Reference values for weight, age, sex, and race comparisons are 88 kg, 55 years old, female, and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function from the respective clinical pharmacology studies. The body weights 70 and 120 kg were the 10th and 90th percentiles of the Phase 3 population. The median body weight for groups: (Age>=65y) 82kg; (Age>=75y) 76kg; (Male) 89kg; (Hispanic) 86kg; (Asian) 76kg; (Black) 91kg

Source: Applicant's Population PK/D Report, Figure 10.4, page 124.

The goodness-of-fit (GOF) plots from the final popPK model, are shown in Figure 2. The plots of the observed concentrations versus population predicted as well as the individual predicted concentrations show random normal scatter around the identity lines, indicating absence of systematic bias. The conditional weighted residuals versus time after dose or versus population predicted concentrations show random normal scatter around zero with no specific trend, indicating no major model misspecifications.

Figure 2. Goodness of Fit Plots from the Final PK Model

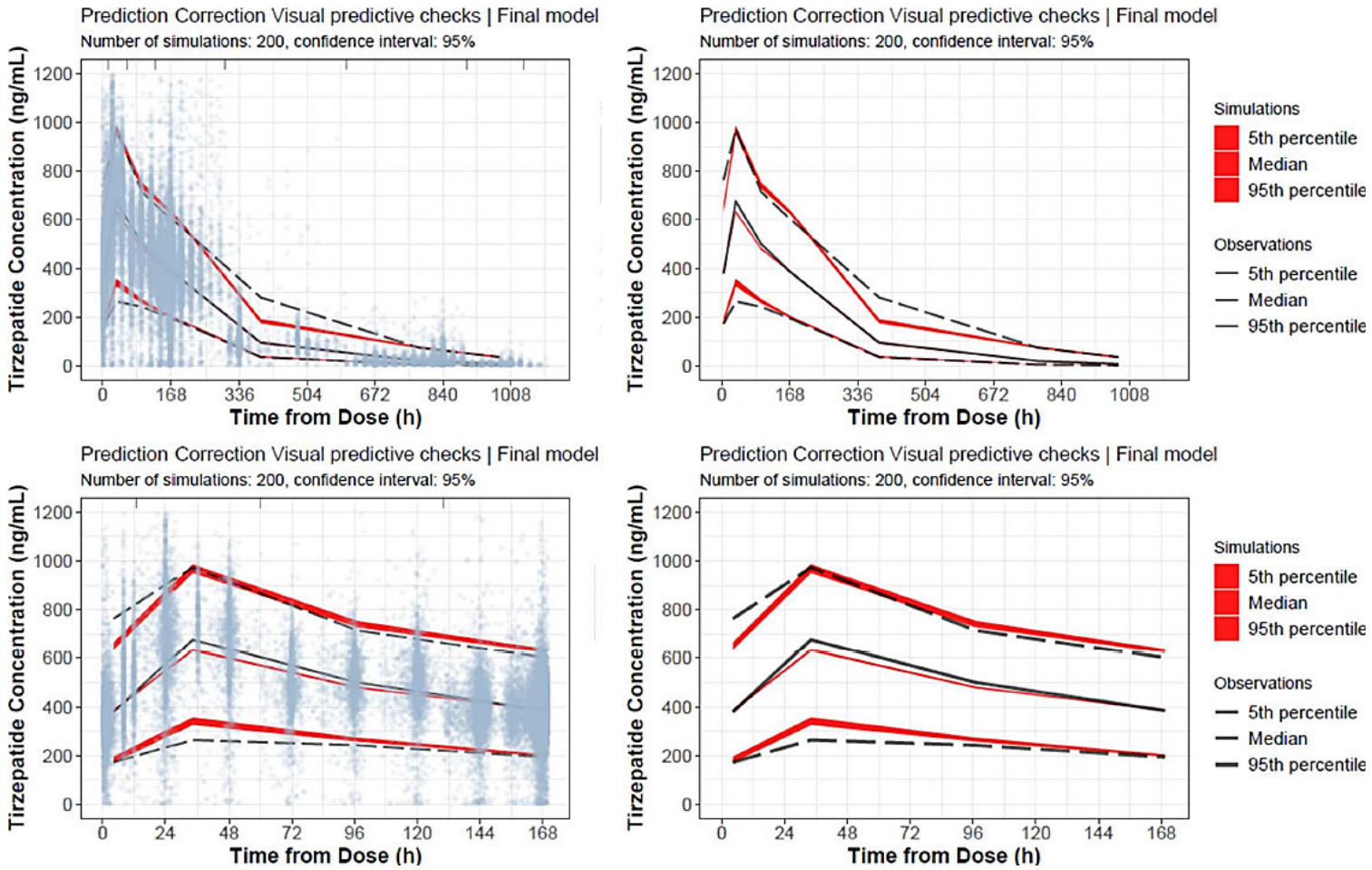


Abbreviations: CWRES = conditional weighted residual; DV = dependent variable (tirzepatide concentration, ng/mL); IPRED = individual prediction; PRED = population prediction; PK = pharmacokinetics; TIME = time from first dose (weeks)

Source: Applicant's Population PK/D Report, Figure ATT.9, page 356.

The prediction-corrected visual predictive check (pcVPC) plots (Figure 3) of concentrations versus time showed a reasonable agreement between the observed and simulated data, with the absence of overt bias. Due to the large number of observations which are incorporated into the simulation replicates (200 replicate of the original dataset with 39644 observations from 5811 subjects), the 95% CI of the 5th, 50th, and 95th percentiles of the simulation were narrow. Overall, the 95% CI bands for simulation of the 5th, 50th, and 95th percentiles corresponded with the observation percentiles. Although modest differences are visually detected between the simulation and observation percentiles, the numerical differences are small.

Figure 3. Prediction-Corrected Visual Predictive Check for the Final PK Model



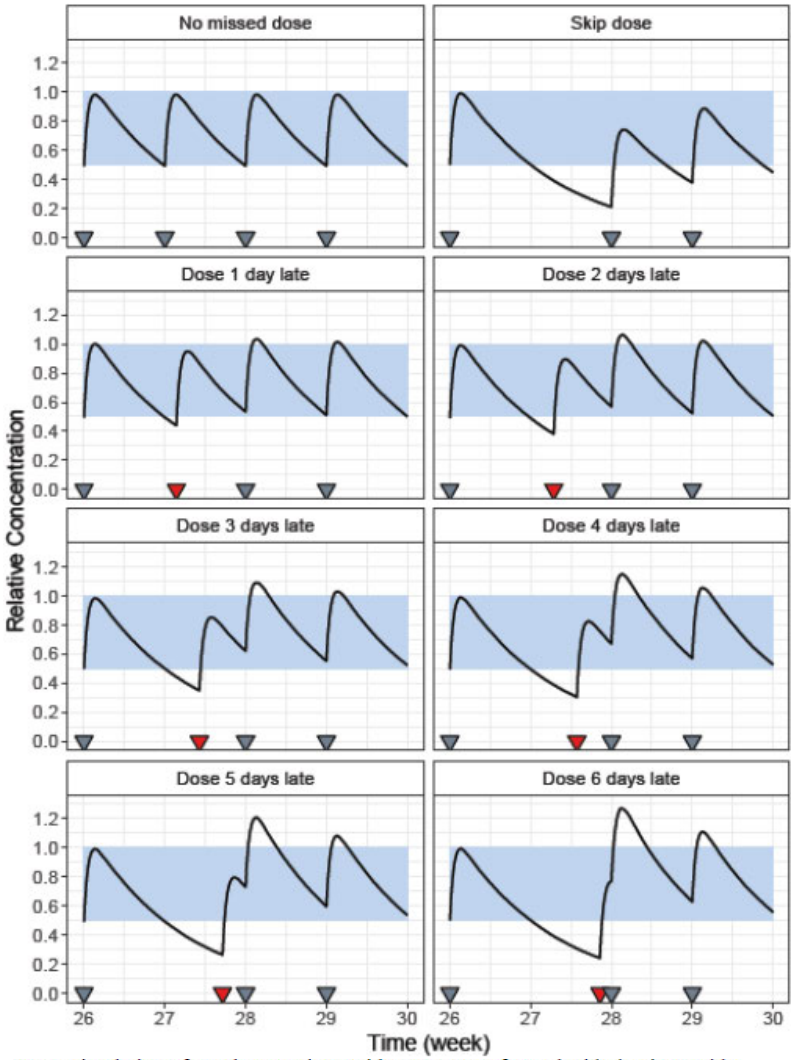
Note: dots represent the observed PK data. Top panels: prediction-corrected concentrations up to 6 weeks (1008 hours) post-dose with (left) and without (right) observed data. Bottom panels: prediction-corrected concentrations up to 1 week (168 h) after tirzepatide dose. The black lines represent the median (solid line), 5th and 95th percentiles (dashed lines) of the observed data. The red narrow bands represent the 95%CI of the median, 5th and 95th percentiles of the simulated concentrations (based of 200 dataset replicates).

Source: Applicant's Response to Information Request on PK model evaluation (01 February 2022), Figure 5.6, page 16.

Application of the PK Model to Justify Handling Missed Doses

The tirzepatide PK model was used to perform simulations to illustrate the impact of administering a tirzepatide dose at different times (1 to 6 days) after a missed scheduled weekly dose (Figure 4). The simulation results showed that if a tirzepatide dose is missed, it should be administered as soon as possible within 4 days after the day of missed dose. Administration of tirzepatide dose within 4 days of the missed dose resulted in <20% increase in C_{max} associated with the subsequent scheduled dose. If more than 4 days have passed, it is recommended that the missed dose be skipped and to resume the regular weekly (QW) dosing schedule by administering tirzepatide on the next regularly scheduled day.

Figure 4. Median Tirzepatide Exposure Under Various Dosing Delays and Handling dosing Delays



Note: Simulation of steady-state tirzepatide PK was performed with the tirzepatide population PK model. Solid black lines denote the simulation median, gray triangles denote once-weekly tirzepatide dosing interval, red triangles denote tirzepatide dosing time beyond 1 week after a dose. The y-axis is tirzepatide concentration relative to the maximum concentration of the PK profile. The shaded area denote the interval between minimum and maximum concentration of the steady-state PK profile.

Source: Applicant's Population PK/D Report, Figure 10.6, page 126.

Reviewer's Assessment of the Population PK Analysis

- The Applicant's PK model appropriately describes the observed tirzepatide concentrations from the conducted clinical studies and is appropriate for evaluating the effects of covariates of tirzepatide PK and for performing model based predictions of PK.
- The PK parameters from the final model were estimated with good precision, with relative standard errors (%RSE) of the typical PK parameters less than 15.8%.
- Among the PK parameters that are affected by the identified covariates, the ETA shrinkage was low for CL (10.4%), Vc (20.9%) and relatively high for Ka (56.8%), which makes the graphical assessment of covariates on Ka parameter less reliable.
- The residual error (Epsilon) shrinkage was low (3.1%), indicating the informativeness of the GOF to diagnose structural and residual error model misspecifications.
- The evaluation of the overall GOF plots as well as the GOF plots by study showed that the Applicant final PK model adequately described the entire range of concentrations from all studies with no major bias.
- The pcVPC plots show that overall, the variability in the data (quantified by the 5th and 95th percentiles) was reasonably well captured and described for tirzepatide. The observed and simulated PK profiles for tirzepatide are in good agreement, with the 5th, 50th and 95th percentiles of the prediction-corrected observed concentrations (black solid and dashed lines) are encompassed within the 95%CI of the 5th, 50th and 95th percentiles of the prediction-corrected simulated concentrations (red areas), during the entire weekly dosing interval.
- No statistically significant relationship between ADA and CL was detected when ADA status or ADA titer was tested as a covariate.
- The Applicant's model used total WT as covariate on CL and Q (allometric relationship), but FFM as covariate on Vc and Vp with an estimated typical contribution of fat mass of 48% on Vc and Vp. An alternative simplified PK model that uses total WT as covariate on both volumes of distributions parameters, resulted in a higher objective function value (OFV) compared to the Applicant PK model (difference in OFV of 542 points). However, the impact on the individual predicted concentrations was minimal, suggesting that a simplified PK model that uses of total WT as a covariate on both clearances and volumes of distribution is acceptable for model based simulations.
- Body weight was the only covariate affecting CL and Vc. However, no dose adjustment is required based on body weight due to the moderate differences (less than 30%) in exposure in patients with body weight ranging from 70 to 120 kg (representing 10^{th} and 90^{th} percentiles of WT in the studied Phase 3 population) compared to a 90 kg patient (median of observed WT). For the lowest observed WT value of about 45 kg, mean tirzepatide exposure is expected to be 75% higher compared to a 90 kg patient. However, given the efficacy and safety profiles under the lowest starting dose of 2.5 mg as well as the proposed gradual titration of tirzepatide treatment (that will allow to control for potential adverse events) no further dose adjustment is likely needed.
- The Applicant's proposal to administer tirzepatide as soon as possible. within 4 days of a missed dose, or to skip the dose before resuming the regular QW regimen If more than 4 days have passed is acceptable.

2. Population Pharmacokinetic-Pharmacodynamic Analyses

Fasting Glucose and HbA1c Model

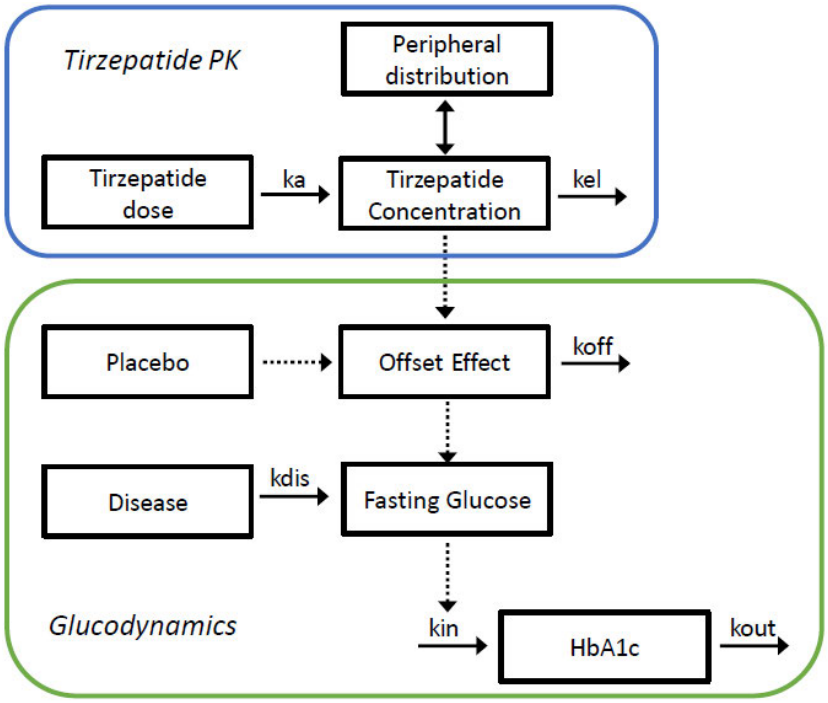
The Exposure-response analysis characterizing the effect of tirzepatide on fasting glucose (FG) and HemoglobinA1c (HbA1c) was based on observations from 9 (Phase 2 and Phase3) studies (Table 2). The final analysis dataset included 50256 FG observations and 48481 HbA1c observations from 5562 patients. Approximately 95% of FG and HbA1c observations were collected up to 67 weeks after start of tirzepatide treatment. A training dataset that consisted of 9030 FG observations and 8804 HbA1c observations from 2708 patients (approximately 200 to 300 patients randomly selected from each of the 9 studies) was used for the PK-PD model development. The PK-PD model evaluation (bootstrap and VPC) used the full dataset.

Base PK-PD model

A sequential modeling approach was used to characterize the effect of tirzepatide on FG and HbA1c. Individual predicted PK parameters from the tirzepatide popPK model were integrated with the FG and HbA1c observations.

The time course of HbA1c response was driven by FG concentrations through a linked model that fitted both FG and HbA1c data jointly (Figure 5). A disease progression model that integrated an offset compartment where tirzepatide and placebo effects were introduced was utilized to describe FG response over time. The time course of HbA1c was described using an indirect response model dependent on FG. A schematic representation of the tirzepatide PK model linked to the glucodynamics of FG and HbA1c is depicted in Figure 5 below.

Figure 5. Schematic of the Structural PK-PD Model Linking Tirzepatide PK to the Fasting Glucose and HbA1c responses:



Abbreviations: HbA1c = hemoglobin A1c; ka = absorption rate constant; kdis = disease progression rate; kel = elimination rate constant; kin = input rate; kout = degradation rate constant; koff = offset rate constant; PK = pharmacokinetics.
Note: The solid arrows denote rates or rate constants. The dashed arrows denote an effect.

Source: Applicant's Population PK/PD Report, Figure 8.1, page 50.

The system of equations that describe the PD (FG-HbA1c) model are provided below:

Fasting Glucose Disease Progression Model

$$\frac{dDisease}{dt} = K_{DIS}$$

$$\frac{dOffset}{dt} = K_{OFF} \times (Effect - Offset)$$

$$FPG = Disease \times (1 - Offset)$$

Where Disease is the projected FPG value in the absence of therapy, K_{DIS} is the rate of disease progression, Offset is the symptomatic therapy effect, Effect is the magnitude of drug effect, and K_{OFF} is the rate constant for delay in drug effect.

Tirzepatide Drug Effect on Fasting Glucose

$$Effect_{Drug} = \frac{Emax \times C_p^{\gamma}}{EC_{50}^{\gamma} + C_p^{\gamma}}$$

Where Cp is the tirzepatide plasma concentration, Emax is the maximum response, EC50 is the concentration at half-maximal response for tirzepatide, γ is the hill coefficient.

HbA1c Turnover Model

$$\frac{dHbA1c}{dt} = K_{IN} \times FPG^{\varphi} - K_{OUT} \times HbA1c$$

Where KIN is the formation rate of HbA1c, φ is the FPG exponent, and K_{OUT} is the degradation rate constant of HbA1c.

$$K_{IN} = \frac{(K_{OUT} * E0_H)}{(E0_G)^{\varphi}}$$

Where E0H is the baseline HbA1c, E0G is the baseline fasting plasma glucose (FPG) and φ is the FPG exponent.

Maximum Response to Tirzepatide Treatment

$$EMAX = 1 - PLAC - \left(\frac{HLIM}{E0_H}\right)^{\frac{1}{\varphi}}$$

Where PLAC is the placebo response, HLIM is the lower limit for HbA1c, E0H is the baseline HbA1c, and φ is the FPG exponent.

Source: Adapted from the Applicant's Population PK/PD Report, Figure 8.2, page 51, and the Applicant PK-PD model (tzpfga1c-370.mod).

In the Applicant PD model, the maximum drug effect (Emax) on lowering FG (and thus indirectly HbA1c levels) was modeled to be dependent on baseline HbA1c, as patients with a higher baseline HbA1c showed a greater reduction in HbA1c at week 40.

Final PK-PD model

The parameter estimates from the final PK-PD model linking tirzepatide exposure to the effect on FG and HbA1c are listed in Table 5. According to the exposure-response model (FG-HbA1c model), the maximum drug effect (Emax) on lowering FG was estimated to be 38%, resulting in a decrease of FG to 5.73 mmol/L from an estimated population baseline fasting glucose levels (E0G) of 9.24 mmol/L. At Emax, tirzepatide was estimated to lower HbA1c to 5.13% (HLIM parameters), a value considered within normal limits for people without prediabetes or T2DM.

The tirzepatide plasma concentrations responsible for 50% of the maximum drug effect on FG (EC50) was estimated to be 174 ng/mL. The tirzepatide average steady-state concentrations (Css) resulting from the 5 mg, 10mg , and 15 mg once weekly (QW) administration ranged from 491 to 1470 ng/mL, and these concentrations were associated with the attainment of 74% to 89% of the maximal effect on FG. Weight loss (calculated as: WT at each visit - baseline WT) was the only covariate included in the model and found to have a statistically significant effect on EC50, with a decrease in EC50 (i.e., increase in drug potency) with a decrease in body weight over time. For instance, a 5% weight loss is predicted to be associated with an average 29% decrease in EC50.

The ETA shrinkage from the final FG-HbA1c model was 9.9%, 4.3%, 47.4%, 55.2%, 68.1%, 72% and 62.4% for E0G, E0H, PLAC, Koff, Kout, HLIM and EC50, respectively.

Table 5. Parameter Estimates from the Final Population FG-HbA1c Model

Parameter	Base model estimate	Final model estimate Median (95% CI)[a]
Baseline fasting glucose (E0G, mmol/L, Θ_1)	9.23	9.24 9.23 (9.14, 9.32)
Interaction E0G and E0H[b]	0.0181	0.0180 0.0179 (0.0168, 0.0192)
Baseline HbA1c (E0H, %, Θ_2)	8.25	8.25 8.24 (8.21, 8.28)
Placebo fractional reduction of FG (PLAC, Θ_3)	0.0846	0.0630 0.0587 (0.0371, 0.0826)
Response Rates		
Offset rate constant (K_{OFF}, 1/h, Θ_4)	0.00306	0.00509 0.00480 (0.00326, 0.00921)
Interaction K_{OFF} and K_{OUT}[b]	-0.329	-0.248 -0.207 (-0.409, -0.0871)
Turnover rate constant for HbA1c (K_{OUT}, 1/h, Θ_5)	0.00156	0.00137 0.00140 (0.00117, 0.00160)
FG disease progression rate (K_{DIS}, mM/week, Θ_6)	0.0215	0.0160 0.0155 (0.00795, 0.0212)
Concentration-Response		
Exponent for effect of FG on HbA1c (γ, Θ_9)	0.799	0.811 0.805 (0.764, 0.857)
Limit for HbA1c-Emax (HLIM, %, Θ_7)	5.02	5.13 5.15 (5.00, 5.36)
Tirzepatide concentration with 50% of maximal effect (EC50, ng/mL, Θ_8)	144	174 172 (128, 216)
Covariate Effects		
Covariate effect on EC50[c] Exponent for effect of fractional weight change (Θ_{12})	NA	6.88 7.16 (2.68, 13.4)
Interindividual variability CV%		
E0G (Ω_1)	21.0%	20.9% 20.8 (20.1, 21.7)
E0H (Ω_2)	11.3%	11.2% 11.2 (10.9, 11.5)
PLAC (Ω_3) - additive	0.0216	0.0198 0.0199 (0.0153, 0.0252)
K_{OFF} (Ω_4)	147%	156% 149 (128, 173)
K_{OUT} (Ω_5)	42.4%	37.0% 33.0 (21.2, 51.8)
HLIM (Ω_7)	8.1%	6.7% 6.7 (5.4, 8.8)
EC50 (Ω_8)	49.2%	71.6% 69.2 (27.2, 89.7)
Residual error		
Proportional FG (%)	15.7%	15.7% 15.8 (15.3, 16.3)
Proportional HbA1c (%)	4.1%	4.1% 4.1 (3.8, 4.4)

Abbreviations: CI = bootstrap-derived confidence interval; CV = coefficient of variation; EC50 = tirzepatide concentration associated with 50% of maximum effect; Emax = maximum effect; E0G = baseline FG; E0H = baseline HbA1c; FG = fasting glucose; HbA1c = hemoglobin A1c; HLIM = limit for HbA1c-Emax; K_{DIS} = FG disease progression rate; K_{OFF} = offset rate constant; K_{OUT} = turnover rate constant for HbA1c; NA = not applicable; PLAC = placebo fractional reduction of FG; WTB = baseline body weight (kg); WTC = change from baseline body weight (kg).

[a] Median and 95% CI derived from bootstrap analysis.

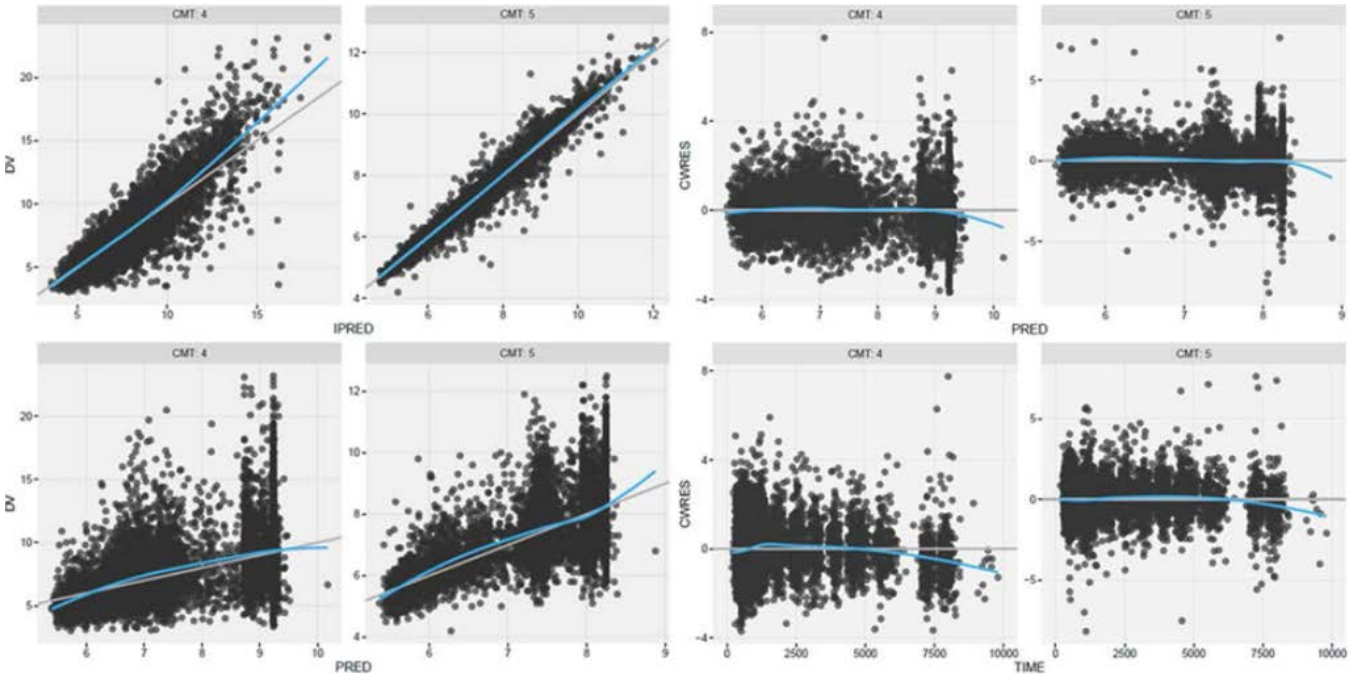
[b] Interaction between IIV terms reported as covariance.

[c] iEC50 = pEC50 * exp(WTC/WTB)^ Θ_{12} where iEC50 is a patient's EC50, pEC50 is the population EC50, and WTC over time and WTB are a patient's change from baseline body weight over time and baseline body weight.

Source: Applicant's Population PK/PD Report, Table 9.3, page 72.

The goodness-of-fit (GOF) plots from the final FG-HbA1c model, are shown in Figure 6. The GOF plots indicate adequate fidelity between model predictions and observed data and the absence of overt bias.

Figure 6. Goodness of Fit Plots from the Final FG-HbA1c Model

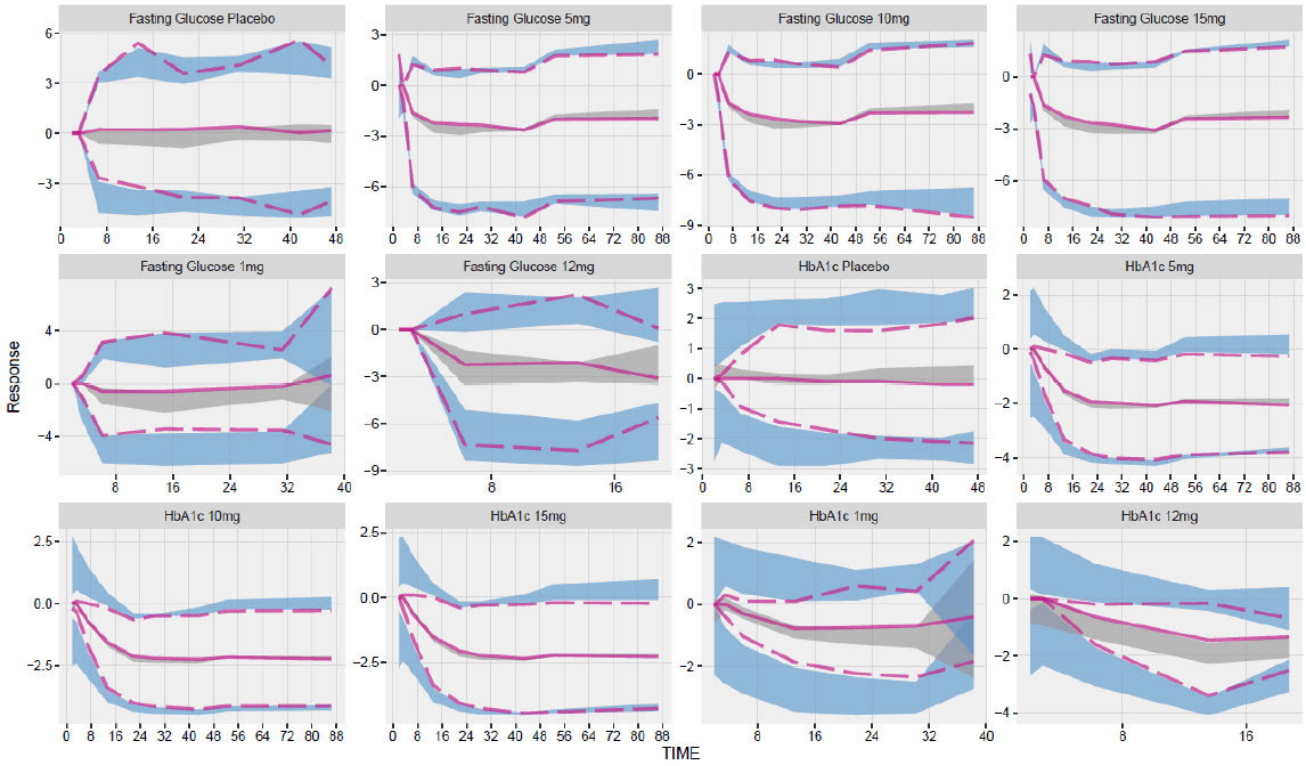


Abbreviations: CMT = compartment (4=FG, 5=HbA1c); CWRES = conditional weighted residual; DV = dependent variable (FG [mmol/L] or HbA1c [%]); FG = fasting glucose; HbA1c = hemoglobin A1c; IPRED = individual prediction; PRED = population prediction; TIME = time from first dose (hours).

Source: Applicant's Population PK/D Report, Figure ATT.14, page 372.

The VPC plots for the final FG-HbA1c model showed good agreement between the full dataset of observed change from baseline and model-predicted FG and HbA1c (Figure 7). The width of the confidence intervals in the VPC were inversely correlated with the amount of data in each stratification. Less data was available for the placebo, 1 mg and 12 mg dose groups and thus, the confidence interval bands appeared wider in these groups compared to the tirzepatide 5 mg, 10 mg, and 15 mg groups.

Figure 7. Visual Predictive Checks for the Change from Baseline in FG and HbA1c from the Final FG-HbA1c Model



Abbreviations: FG = fasting glucose; HbA1c = hemoglobin A1c; VPC = visual predictive check.
Note: The upper dashed line represents the 95th percentile of the observed data. The middle continuous line represents the 50th percentile of the observed data. The lower dashed line represents the 5th percentile of the observed data. The shaded areas represent the model-predicted 95% confidence interval of the corresponding percentiles. Due to their high density, the observed data points have been removed from the plot to increase the clarity of the percentiles.

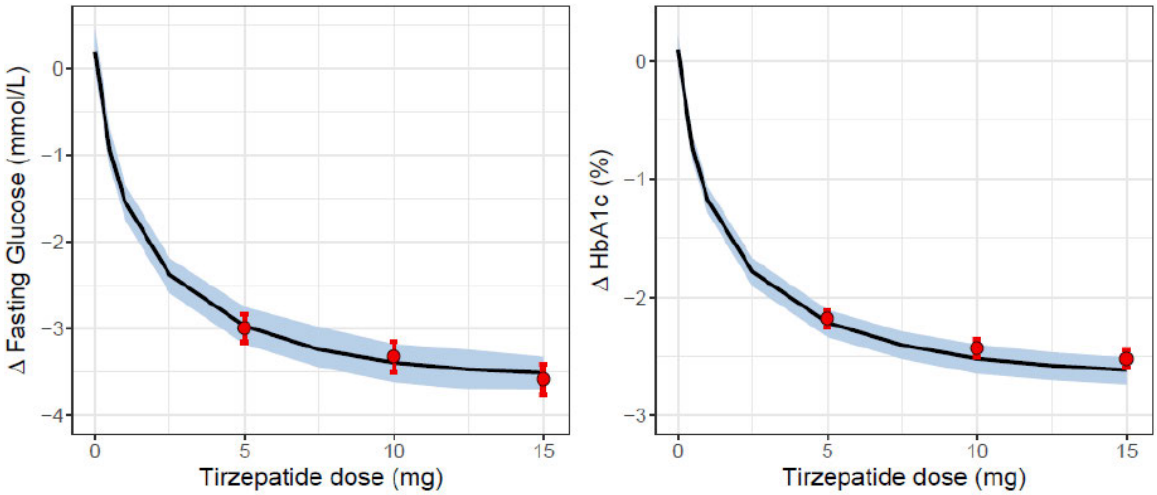
Source: Applicant's Population PK/PD Report, Figure 9.6, page 75.

Application of the FG-HbA1c Model Demonstrating the Dose-dependent Response

The Applicant's simulations performed with the FG-HbA1c model showed that the effect of tirzepatide on FG and HbA1c increased with increasing tirzepatide doses (

Figure 8) with a significant glycemic improvement associated with tirzepatide 5, 10, or 15 mg QW evident after 40 and 52 weeks after the start of tirzepatide treatment.

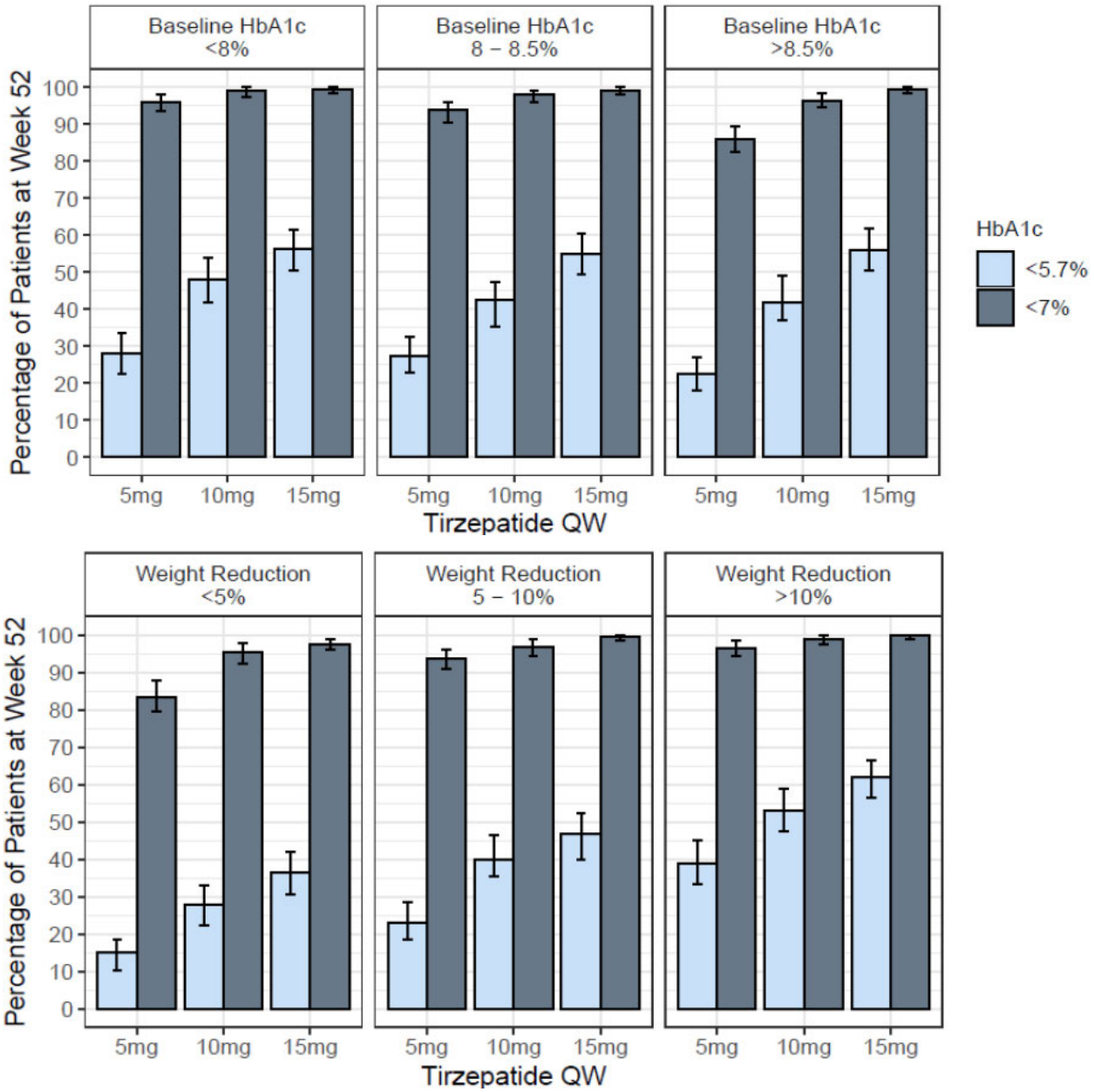
Figure 8. Model-Predicted Change from Baseline in Fasting Glucose and Hb1Ac at Week 52, Across Tirzepatide Doses of 5, 10 and 15 mg



Abbreviations: Δ = change from baseline; HbA1c = hemoglobin A1c.
Note: Solid black lines denote the simulation median and the shaded areas denote the 90% confidence interval. Red circles and error bars denote the mean and 95% confidence interval of observed data.

The FG-HbA1c model simulations showed a dose-dependent glycemic improvement with tirzepatide treatment across a range of baseline HbA1c (Figure 9 upper panel) as well as across categories of body weight reduction (Figure 9 lower panel). Tirzepatide treatment was associated with the attainment of key clinical thresholds for glycemic improvement (HbA1c < 7% and HbA1c < 5.7%). Across the Phase 3 (SURPASS) studies, the percentage of patients with HbA1c < 7% ranged between 81 to 97% and with HbA1c <5.7% ranged between 23 to 62% at Weeks 52.

Figure 9. Model-Predicted Change from Baseline in Hb1Ac at Week 52 Across Tirzepatide Doses of 5, 10 and 15 mg, Stratified by Baseline HbA1c (Upper Panel) and Weight Reduction (Lower Panel)



Abbreviations: HbA1c = hemoglobin A1c; QW = once weekly.
Note: Bar height denotes the simulation median and error bars denote the 90% confidence interval.

Reviewer's Assessment of the Population FG-HbA1c Model

- The Applicant's FG-HbA1c model appropriately describes the observed FG, HbA1c and the change from baseline in FG and HbA1c over time following placebo and tirzepatide treatment.
- The FG-HbA1c model parameters were estimated with good precision, with relative standard errors (%RSE) of the typical PD parameters less than 14.3% for all parameters, except for a relatively higher %RSE of 38.5% for the estimated exponent describing the effect of weight loss on the decrease of EC50.
- The ETA shrinkage was low for the baseline fasting glucose (9.9%) and baseline Hb1Ac (4.3%). However, no covariate effect on these PD parameters was identified from the graphical assessment of covariates plots. The ETA shrinkage was relatively high (47.4% to 72%) for all the other PD parameters. The residual error (Epsilon) shrinkage was low (17.9%).
- Although, the covariate effect on EC50 was relatively less precisely estimated (%RSE 38.5%) and the ETA shrinkage on EC50 was relatively high (62.4%), weight loss was the only identified statistically significant covariate on EC50 (a backward deletion of the covariate increased the OFV by 41.8 points), suggesting a higher potency of tirzepatide with weight loss.
- The Applicant's FG-HbA1c model simulations appropriately captured the observed tirzepatide dose-dependent effect in reducing FG and HbA1c with increasing tirzepatide dose of 5mg, 10 mg and 15 mg QW at week 52, as well as the increasing effect of weight loss on HbA1c reduction.

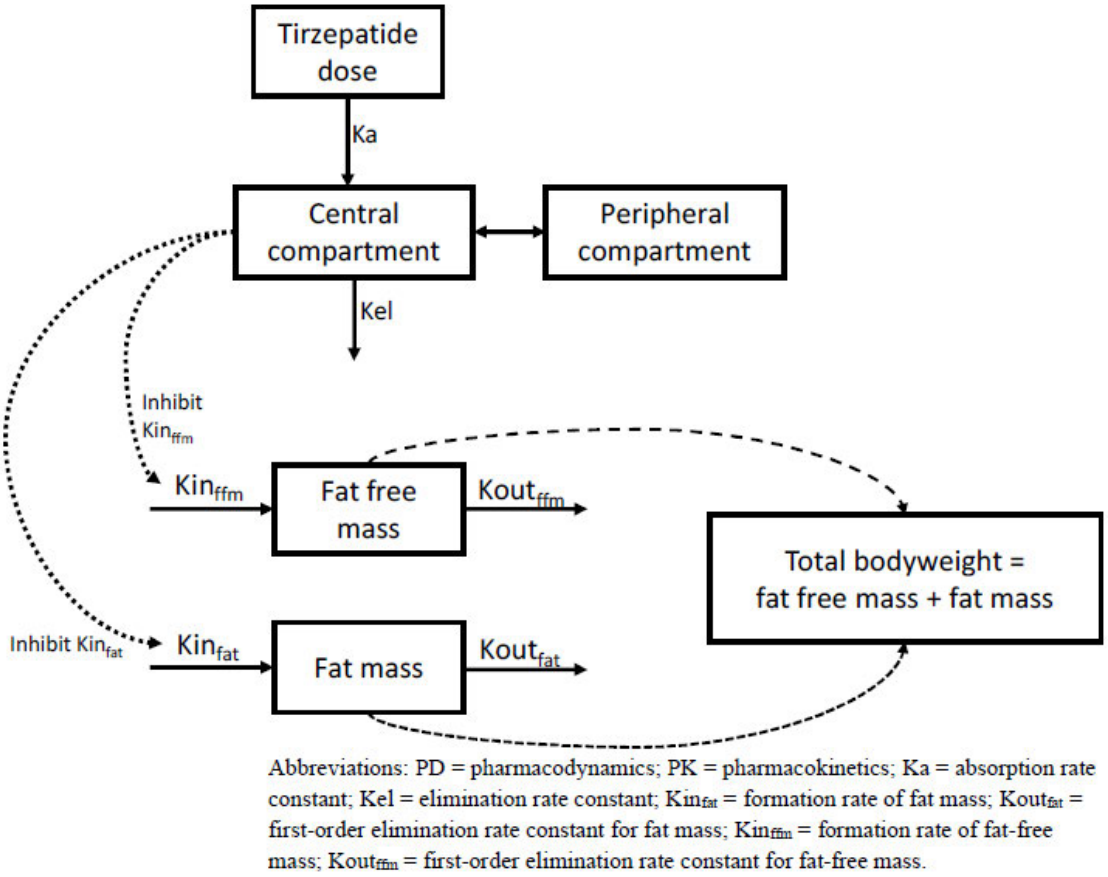
Body Weight Model

The Exposure-response analysis characterizing the effect of tirzepatide on lowering body weight (weight loss) was based on observations from 9 (Phase 2 and Phase3) studies (Table 2). The dataset for exposure-response analysis included 128638 body weight (FFM and fat mass) observations from 5607 patients. A training dataset that consisted of 64422 body weight (WT) observations from 2804 patients (randomly selected from each of the 9 studies) was used for the PK-PD model development. The remaining dataset was used as an external validation dataset (through VPC).

Base PK-PD model

A sequential modeling approach was used to characterize the effect of tirzepatide on lowering WT. Individual predicted PK parameters from the tirzepatide popPK model were integrated with the FFM and fat mass observations. An indirect response model was used to account for a delay in the effect of tirzepatide in reducing WT. The dependent variables used for the PD modeling, and representing total WT, were FFM and fat mass (the sum of the predicted FFM and fat mass gives the model-predicted total WT). A schematic representation of the tirzepatide PK model linked to the weight loss model is depicted in Figure 10 below.

Figure 10. Schematic of the Structural PK-PD Model Linking Tirzepatide PK to Body Weight



Source: Applicant's Population PK/PD Report, Figure 8.3, page 53.

As FFM and fat mass are derived from total WT, a correlation between the proportional residual error model for each dependent variable was included in the PD model using the L2 data item in NONMEM. The tirzepatide effect on inhibiting the formation rate (Kin) of FFM and fast mass were best described using a linear model provided below:

$$Kin_t = Baseline\ Kin - Baseline\ Kin \times (Placebo\ + Slope \times concentration_t)$$

where Kin_t is the formation rate of either FFM or fast mass at time t, $Baseline\ Kin$ is the stead-state formation rate in the absence of drug (expressed in kg/week), $Placebo$ is the additive placebo effect on Kin reduction and $Slope$ is the proportional effect of tirzepatide concentrations on the reduction of kin.
Source: Adapted from the Applicant's Population PK/PD Report, page 53, and the Applicant PK-PD model for weigh loss (run4.mod).

Final PK-PD model

The parameter estimates from the final PK-PD model linking tirzepatide exposure to the effect on lowering WT are listed in Table 6. According to the exposure-response model (weight loss model), tirzepatide predominantly lowers fat mass than FFM, with an estimated steeper slope on Kin for fat mass (linear effect of tirzepatide concentrations with a slope of 1.19×10^{-4} for fat mass vs. 3.71×10^{-5} for FFM) and a ratio between slopes of 3.2, indicating that under a given dose/exposure tirzepatide reduces about 3 times more fat mass than FFM. For model parsimony, the same Kout was used for FFM and fat mass, as the separate estimates for the Kout for FFM and fat mass were very similar. The estimated elimination rate constant for FFM and fat mass (Kout) was 0.0797 $week^{-1}$, suggesting a typical half-life for weight loss of about 9 weeks and that it would take about 45 weeks on a stable dose to get to a new steady state of body weight.

According to the Applicant covariate modeling, gender and Japanese were significant covariates on baseline FFM and baseline fat mass and were the only covariate included in the final model. Females were estimated to have 29% lower baseline FFM and 26% higher baseline fat mass than males. Japanese patients were estimated to have 11% and 29% lower FFM and fat mass at baseline compared to non-Japanese, respectively.

The estimated IIV expressed as coefficient of variation (%CV) were 12.9% and 34.4% for baseline FFM and baseline fat mass, 158% for Kout, 99.9% and 90.2% for the *Slope* or proportional effect of tirzepatide concentrations on reducing FFM and fat mass formation rate (Kin), and 123% and 121% for the fractional *Placebo* effect on reducing Kin for FFM and fat mass. The ETA shrinkage from the final weight loss model was 0.1%, 0.2%, 15.3%, 15.9%, 18.8%, 14% and 12.9% for baseline FFM, baseline fat mass, Kout, *Slope* for tirzepatide effect on Kin of FFM, *Slope* for effect on Kin of fat mass, *Placebo* effect on Kin of FFM and fat mass, respectively.

Table 6. Parameter Estimates from the Final Weight Loss Model

Population Parameter	Estimate (95% CI)[a]
Baseline fat-free mass (kg)	65.2 (64.7, 65.7)
Baseline fat mass (kg)	30.5 (29.9, 31.3)
First-order elimination rate constant, Kout ($week^{-1}$)	0.0797 (0.0743, 0.0851)
Slope for drug effect reducing fat-free mass Kin	3.71×10^{-5} (3.62×10^{-5}, 3.92×10^{-5})
Slope for drug effect reducing fat mass Kin	1.19×10^{-4} (1.16×10^{-4}, 1.26×10^{-4})
Placebo fractional reduction in fat-free mass Kin	0.0205 (0.0191, 0.0219)
Placebo fractional reduction in fat mass Kin	0.0796 (0.0741, 0.0847)
Covariate Effects	
Fractional decrease in baseline fat-free mass in females	0.293 (0.285, 0.301)
Fractional increase in fat mass in females	0.261 (0.228, 0.293)
Fractional decrease in baseline fat-free mass in Japanese	0.107 (0.0993, 0.118)
Fractional decrease in baseline fat mass in Japanese	0.293 (0.274, 0.321)
Interindividual variability (CV%)	
Baseline fat-free mass	12.9% (12.6, 13.4)
Baseline fat mass	34.4% (33.3, 35.4)
Correlation between the random effects for baseline fat and fat-free mass	87.0% (85.5, 88.4)
Correlation between the random effects for baseline fat-free mass and Kout	-22.6% (-27.0, -18.3)
Correlation between the random effects for baseline fat mass and Kout	-26.4% (-30.3, -22.6)
First-order elimination rate constant, Kout	158% (141, 183)
Slope for drug effect on fat-free mass	99.9% (91.5, 105)
Slope for drug effect on fat mass	90.2% (81.2, 96.2)
Correlation between the random effects for slope	96.5% (95.9, 96.7)
Placebo effect for fat-free mass	123% (108, 139)
Placebo effect on fat mass	121% (107, 135)
Correlation between the random effects for placebo	97.9% (97.4, 98.2)
Residual error	
Proportional for fat-free mass (%)	0.858% (0.837, 0.886)
Proportional for fat mass (%)	3.32% (3.21, 3.44)
Correlation between residual error (%)	98.4% (98.3, 98.5)

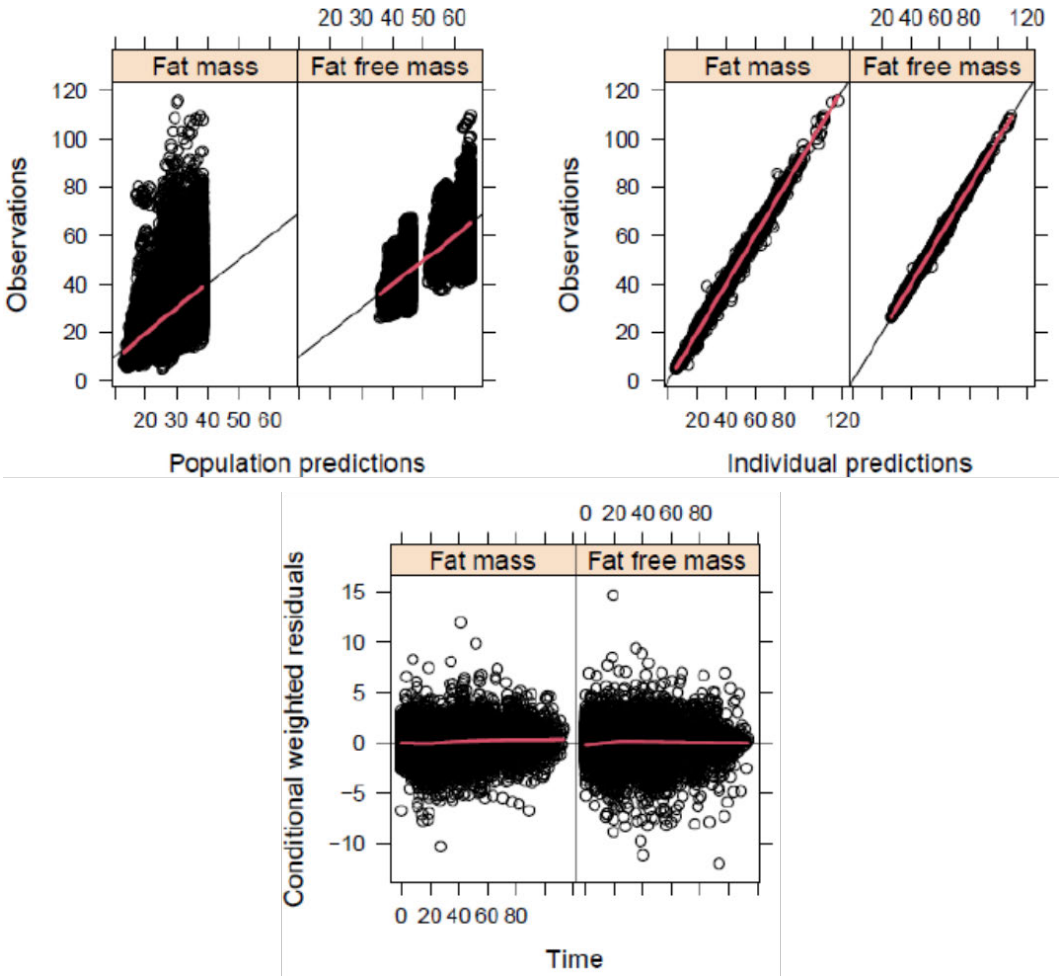
Abbreviations: CI = confidence interval; CV = coefficient of variation; Kin = formation rate; Kout = first-order elimination rate constant.

[a] Confidence interval obtained from a bootstrap analysis.

Source: Applicant's Population PK/PD Report, Table 9.4, page 77.

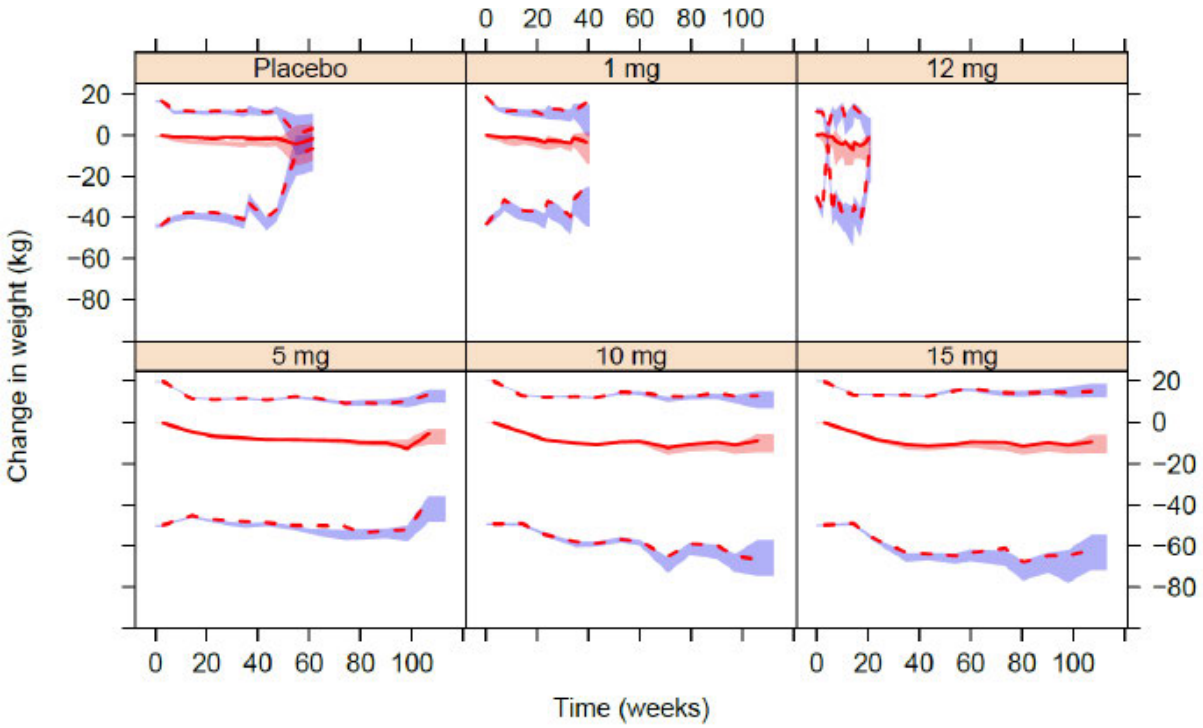
The goodness-of-fit (GOF) plots and the VPC plots from the final weight loss model, are shown in Figure 11 and Figure 12, respectively. The VPC plots from all observed data showed the model was able to accurately predict the observed change form baseline in total body weight (Figure 12). There was less data for the 1- and 12-mg dose levels, hence the pattern of the observed data. Similarly, the VPC also showed that the model could adequately predict the data in terms observed total body weight, FFM and fat mass.

Figure 11. Goodness of Fit Plots from the Final Weight Loss Model



Source: Applicant's Population PK/D Report, Figure ATT.17, page 380.

Figure 12. Visual Predictive Check for the Change from Baseline in body from the Final Weight Loss Model



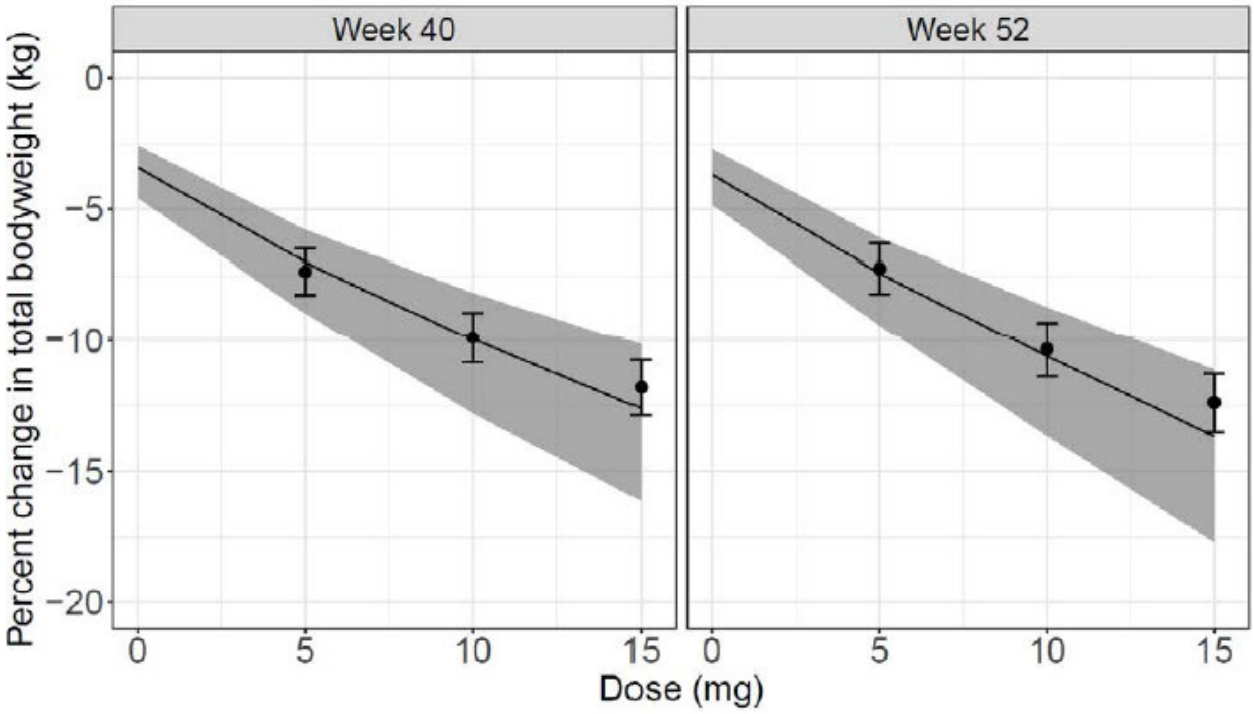
Note: The upper dotted line represents the 95th percentile of the observed data. The middle continuous line represents the 50th percentile of the observed data. The lower dotted line represents the 5th percentile of the observed data. The shaded areas represent the model-predicted 95% confidence interval of the corresponding percentiles. Due to their high density, the observed data points have been removed from the plot to increase the clarity of the percentiles.

Source: Applicant's Population PK/PD Report, Figure 9.9, page 81.

Application of the Weight Loss Model Demonstrating the Dose-dependent Response

The Applicant's simulations performed with the developed weight loss model showed a dose-exposure-response relationship for weight loss across the tirzepatide QW doses of 5, 10, and 15 mg after 40 and 52 weeks of tirzepatide treatment (Figure 13).

Figure 13. Model-predicted Change from Baseline in Total Body Weight, Across Tirzepatide Doses of 5, 10 and 15 mg



The continuous line is the median prediction. The shaded area is the 95% confidence interval of the prediction. The points and error bars are the observed mean and 95% confidence interval respectively.

The upper panel of Figure 14 shows the model-predicted decrease in total WT over time under tirzepatide QW doses of 5, 10, and 15 mg, with continuing decrease in total WT up to week 52 and a more pronounced decrease in total WT with increasing tirzepatide dose. The lowest panel of Figure 14 as well as Figure 15 show that patients lose more fat mass than FFM over time with a gradual proportion of FFM contributing to total WT (Figure 14 lower panel) and across tirzepatide QW doses of 5, 10, and 15 mg after 40 and 52 weeks of tirzepatide treatment (Figure 15). According to the weight loss model, tirzepatide reduces about 3 times more fat mass than FFM.

Figure 14. Model-Predicted Decrease in Total Body Weight and Change in Body Weight Composition Over Time, Across Tirzepatide Doses of 5, 10 and 15 mg

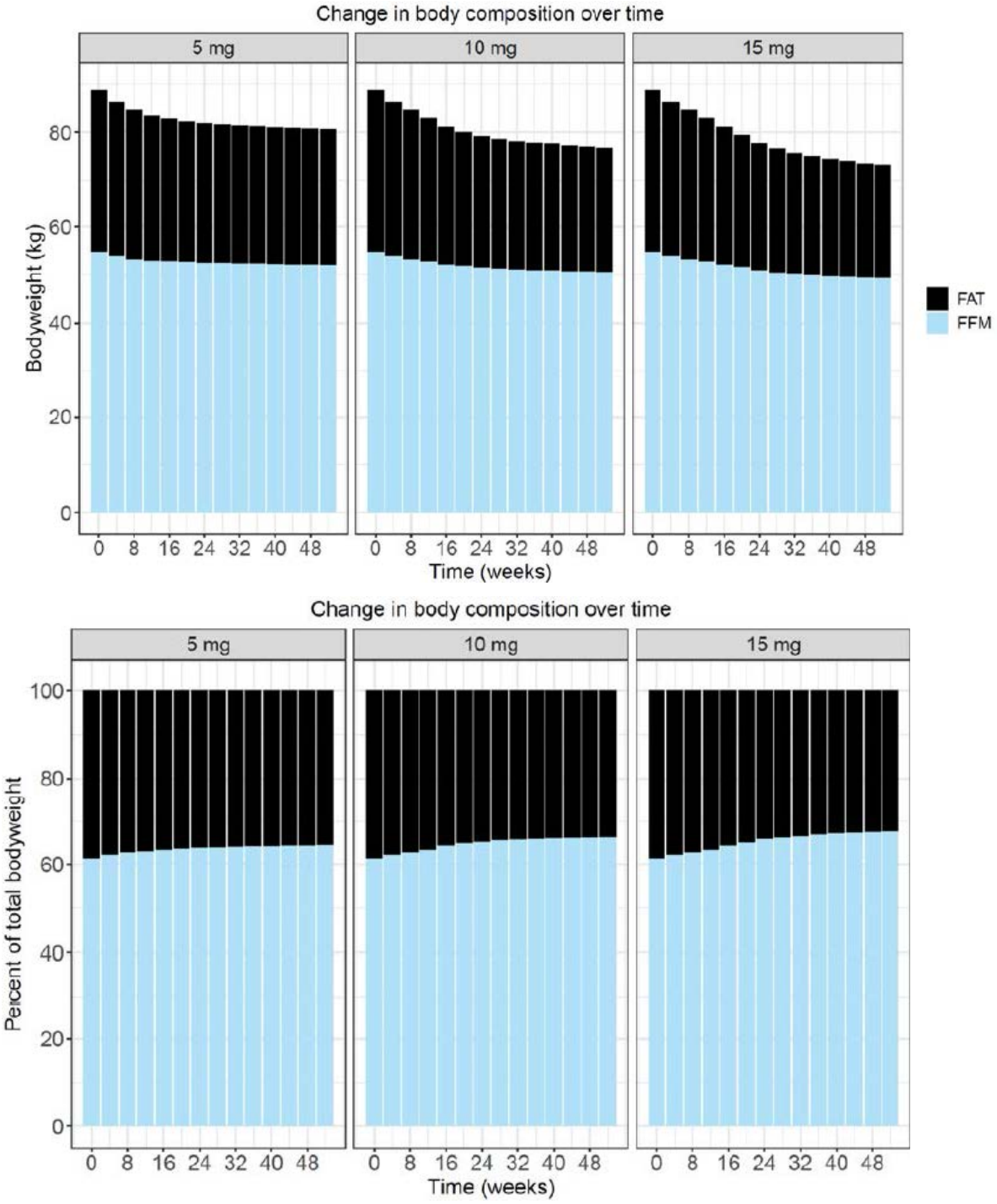
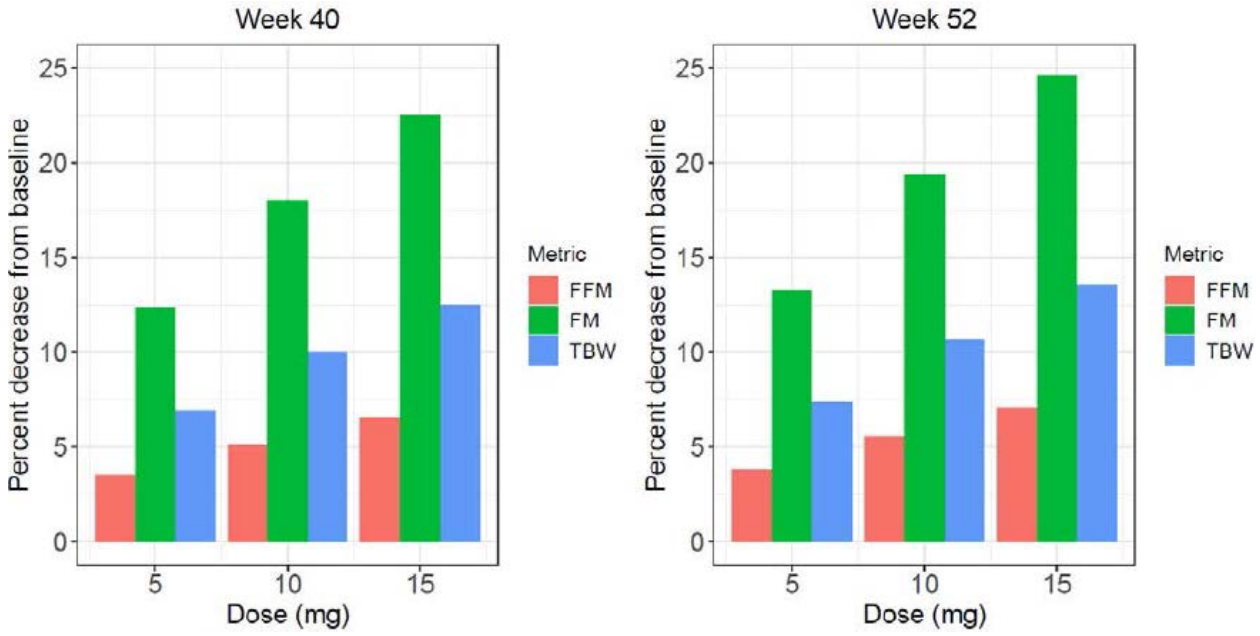


Figure 15. Model-Predicted Median Change in Weight after 40 or 52 Weeks of Tirzepatide Treatment



Reviewer's Assessment of the Population Weight Loss Model

- The Applicant's Weight loss model appropriately describes the observed change from baseline in FFM, fat mass and total WT over time, under placebo and tirzepatide treatment.
- The Weight loss model parameters were estimated with good precision, with relative standard errors (%RSE) of the typical PD parameters less than 3.9% for all parameters.
- The ETA shrinkage was low (less than 18.8%) for all parameters, suggesting the reliability of the ETA versus covariate plots for covariates assessment. The residual error (Epsilon) shrinkage was low (11.2%), indicating the informativeness of the GOF to diagnose structural and residual error model misspecifications.
- All covariates (sex and Japanese) were identified on the baseline FFM and fat mass and are considered physiologically relevant. No covariates were identified on the drug effect in reducing FFM or fat mass, and therefore no dose adjustment based on sex or ethnicity is warranted.
- The Applicant's weight loss model simulations appropriately captured the observed tirzepatide dose-dependent effect in reducing total body weight and more specifically fat mass with increasing tirzepatide dose of 5mg, 10 mg and 15 mg QW at week 40 and week 52.

Nausea-Vomiting and Diarrhea Events Models

The Exposure-response analysis characterizing the effect of tirzepatide on the probability of occurrence of nausea, vomiting or diarrhea adverse events (AEs) and the probabilities of transitioning between AE states (no AE, mild and moderate to severe) was based on observations from 9 (Phase 2 and Phase3) studies (Table 2). The dataset for exposure-response analysis contained a total 212633 observations for each PD response (nausea, vomiting or diarrhea) that were collected daily.

Base PK-PD model

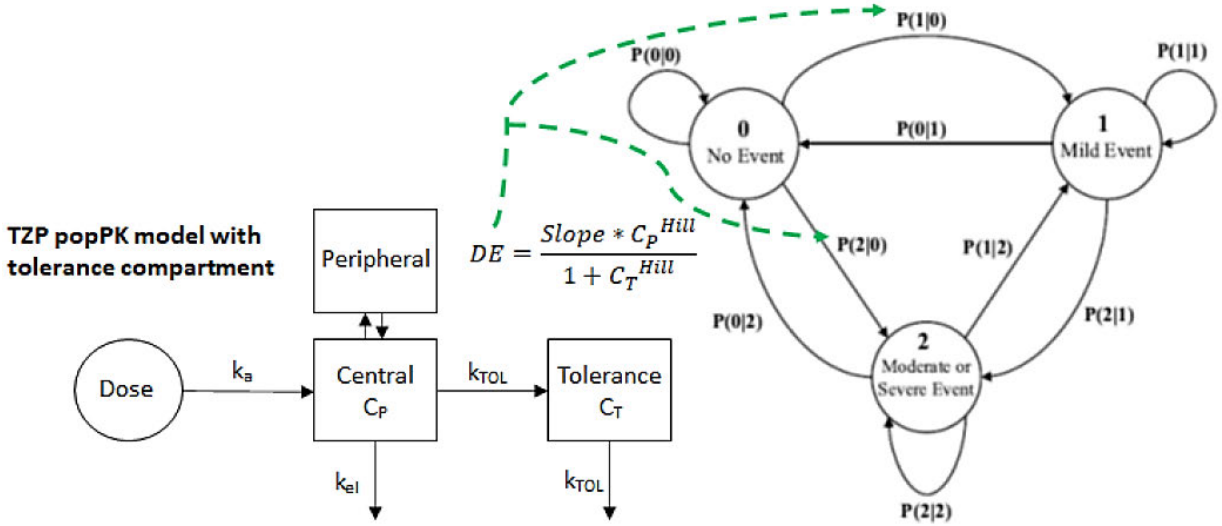
A sequential modeling approach was used to fit the individual patient's PK with the occurrence of nausea, vomiting and diarrhea AEs and transition probabilities between AE states (3 states categories: no AE, mild or moderate/severe). A discrete-time Markov model was used to estimate the probabilities for remaining in the current state or transitioning between AE states and assess the impact of drug effects and covariates on these probabilities. The Nausea and vomiting events data were analyzed using a single integrated model, while the diarrhea data were analyzed separately with the same model structure. A schematic representation of the tirzepatide's Markov chain exposure-response model is depicted in Figure 16 below

In order to describe the tolerance that develops with sustained drug exposure, tolerance was incorporated into the drug effects acting on the probability of transitioning from no AE to mild AE [P(1|0)], and no AE to moderate/severe AE [P(2|0)], using an additional model compartment. Accumulation and decay of the hypothetical tolerance compartment concentration is driven by the first-order rate constant, KTOL. In the Applicant PD model (as illustrated in Figure 16) the drug effect (DE) was not only based on the concentrations in the tolerance compartment but incorporated both the plasma concentrations (Cp) and the tolerance compartment concentrations (C_T).

Based on prior knowledge of applying Markov models to dulaglutide's nausea, vomiting and diarrhea (N/V/D) data, a "first-event" effect was tested and applied to capture the increased probability of transitioning to a mild or moderate/severe state following occurrence of the first event. The first-event effect was introduced in the model as a proportional additive effect in the logit of baseline P(1|0) and P(2|0). In addition, the presence of nausea was shown to increase the transition probability to vomiting and improved the model fit. Similarly, the current nausea effect was introduced in the model as a proportional additive effect in the logit of baseline P(1|0) and P(2|0).

The duration of nausea events was also found to be dependent to tirzepatide's plasma concentration (Cp), and a separate linear drug effect was added to the probability of transition from mild to no nausea P(0|1) and from moderate/severe to no nausea P(0|2).

Figure 16. Schematic of the Structural Tirzepatide-Nausea, Vomiting, and Diarrhea Markov Model



Abbreviations: AE = adverse event; ka = absorption rate constant; kel = elimination rate constant; C_P = drug concentration in central compartment; Hill = power model exponent; C_T = drug concentration in hypothetical tolerance compartment; DE = drug effect; K_{TOL} = tolerance rate constant; P(0|0) = probability of staying in the state of no AE; P(1|0) = probability of transition from the state of no AE to mild event; P(2|0) = probability of transition from the state of no AE to moderate/severe event; P(0|1) = probability of transition from the state of mild event to no AE; P(0|2) = probability of transition from the state of moderate/severe event to no AE; P(2|1) = probability of transition from state of mild to moderate/severe event; P(1|2) = probability of transition from state of moderate/severe to mild event; P(1|1) = probability of staying in the state of mild event; P(2|2) = probability of staying in the state of moderate/severe event; PopPK = population pharmacokinetics; TZP = tirzepatide.
Note: Green dotted lines indicate application of drug effect with tolerance on the transition probability from no AE to mild or moderate/severe events.

Source: Applicant's Population PK/PD Report, Figure 8.4, page 56.

Final PK-PD model

The parameter estimates from the final PK-PD models linking tirzepatide exposure to the probability of developing nausea, vomiting or diarrhea AEs and the probabilities of transitioning between AE states are listed in Table 7 for the nausea and vomiting Markov model and in Table 8 for diarrhea Markov model.

Table 7. Parameter Estimates from the Final Tirzepatide-Nausea and Vomiting Markov Model

Population Parameter	Estimate (95% CI)[a]
Baseline transition probability from no to mild nausea, NP10 (logit)	-13.1 (-14.3, -12.3)
Baseline transition probability from no to moderate/severe nausea, NP20 (logit)	-13.9 (-15.0, -13.2)
Baseline transition probability from mild to no nausea and from moderate/severe to no nausea, NP01 & NP02 (logit)	-2.96 (-3.19, -2.73)
Baseline transition probability from mild to moderate/severe nausea and from moderate/severe to mild nausea, NP21 & NP12 (logit)	-8.20 (-8.72, -7.80)
Baseline transition probability from no to mild vomiting, VP10 (logit)	-12.0 (-13.0, -11.3)
Baseline transition probability from no to moderate/severe vomiting, VP20 (logit)	-13.3 (-14.5, -12.6)
Baseline transition probability from mild to no vomiting and from moderate/severe to no vomiting, VP01 & VP02 (logit)	-2.22 (-2.53, -1.82)
Baseline transition probability from mild to moderate/severe vomiting and from moderate/severe to mild vomiting, VP21 & VP12 (logit)	-30 FIXED
Slope of drug effect with tolerance on NP10, SLPN10	1.61 (1.14, 2.38)
Slope of drug effect with tolerance on NP20, SLPN20	1.53 (1.07, 2.22)
Slope of drug effect on NP01 and NP02, SLPN012 (log) (mL/ng)	-7.24 (-7.56, -6.99)
Slope of drug effect with tolerance on VP10, SLPV10	0.572 (0.299, 1.11)
Slope of drug effect with tolerance on VP20, SLPV20	0.684 (0.364, 1.32)
Power model exponent for nausea drug effects with tolerance, HILLN (log)	-0.964 (-1.09, -0.851)
Power model exponent for vomiting drug effects with tolerance, HILLV (log)	-0.751 (-0.942, -0.579)
Tolerance rate constant, K_{TOL} (log) (h^{-1})	-11.2 (-11.4, -10.9)
First event effect on NP10 & NP20	-0.202 (-0.218, -0.181)
First event effect on VP10 & VP20	-0.194 (-0.217, -0.165)
Current nausea effect on VP10 & VP20	-0.217 (-0.239, -0.195)
Study GPGL effect on NP01 & NP02	0.300 (0.202, 0.411)
Study GPGL effect on VP01 & VP02	0.515 (0.260, 0.851)
Covariate Effects	
Hispanic ethnicity effect on K_{TOL}	0.369 (0.182, 0.588)
Japanese subrace effect on K_{TOL}	-0.426 (-0.583, -0.211)
Gender effect on K_{TOL}	-0.210 (-0.317, -0.098)
Caucasian race effect on NP10	-0.655 (-0.971, -0.409)
Japanese subrace effect on NP20	-3.57 (-4.71, -2.74)
Japanese subrace effect on VP10	-0.563 (-1.08, -0.086)
Japanese subrace effect on VP20	-3.79 (-6.45, -2.55)

Abbreviation: CI = confidence interval.

[a] CI obtained from a bootstrap analysis.

Source: Applicant's Population PK/PD Report, Table 9.5, page 83.

In the nausea and vomiting Markov model (Table 7), the baseline transition probability from mild to moderate/severe vomiting [P(2|1) or VP21] and from moderate/severe to mild vomiting [P(1|2) or VP12] were not estimable due to the low number of transitions between mild and moderate/severe states and were fixed to low probability value (fixed to a logit of probability of -30). For nausea, the logit of the population baseline transition probabilities between mild and moderate/severe states (NP21 and NP12) was estimated to -8.2 (i.e., 2.75 x 10^{-4} for NP21 and NP12). The estimated natural-log of KTOL parameter driving the delayed accumulation and decay of tirzepatide concentrations in the hypothetical tolerance compartment was -11.2 (i.e., 1.37x10^{-5} h^{-1} or 0.0023 $week^{-1}$), with an equilibration half-life of 302 weeks.

For nausea, increasing tirzepatide plasma concentrations (Cp) was associated to a longer duration of nausea and was found to decrease the probability of resolving nausea. This relationship was described in the nausea Markov model using a linear relationship between Cp and the probability of transitioning from mild to no nausea [NP01 or P(0|1)] and from moderate/severe to no nausea [NP02 or P(0|2)]. The estimated natural-log of the slope describing this relationship was -7.24 (i.e., a slope of 7.2 x 10^{-4} mL/ng). According to the Applicant model, the baseline NP01 or NP02 decreases from 5% to 1.8% for a Cp of 1440 ng/mL (average steady-state concentration [Css] in a 90kg subject under 15 mg dose) and decreases from 5% to 1.3% for a Cp of 1920 ng/mL (steady-state Cmax [Cmax,ss] in a 90kg subject under 15 mg dose). In a 70 kg subject under 15 mg dose, the model-predicted Css and Cmax,ss of 1770 ng/mL and 2370 ng/mL are expected to be associated with a decrease in the baseline NP01 or NP02 from 5% to 1.4% (under Css exposure) and 0.9% (under Cmax,ss exposure), respectively. Similar drug effect was not described for the transitioning probability from mild to no vomiting (VP01) and from moderate/severe to no vomiting (VP02).

The mean duration of nausea as well as vomiting events reported in Study GPGL was noticeably longer than the other Phase 3 studies. According to the Applicant, this may be related to a possible operational issue where the end date of AEs was not properly recorded for a subset of patients. A fixed-effect parameter was applied to the transition probabilities from event to no event (NP01, NP02, VP01 and VP02) to account for longer nausea and vomiting durations in Study GPGL. The Study effect was introduced in the model as a proportional additive effect in the logit of baseline NP01, NP02, VP01 and VP02. The estimated Study GPGL effect was 0.3 for nausea and 0.515 for vomiting. According to the Applicant model, Study GPGL have 57.6% lower baseline NP01 and NP02 and 65.8% lower baseline VP01 and VP02.

The first-event effect describing the increased probability of transitioning from no event to a mild or a moderate/severe state following the prior occurrence of a first event, was estimated to be -0.202 for nausea (NP10 and NP20) and -0.194 for vomiting (VP10 and VP20). According to the Applicant model, prior occurrence of nausea is associated with a 1310% and 1557% increase in baseline NP10 and NP20, respectively. Prior occurrence of vomiting is associated with a 926% and 1220% increase in baseline NP10 and NP20, respectively.

The effect of current nausea on the increased probability of vomiting events (VP10 or VP20) was estimated to be -0.217. According to the Applicant model, current nausea on the increased baseline VP10 and VP20 by 1252% and 1692%, respectively.

Demographic characteristics like sex, Hispanic ethnicity, and Japanese were significant covariates in the final model on the tolerance rate constant (KTOL). Females have a 21.0% decrease in the KTOL for nausea and vomiting relative to males. Therefore, females will develop tolerance slower than men resulting in a higher and more persistent probability of nausea and vomiting. Hispanics have a 36.9% increase in KTOL relative to non-Hispanics, and Japanese have a 42.6% decrease in KTOL relative to non-Japanese.

Although having a slower development tolerance, Japanese patients were found to have a 97% decrease in baseline probability of moderate/severe nausea (NP20), and a 43% and 98% decrease in baseline probability of mild (VP10) and moderate/severe vomiting (VP20) relative to non-Japanese, respectively.

Caucasian patients have a 92.5% increase in baseline probability of mild nausea (NP10) relative to non-Caucasians.

Covariate related to patient's race/ethnicity and gender may be associated with social and cultural bias in reporting discomfort and gastrointestinal AEs. Therefore, it is not known if there is an underlying physiological explanation for the differences in gastrointestinal AEs. The population PK and PK/PD modeling did not identify a specific demographic that would benefit from an alternative dose titration.

In the diarrhea Markov model (Table 8), the KTOL parameter was comparable to nausea and vomiting model and the estimated natural-log of KTOL -11.2 (i.e., $1.5x10^{-5}$ h^{-1} or 0.0025 $week^{-1}$), with an equilibration half-life of 273 weeks. Unlike nausea, there was no gender effect on KTOL parameter.

Table 8. Parameter Estimates from the Final Tirzepatide-Diarrhea Markov Model

Population Parameter	Estimate (95% CI)[a]
Baseline transition probability from no to mild diarrhea, DP10 (logit)	-10.3 (-10.7, -10.0)
Baseline transition probability from no to moderate/severe diarrhea, DP20 (logit)	-11.8 (-12.2, -11.3)
Baseline transition probability from mild to no diarrhea and from moderate/severe to no diarrhea, DP01 & DP02 (logit)	-3.01 (-3.21, -2.80)
Baseline transition probability from mild to moderate/severe diarrhea and from moderate/severe to mild diarrhea, DP21 & DP12 (logit)	-8.09 (-9.08, -7.50)
Slope of drug effect with tolerance on DP10, SLPD10	0.332 (0.244, 0.469)
Slope of drug effect with tolerance on DP20, SLPD20	0.371 (0.273, 0.508)
Power model exponent for diarrhea drug effects with tolerance, HILLD (log)	-0.577 (-0.664, -0.502)
Tolerance rate constant, K_{TOL} (log) (h^{-1})	-11.1 (-11.3, -11.0)
First event effect on DP10 & DP20	-0.214 (-0.229, -0.197)
Study GPGL effect on DP01 & DP02	0.268 (0.161, 0.406)
Covariate Effects	
Japanese subrace effect on DP20	-2.28 (-3.42, -1.73)

Abbreviation: CI = confidence interval.
Source: Applicant's Population PK/PD Report, Table 9.6, page 84.

Unlike nausea, there was no direct effect tirzepatide plasma concentrations (Cp) on the duration of diarrhea and the probability of resolution of diarrhea events.

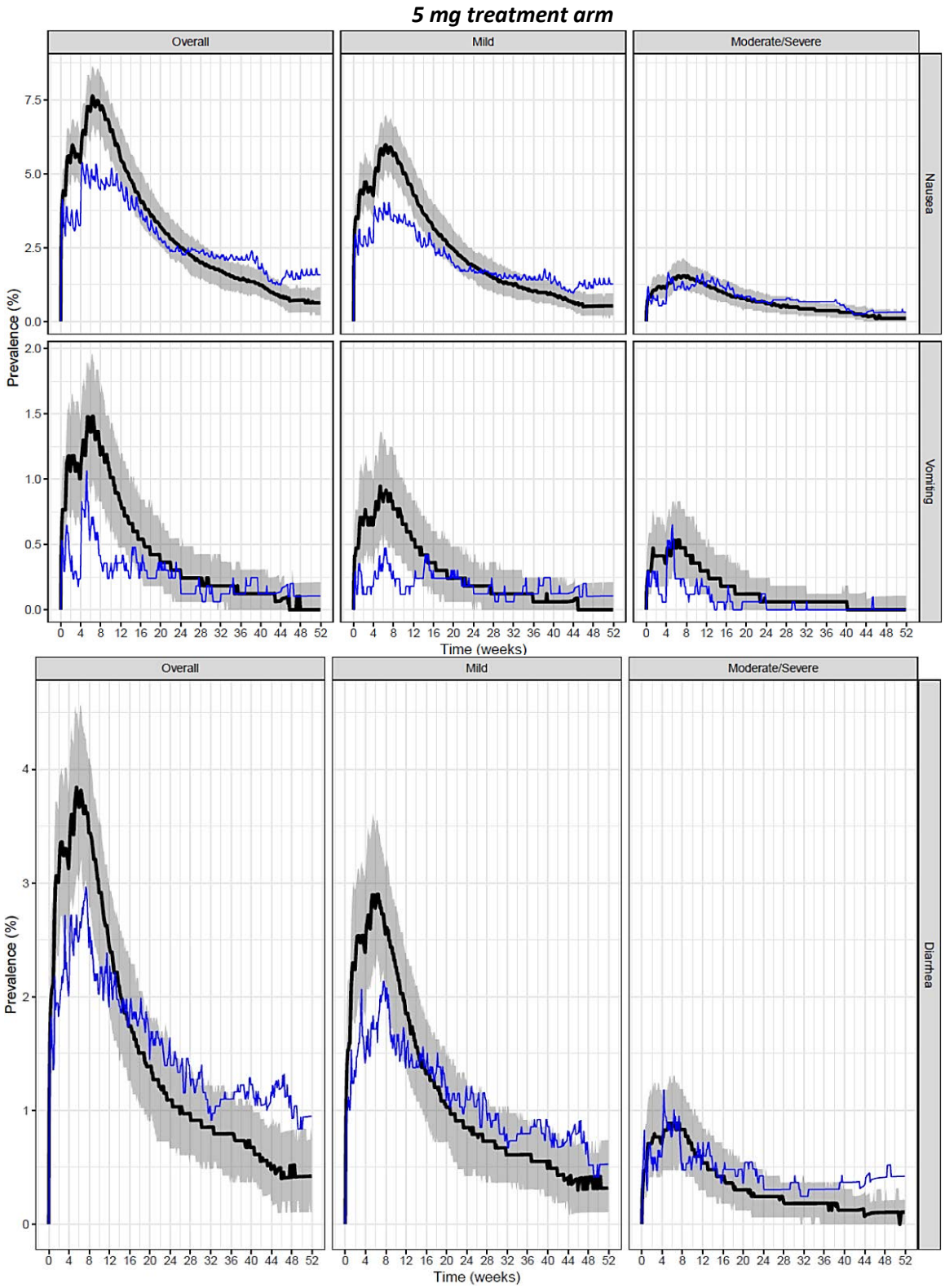
The mean duration of diarrhea in Study GPGL was longer than the other Phase 3 studies. According to the Applicant model, Study GPGL have 54.2% lower baseline DP01 and DP02.

Prior occurrence of diarrhea (first-event effect) is associated with a 806% and 1149% increase in baseline DP10 and DP20, respectively.

Japanese subrace was the only significant covariates in the final model. Japanese patients were found to have a 90% decrease in baseline probability of moderate/severe diarrhea (DP20) relative to non-Japanese.

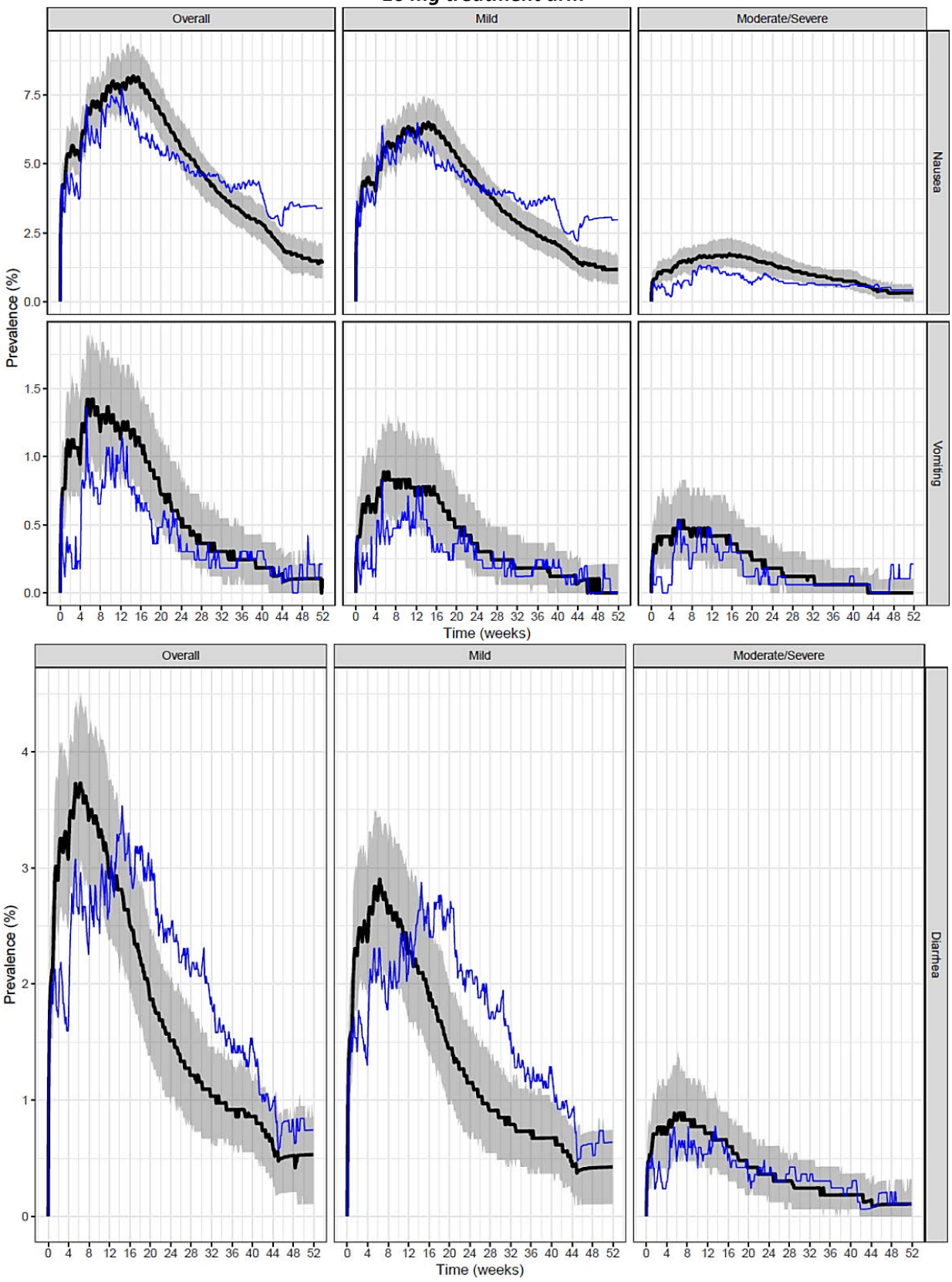
VPC was the primary diagnostic utilized to evaluate the Markov models. Prevalence or proportion of patients with events was summarized at each day for the observed and model simulated results. VPCs were stratified by study and treatment arm due to the different dose titration regimens. A majority of the N/V/D data informing the model were from patients assigned to the 3 different tirzepatide dose titration regimens evaluated in the Phase 3 studies. VPCs for the nausea-vomiting Markov model and the diarrhea Markov model are shown in Figure 17.

Figure 17. Visual Predictive Check for the Nausea-Vomiting and Diarrhea Models with overlaid observed daily prevalence (blue line) for the 5mg, 10 mg and 15 mg Phase 3 treatment arms



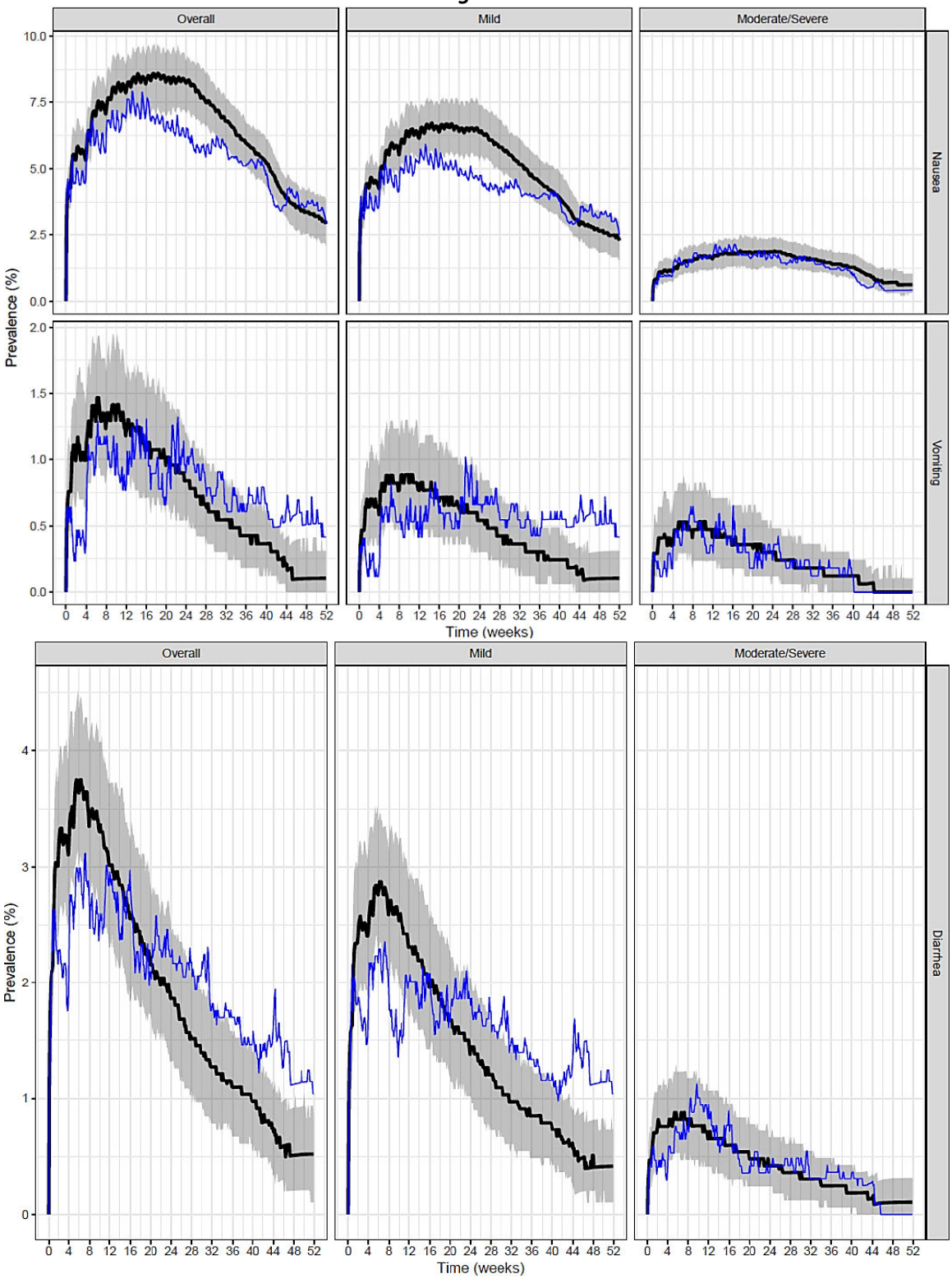
Source: Applicant's Population PK/PD Report, Figure 9.10 and 9.13, page 85 and 88. (Continued next page)

10 mg treatment arm



Source: Applicant's Population PK/PD Report, Figure 9.11 and 9.14, page 86 and 89. (Continued next page)

15 mg treatment arm



Abbreviation: VPC = visual predictive check.
Black lines denote median of model predictions and gray bands represent 90% confidence intervals. Blue lines are observed prevalence of event.

Source: Applicant's Population PK/PD Report, Figure 9.12 and 9.15, page 87 and 90.

Reviewer's Assessment of the Population Nausea-Vomiting and Diarrhea Markov Models

- The Applicant's nausea-vomiting and diarrhea Markov models reasonably describe the observed occurrence of nausea, vomiting or diarrhea and the development of tolerance over time under tirzepatide treatment.
- The PD parameters were estimated with good precision, with relative standard errors (%RSE) of the typical PD parameters less than 27.4% for the nausea-vomiting Markov models parameters, and %RSE less 16.3% for the diarrhea Markov model.
- Both nausea-vomiting and diarrhea Markov models were average models with no between-subject variability included on the baseline probabilities of developing AEs, probabilities of transitioning between AEs status, tolerance parameters or drug effects parameters.
- Females and Japanese were found to develop tolerance slower than men and non-Japanese resulting in a higher and more persistent probability of nausea and vomiting. However, Japanese patients were found to have a lower baseline probability of developing moderate/severe nausea, and a lower baseline probability of developing mild and moderate/severe vomiting relative to non-Japanese. Japanese patients also had a lower probability of developing moderate/severe diarrhea.
- According to the Phase 3 studies data, no alternative dose titration appeared to be required based on specific demographics and appears acceptable, as the gradual titration of tirzepatide treatment starting at 2.5-mg dose for 4 weeks followed by increases in doses by 2.5-mg increments every 4 weeks to attain maintenance dose levels of 5, 10, or 15 mg in Phase 3 studies, will allow to mitigate the AEs and reassess treatment benefit/risk. In addition, the current dosing regimen appears to have mitigated the incidence of gastrointestinal AEs that were noted in Phase 2 Study GPGB. The majority of nausea, vomiting, and diarrhea AEs were reported during the dose-escalation phase, and their incidence decreased with time with a prevalence <10% once steady-state concentrations for the maintenance doses were attained (after 24 weeks).

Exposure-Response Analysis for Heart Rate

Applicant's Analysis

The Applicant's analysis found a positive linear relationship between tirzepatide plasma concentrations and the increase in heart rate (HR), as assessed from all Phase 3 studies at week 12, 24, 40, and 52 separately using linear regression analyses.

The analysis suggested that at week 12, HR showed a greater increase across tirzepatide concentrations compared to later study time points (Weeks 24, 40, or 52). Week 12 was in the dose-escalation period when patients were receiving tirzepatide 10 mg or less. At week 12, the Applicant model estimated a 13 beats per minute (bpm) change from baseline in HR (ΔHR) for a tirzepatide Cmax of 1920 ng/mL (representing the PK model predicted average steady-state Cmax in a 90 kg subject under the highest tirzepatide dose of 15 mg). At week 24, 40 and 52, the Applicant analysis estimated a 7.0 to 9.2 bpm ΔHR at the predicted steady-state Cmax of 1920 ng/mL. Table 9 summarizes the concentration-ΔHR linear model parameters and predicted increase in HR for all Phase 3 studies.

A separate exposure-ΔHR analysis was conducted by the Applicant using the Japan Phase 3 studies (GPGO and GPGP), representing <20% of the total HR data available from the combined 7 Phase 3 studies. Consistently with the previous analysis combining all Phase 3 studies, the Applicant linear regression analysis found that at Week 12, HR showed a greater increase across tirzepatide concentrations compared to Weeks 24, 40, or 52. According to the applicant model from the Japan studies, the expected mean ΔHR at week 12 is 15.9 bpm for a tirzepatide Cmax of 1920 ng/mL. At week 24, 40 and 52, expected mean ΔHR ranges from 10.7 to 12.4 bpm ΔHR at the predicted steady state Cmax of 1920 ng/mL. Table 10 summarizes the concentration-ΔHR linear model parameters and predicted increase in HR for the Japan Phase 3 studies.

For a predicted mean steady-state Cmax of 2370 ng/mL in a 70 kg patient (closer to the observed median WT of the Japanese population), the expected mean ΔHR in Japanese population at week 12 and week 24 to 52 are 18.9 bpm and 12.4 to 14.5 bpm, respectively. Conversely, based on the analysis combining all Phase 3 studies (regardless of Japanese subrace or ethnicity), the expected mean ΔHR at week 12 and week 24 to 52 are 15.8 bpm and 8.4 to 10.8 bpm, respectively.

The Applicant's concentration-ΔHR model from the Japan Phase 3 studies showed comparable slope parameter estimates for week 12 to 52, with 10% to 30% higher slope compared to the estimated slope from the analysis using the combined Phase 3 studies. However, the intercept parameter from the Japan Phase 3 studies was 50% to 180 %higher compared to the analysis using the combined Phase 3 studies. According to the Applicant separate analyses, the Japanese patients from the Japan Phase 3 studies have about 3 to 4 bpm differences in ΔHR.

Table 9. Linear Regression Parameters from the Heart Rate and ΔHR Matched with Observed Tirzepatide Concentrations from Combined Data from Phase 3 Studies

Heart Rate Measurement	Study Week	Number of data pairs	Intercept (bpm)	Slope (bpm/[ng/mL])	p-value	Prediction at Css[a] (15 mg)	Prediction at Cmax[b] (15 mg)
Absolute							
Vital signs	12	4294	76.8	0.00329	p<0.001	81.5	83.1
	24	4268	76.6	0.00293	p<0.001	80.8	82.2
	40	4608	75.5	0.00282	p<0.001	79.6	80.9
	52	2197	75.3	0.00318	p<0.001	79.9	81.4
ECG	40	3857	72.1	0.00347	p<0.001	77.1	78.8
	52	2162	72.4	0.00294	p<0.001	76.6	78.0
Change from Baseline							
Vital signs	12	4294	1.45	0.00604	p<0.001	10.1	13.0
	24	4268	2.17	0.00364	p<0.001	7.4	9.2
	40	4608	1.32	0.00297	p<0.001	5.6	7.0
	52	2197	0.508	0.00421	p<0.001	6.6	8.6
ECG	40	3741	1.65	0.00377	p<0.001	7.1	8.9
	52	2100	1.70	0.00408	p<0.001	7.6	9.5

Abbreviations: bpm = beats per minute; Cmax = maximum observed drug concentration; Css = average steady-state concentration; ECG = electrocardiogram; QW = once weekly.

[a] The model-predicted steady-state concentrations following tirzepatide 15 mg QW in a 90-kg individual were Css=1440 ng/mL and Cmax=1920 ng/mL (Table 10.3).

Source: Applicant's Population PK/PD Report, Table 9.10, page 99.

Table 10. Linear Regression Parameters for Heart Rate and ΔHR Matched with Observed Tirzepatide Concentrations from Japan Phase 3 studies

Heart Rate Measurement	Study Week	Number of Data Pairs	Intercept (bpm)	Slope (bpm/[ng/mL])	p-value	Prediction at Css[a] (15 mg)
Absolute						
Vital signs	12	790	79.2	0.00173	0.282	82.1
	24	780	78.1	0.00297	p<0.001	83.1
	40	724	77.9	0.00267	p<0.001	82.4
	52	752	76.6	0.00323	p<0.001	82.1
ECG	12	784	73.5	0.00249	0.133	77.7
	40	718	73.0	0.00261	p<0.001	77.4
	52	748	72.2	0.00278	p<0.001	76.9
Change from Baseline						
Vital signs	12	790	3.31	0.00656	p<0.001	14.5
	24	780	3.18	0.00478	p<0.001	11.3
	40	724	3.42	0.00378	p<0.001	9.8
	52	752	1.42	0.00509	p<0.001	10.1
ECG	12	775	4.39	0.00565	p<0.001	14.0
	40	710	4.33	0.00357	p<0.001	10.4
	52	739	3.39	0.00412	p<0.001	10.4

Abbreviations: Cmax = maximum observed drug concentration; Css = average steady-state concentration; ECG = electrocardiogram; QW = once weekly.

[a] The model-predicted steady-state concentration following tirzepatide 15 mg QW in Japanese was Css=1700 ng/mL (Table 10.8).

Source: Applicant's Population PK/PD Report, Table 10.9, page 148.

Reviewer's Assessment

The review team assessed the effect of tirzepatide on the increase in pulse rate (including differences in ΔHR between studies, populations, or demographic characteristics) based on PK and PD time-matched observations from all Phase3 studies (n=7), using linear or non-linear mixed-effects modeling approaches. The aim of this additional analysis was to further test the applicant's findings regarding HR and ascertain the extent of the difference in relationship by Japanese subrace. The dataset for exposure-response analysis contained 29026 observations for time-matched tirzepatide concentrations and HR, collected on one or multiple visits per patient (5066 patients), with a median of 6 paired observations per individual (range= 1 to 13) up to week 109. Most of the time-matched tirzepatide concentrations, HR and ΔHR were collected on week 4, 12, 24, 40, 44, 52, and 56 representing 15%, 14%, 14%, 10%, 3%, 6% and 4% of the 29026 paired PK-PD observations, respectively. Asian population and particularly patients identified as Japanese "subrace" were the second most prevalent patient population (24%) that contributed to the PK and HR observations (Table 11).

The relationship between tirzepatide concentrations and ΔHR (from all weeks of Phase 3 studies) was best described with a combined linear and Emax mixed effects model with the general average equation below:

$$\Delta HR = Baseline\ \Delta HR + \frac{Emax \times Cp}{(EC50 + Cp)} + (Slope\ \times Cp)$$

Where $Baseline\ \Delta HR$ is the population mean ΔHR in the absence of tirzepatide, Cp is the measured tirzepatide concentrations, $Emax$ is the population mean maximum tirzepatide effect on ΔHR, $EC50$ is the tirzepatide concentration responsible for 50% of the maximum drug effect on ΔHR, $Slope$ is the population mean slope describing the linear effect of Cp on ΔHR. The between-subject variability on the model parameters was included as an additive error on $Baseline\ \Delta HR$, $Emax$ and $Slope$, and as an exponential error on $EC50$. The residual error model consisted of an additive error model.

The combined linear and Emax mixed effects model provided a better fit compared to either a linear mixed effects model (difference in OFV of 1059 points) or an Emax mixed effects model (difference in OFV of 43 points). Japanese subrace was found to be a statistically significant covariate on Emax and on Slope parameters but not on Baseline ΔHR. Japanese represented 85% of the Asian population in the Phase 3 studies, and Asian population (other than Japanese) was not found to a be a significant covariate on the model parameters when not accounting for the Japanese subrace. Black and African American were not found to be significant covariates.

The final parameter estimates from the final PK-PD model linking tirzepatide exposure to the effect on HR increase are listed in Table 12.

Table 11. Summary Of Demographic Characteristics of Patients in the Exposure-HR Analysis

	Study CPGH (N=1066)	Study CPGI (N=349)	Study CPGK (N=359)	Study GPGL (N=1391)	Study GPGM (N=982)	Study GPGO (N=476)	Study GPGP (N=443)	Overall (N=5066)
Age (years)								
Mean (SD)	57.3 (9.95)	60.8 (9.96)	54.3 (11.6)	56.4 (10.3)	63.4 (8.64)	56.3 (10.3)	57.0 (10.8)	58.2 (10.5)
Median [Min, Max]	58.0 [22.0, 84.0]	62.0 [27.0, 82.0]	54.0 [23.0, 83.0]	57.0 [21.0, 91.0]	64.0 [32.0, 91.0]	55.5 [26.0, 86.0]	57.0 [21.0, 83.0]	59.0 [21.0, 91.0]
Weight (kg)								
Mean (SD)	94.5 (19.9)	95.7 (21.5)	86.1 (19.5)	93.8 (22.1)	90.4 (18.4)	78.8 (14.8)	77.5 (16.1)	90.0 (20.5)
Median [Min, Max]	91.7 [53.2, 201]	94.3 [43.1, 198]	83.4 [44.6, 175]	90.0 [50.1, 222]	88.6 [53.4, 227]	76.2 [48.3, 159]	74.7 [48.6, 188]	86.9 [43.1, 227]
Sex								
Female	482 (45.2%)	153 (43.8%)	171 (47.6%)	742 (53.3%)	381 (38.8%)	113 (23.7%)	107 (24.2%)	2149 (42.4%)
Male	584 (54.8%)	196 (56.2%)	188 (52.4%)	649 (46.7%)	601 (61.2%)	363 (76.3%)	336 (75.8%)	2917 (57.6%)
Japanese								
No	1066 (100%)	289 (82.8%)	293 (81.6%)	1391 (100%)	980 (99.8%)	0 (0%)	0 (0%)	4019 (79.3%)
Yes	0 (0%)	60 (17.2%)	66 (18.4%)	0 (0%)	2 (0.2%)	476 (100%)	443 (100%)	1047 (20.7%)
Race								
White	968 (90.8%)	278 (79.7%)	122 (34.0%)	1135 (81.6%)	793 (80.8%)	0 (0%)	0 (0%)	3296 (65.1%)
Black/African American	33 (3.1%)	6 (1.7%)	16 (4.5%)	62 (4.5%)	40 (4.1%)	0 (0%)	0 (0%)	157 (3.1%)
Asian	58 (5.4%)	63 (18.1%)	129 (35.9%)	22 (1.6%)	39 (4.0%)	476 (100%)	443 (100%)	1230 (24.3%)
Native Hawaiian/Others	2 (0.2%)	2 (0.6%)	92 (25.6%)	162 (11.6%)	88 (9.0%)	0 (0%)	0 (0%)	346 (6.8%)
American Indian/Alaska	3 (0.3%)	0 (0%)	0 (0%)	1 (0.1%)	2 (0.2%)	0 (0%)	0 (0%)	6 (0.1%)
Multiple	2 (0.2%)	0 (0%)	0 (0%)	9 (0.6%)	20 (2.0%)	0 (0%)	0 (0%)	31 (0.6%)
Ethnicity								
Hispanic or Latino	308 (28.9%)	17 (4.9%)	157 (43.7%)	968 (69.6%)	465 (47.4%)	0 (0%)	0 (0%)	1915 (37.8%)
Not Hispanic or Latino	751 (70.5%)	276 (79.1%)	137 (38.2%)	423 (30.4%)	508 (51.7%)	0 (0%)	0 (0%)	2095 (41.4%)
Not reported	7 (0.7%)	56 (16.0%)	65 (18.1%)	0 (0%)	9 (0.9%)	476 (100%)	443 (100%)	1056 (20.8%)

Source: FDA Reviewer

Table 12. Parameter Estimates from the Final Tirzepatide Concentrations-ΔHR Model

Parameters	Estimates (95% CI[a])	BSV[b] (95% CI)
Baseline ΔHR (bpm)	-2.02 (-2.3, -1.7)	5.84
EC50 (ng/mL)	209 (172, 260)	0.003
Emax (bpm)	7.7 (7.2, 8.4)	4.56
Slope (bpm.mL/ng)	0.0005 (0.0001, 0.0008)	0.002
Japanese subrace effect on Emax	0.32 (0.23, 0.44)	-
Japanese subrace effect on Slope	2.82 (1.24, 11.63)	-
Additive residual error (bpm)	6 (5.9, 6.1)	

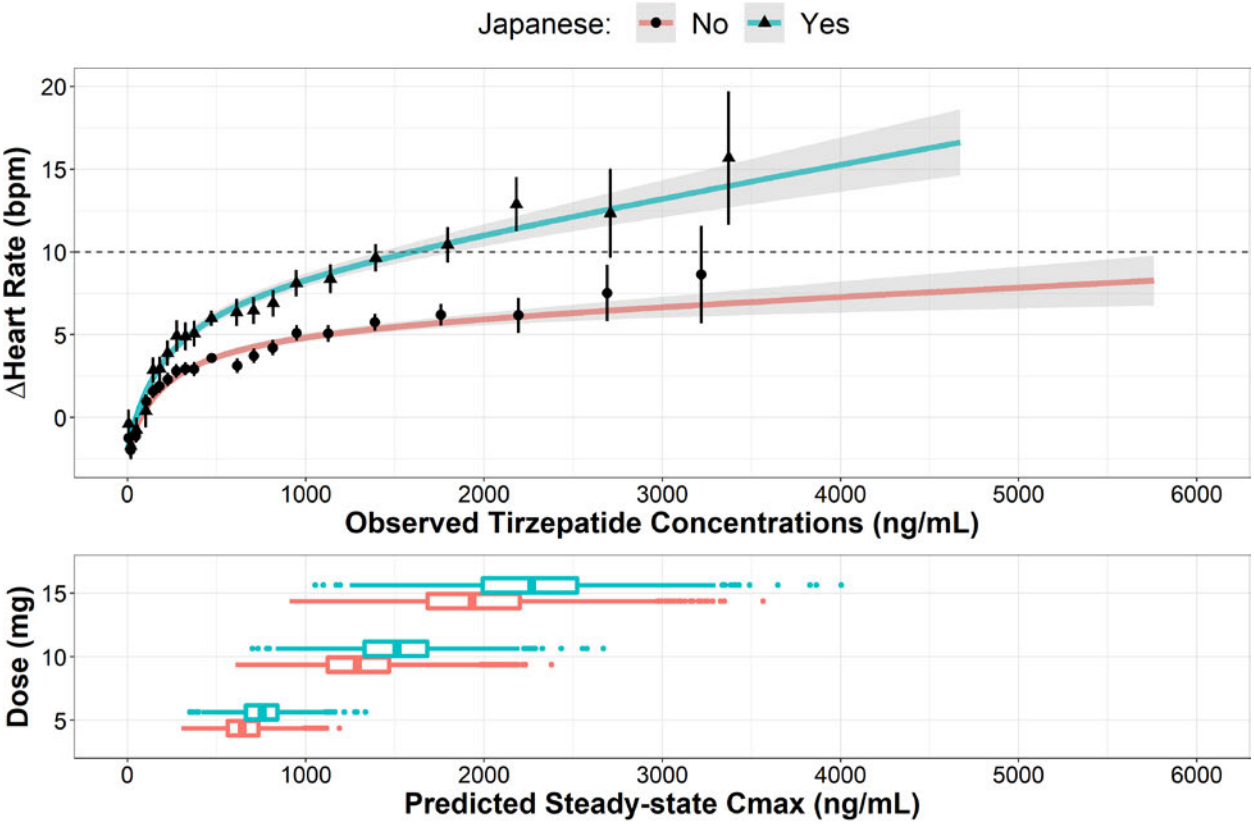
[a]. The 95% CI were derived from the bootstrap analysis (973 successful runs over 1000). [b] BSV: between-subject variability reported as standard deviation (SD).
Source: FDA Reviewer

The estimated mean Baseline ΔHR and EC50 parameters are -2.02 bpm and 209 ng/mL, respectively. The estimated mean Emax and Slope for non-Japanese populations are 7.7 bpm and 0.0005, respectively. Japanese were found to have significantly higher ΔHR compared to non-Japanese, with Japanese patients having 32% higher Emax and 282% higher Slope compared to non-Japanese.

Figure 18 (upper panel) shows the model-predicted mean ΔHR for non-Japanese (solid red line) and for Japanese patients (solid blue line). The black circles and triangles represent the mean of the observed ΔHR in non-Japanese and Japanese patients, respectively. The vertical error bars represent the 90%CI around the mean of the observed ΔHR in each quantile of tirzepatide plasma concentrations. The model-predicted mean ΔHR for non-Japanese and Japanese appropriately captures the trend of the observed mean ΔHR at different tirzepatide concentration quantiles, confirming the adequacy of the combined linear and Emax mixed effects model in describing the effect of tirzepatide concentrations on the average increase in HR in non-Japanese and Japanese.

The lower panel of Figure 18 show the distribution of the expected tirzepatide steady-state Cmax (Cmax,ss) under a tirzepatide dose of 5 mg , 10 mg, and 15 mg in non-Japanese (red box plots) and Japanese (blue box plots), predicted using the individual PK parameters of Phase 3 studies patients and derived from the applicant PK model.

Figure 18. Mean Predicted ΔHR versus Tirzepatide Concentrations (upper panel) and Distribution of Tirzepatide Steady-State Cmax Under Tirzepatide 5 mg, 10 mg, and 15 mg (lower panel)



Note: In the upper panel, the shared areas around the model-predicted mean ΔHR (solid blue and red line) represent the 90%CI around mean ΔHR.

Source: FDA Reviewer

Japanese patients from the Phase 3 studies have about 17% higher tirzepatide exposure and Cmax,ss compared to non-Japanese patients due to lower body weight, with a median WT of 90 kg in non-Japanese patients compared to a median WT of 76 kg in the Japanese patients from the Phase 3 studies. At the highest maintenance dose of 15 mg, the predicted median, 95th percentile and maximum tirzepatide Cmax,ss in Japanese patients are 2268 ng/mL, 2952 ng/mL and 4006 ng/mL (Figure 18, lower panel and Table 13), and the associated predicted mean ΔHR are 11.6 bpm, 13.1 bpm and 15.3 bpm, respectively (Figure 18, upper panel and Table 13). At the same Cmax,ss of tirzepatide, the expected mean ΔHR in non-Japanese patients are 5.9 bpm, 6.4 bpm and 7 bpm, respectively (Figure 18, Table 13). Under similar exposure, Japanese patients had higher mean increase in HR compared to non-Japanese. Therefore, the average difference in HR between Japanese and non-Japanese is not driven by the difference in exposure due to an average lower body-weight in non-Japanese.

Table 13. Mean (90%CI) Predicted ΔHR in Japanese and Non-Japanese Under Similar Tirzepatide Exposure (steady-state Cmax)

Dose (mg)	Cmax,ss level	Cmax,ss (ng/mL)	Model-predicted mean ΔHR (bpm)		Lower 90%CI of mean ΔHR (bpm)		Upper 90%CI of mean ΔHR (bpm)	
			Non-Japanese	***Japanese***	***Non-Japanese***	***Japanese***	***Non-Japanese***	***Japanese***
15 mg	**median**	2268	6.1	11.6	5.7	10.8	6.5	12.4
	75th percentile	2523	6.3	12.2	5.8	11.3	6.8	13.1
	95th percentile	2952	6.6	13.1	6.0	12	7.2	14.2
	maximum	4006	7.3	15.3	6.4	13.7	8.2	16.9

Note: Cmax,ss = steady-state maximum concentrations predicted using the individual PK parameters of Phase 3 studies Japanese patients and derived from the applicant PK model.

Source: FDA Reviewer

In conclusion, the concentration-HR analysis showed a positive effect of tirzepatide exposure on HR increase, with a non-linear relationship between tirzepatide concentrations and ΔHR. Japanese patients appear to be more sensitive to HR increase than non-Japanese under similar tirzepatide exposure. Japanese patients may need to be closely monitored for HR increase and potential cardiovascular events given the higher sensitivity to HR increase compared to non-Japanese. However, no dose adjustment is likely required in Japanese population, given the cardiovascular safety profile of tirzepatide in non-Japanese as well as in Japanese population (see the Clinical Review for further details) and the proposed gradual titration of tirzepatide treatment that will allow to control for potential adverse events.

4.5 Physiologically based Pharmacokinetic Modeling and Simulation Review

Physiologically based Pharmacokinetic Modeling and Simulation Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	215866
Drug Product	MOUNJARO (Tirzepatide)
Clinical Division	DCEP
Primary PBPK Reviewer	Yuching Yang, Ph.D.
Secondary PBPK Reviewer	Manuela Grimstein, M.Sc., Ph.D.
Applicant	Eli Lilly

EXECUTIVE SUMMARY

The aim of this review is to evaluate the adequacy of physiologically based pharmacokinetic (PBPK) modeling to predict the effect of tirzepatide-mediated delayed gastric emptying on the pharmacokinetics of acetaminophen, atorvastatin, digoxin, ethinyl estradiol, lisinopril, metformin, metoprolol, norgestimate, sitagliptin, and S-warfarin.

The Division of Pharmacometrics has reviewed the PBPK report (Study: LY3298176 PBPK GED 2), supporting modeling files, and the Applicant's responses to Clinical Pharmacology Information Request (IR) to conclude the following:

- PBPK analysis was considered adequate to provide a qualitative assessment of the effect of tirzepatide-mediated delayed gastric emptying on the PK of acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin. Results of PBPK analysis suggested that tirzepatide-mediated delayed gastric emptying is not expected to result in clinically meaningful impact on the PK of acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin.

Clinical DDI data (Study GPGR) will be used to address the effect of tirzepatide on the PK of ethinyl estradiol and norgestimate/norelgestromin

A. BACKGROUND

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) to improve glycemic control for patients with type 2 diabetes mellitus (T2DM). Tirzepatide is administered subcutaneously. The proposed starting dose is 2.5 mg weekly and can be increased in 2.5 mg increments after a minimum of 4 weeks up to 15 mg. The apparent clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days. Tirzepatide exhibited linear pharmacokinetics (PK) and the PK of tirzepatide is similar between healthy subjects and T2DM patients.

GLP-1 RAs like dulaglutide and tirzepatide have been shown to delay gastric emptying time. Dulaglutide delayed the gastric emptying (GE) time by about 2 hours in T2DM patients after the first dulaglutide

dose in a scintigraphy study[1]. The delay is largest after the first dose and diminishes after subsequent doses. The impact of dulaglutide on the PK of acetaminophen (a surrogate marker for gastric emptying delay) was also evaluated. For tirzepatide, the Applicant did not conduct a scintigraphy study. Study GPGA evaluated the impact of tirzepatide on acetaminophen PK in healthy subjects and T2DM patients after single or multiple doses of tirzepatide at a fix or at escalation dose levels. Table 1 presented the observed effect of GE delay on acetaminophen pharmacokinetic parameters before and after single or multiple dulaglutide or tirzepatide treatment.

Table 14. Observed acetaminophen pharmacokinetic parameters before and after single or multiple dulaglutide or tirzepatide treatment

		Observed PK ratio w/wo dulaglutide (Geo. Mean)	
Dose	Sub.	C_{max}	AUC
1 mg [Day 3] [a]	HV	0.64	0.88
1 mg [Day24] [b]	HV	0.95	0.99
3 mg [Day 3] [a]	HV	0.50	0.88
3 mg [Day24] [b]	HV	0.96	1.13

Source: BLA 125469 CSR GBCH Table 7.2
[a] Collected-on Day 2 after a single dose of dulaglutide
[b] Collected on Day 23 after fourth dose of dulaglutide

		Observed PK ratio w/wo tirzepatide (Geo. Mean)		
Dose	Sub.	C_{max}	T_{max} diff. (hour)	AUC
0.5 QW [Day 2] [a]	HV	0.95	0.17	0.97
0.5 QW [Day 23] [b]	HV	1.11	-0.17	1.07
1.5 QW [Day 2] [a]	HV	0.95	0	0.92
4.5 QW [Day 2] [a]	HV	0.5	1	0.87
4.5 QW [Day 23] [b]	HV	1.04	0.5	1.2
5/5/8/10 [Day 23] [c]	HV	0.99	1	1.21
0.5 QW [Day 2] [a]	T2M	1.1	0	1.11
0.5 QW [Day 23] [b]	T2M	1.15	-0.17	1.09
5 QW [Day 2] [a]	T2M	0.5	1	0.75
5 QW [Day 23] [b]	T2M	0.92	0.83	1.05
5/5/10/15 [Day 23] [d]	T2M	0.6	1	1.07

Source: PBPK report Section 6
[a] Collected on Day 2 after a single dose of tirzepatide
[b] Collected on Day 23 after fourth dose of tirzepatide administered QW for 4 weeks
[C] Collected on Day 23 after dosing 5 mg once a week on the first and second weeks, 8 mg on the third week, and 10 mg on the fourth week
[d] Collected on Day 23 after dosing 5 mg once a week on the first and second weeks, 10 mg on the third week, and 15 mg on the fourth week

Study GPGR evaluated the effect of tirzepatide on the PK of a combination oral contraceptive (OC), ethinyl estradiol 0.035 mg + norgestimate 0.25 mg, in healthy female subjects. Table 2 summarized the OC exposures with and without a single 5- mg dose of tirzepatide. Results of this study showed that C_{max} was reduced by 55% to 66% when the OC was administered in the presence of 5 mg tirzepatide compared to dosing with OC alone, while the AUC was reduced by 16% to 23%.

[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000ClinPharmR.pdf

Table 15. Observed OC PK before and after a single dose of tirzepatide

		Observed PK ratio w/wo 5 mg tirzepatide SD Geometric Means (90% CI range)					
		Ethinyl Estradiol			Norelgestromin		
Dose	Sub.	C_{max}	T_{max} diff. (hour)	AUC	C_{max}	T_{max} diff. (hour)	AUC
5 mg	HV, F	0.41 (0.36, 0.47)	4.23 (1.50, 6.50)	0.78 (0.73, 0.85)	0.45 (0.40, 0.50)	4.50 (1.50, 5.00)	0.78 (0.71, 0.84)

Source: Applicant's ClinPharSum Table 2.7.2.13.

A model risk evaluation form[2] was requested to identify the necessary level of validation and verification. In response to FDA's information request dated 11/23/2022, the Applicant considered the overall model risk as low. It is mainly driven by a large body of clinical evidence with several GLP-1 RAs, and the effect of delayed gastric emptying on small molecule pharmacokinetics is primarily a decrease in C_{max}, with minimal change in overall AUC. Also, as with other GLP-1 RAs, the effect of tirzepatide on gastric emptying is decreased with time (Applicant's Clin Pharm Summary).

In this submission, the extent of tirzepatide effect on gastric emptying was determined using compartment PK model and clinical data with acetaminophen. The PBPK modeling approaches were used to characterize the tirzepatide-mediated extent of GE delay and assess impact of the delayed GE on the PK exposures of other orally co-administered drugs, namely acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, S-warfarin, ethinyl estradiol, and norgestimate/ norelgestromin. The objective of this review is to evaluate the adequacy of the submitted PBPK analysis to estimate the effect of a single dose of 5 mg tirzepatide and of multiple doses rapidly escalated to either 10 or 15 mg tirzepatide on the exposure of the tested drugs.

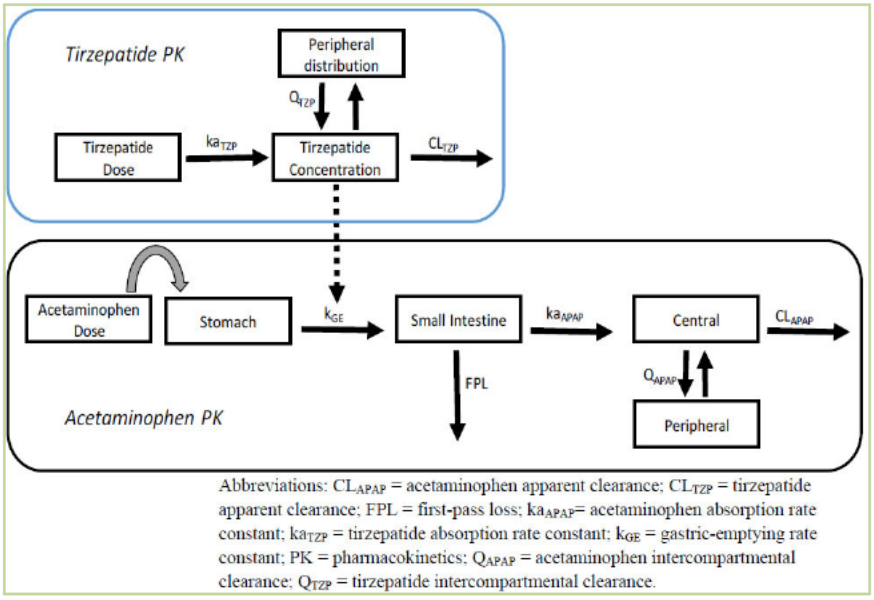
B. METHODS

1. Estimated delay in GE

Tirzepatide-mediated delay in GE time has been characterized using acetaminophen, which is a prototypical highly soluble and permeable drug for which the rate of absorption reflects GE rate. To evaluate the potential impact of delayed GE, a semi-mechanistic PK model was used to estimate the magnitude of delayed GE based on acetaminophen PK profiles following tirzepatide treatment (study GPGA). Figure 1 presents the schematic of the semi-mechanistic PK model for acetaminophen. Applicant reported that the GE delay was investigated in both healthy subjects and T2DM patients using acetaminophen PK as a surrogate of GE. Table 3 presents the estimated GE delay as a ratio of time to 50% GE of acetaminophen with and without dulaglutide or tirzepatide based on the observed acetaminophen PK profiles and semi-mechanistic PK model.

Figure **19.** *Schematic summary of the semi-mechanistic gastric emptying acetaminophen PK model*

[2] https://pubmed.ncbi.nlm.nih.gov/31652029/



Abbreviations: CL_{APAP} = acetaminophen apparent clearance; CL_{TZP} = tirzepatide apparent clearance; FPL = first-pass loss; ka_{APAP}= acetaminophen absorption rate constant; ka_{TZP} = tirzepatide absorption rate constant; k_{GE} = gastric-emptying rate constant; PK = pharmacokinetics; Q_{APAP} = acetaminophen intercompartmental clearance; Q_{TZP} = tirzepatide intercompartmental clearance.

Source: Applicant's Tirzepatide Population PK/PD Report (T2D) Figure 8.5

Table 16 Estimated dulaglutide- and tirzepatide-mediated fold change in gastric emptying time

Study GBCD T2DM subjects		Study GPGA Part B- Healthy subjects		Study GPGA Part C- T2DM subjects	
Dulaglutide (mg)	GE50 ratio (90% CI)	Tirzepatide (mg)	GE50 ratio (90% CI)	Tirzepatide (mg)	GE50 ratio (90% CI)
1[a]	2.6 (2.4, 2.8)	0.5[a]	1.06 (1.05, 1.07)	0.5[a]	1.01 (1.00, 1.01)
1.5[a]	3.1 (2.9, 3.3)	1.5[a]	1.30 (1.25, 1.38)	2.5[a]	1.43 (1.28, 1.77)
4.5[a]	4.8 (4.6, 5.0)	2.5[a]	1.66 (1.54, 1.82)	5[a]	3.78 (2.92, 5.58)
[a] Data collected on Day 2 after a single dose of dulaglutide		4.5[a]	2.58 (2.29, 2.99)	0.5 [Day 23][b]	1.00 (1.00, 1.00)
		5.0[a]	2.86 (2.48, 3.29)	5 [Day 23][b]	1.09 (1.06, 1.16)
		0.5 [Day 23][b]	1.01 (1.01, 1.01)	5/5/10/10 [Day 23][b]	1.60 (1.40, 2.01)
		1.5 [Day 23][b]	1.04 (1.04, 1.06)	5/5/10/15 [Day 23][d]	2.67 (2.08, 3.77)
		4.5 [Day 23][b]	1.23 (1.19, 1.29)		
		5/5/8/10 [Day 23][c]	1.77 (1.62, 1.94)		
		[a] Collected on Day 2 after a single dose of tirzepatide [b] Collected on Day 23 after fourth dose of tirzepatide administered QW for 4 weeks [c] Collected on Day 23 after dosing 5 mg once a week on the first and second weeks, 8 mg on the third week, and 10 mg on the fourth week [d] Collected on Day 23 after dosing 5 mg once a week on the first and second weeks, 10 mg on the third week, and 15 mg on the fourth week			

Source: LY2189265 PBPK GED report table 3.2.1and LY3298176 PBPK GED 2Table 3.1, 3.2

Reviewer's comments:

The values for baseline GE rate constant (K_{GE}) were generally similar for the healthy subjects and T2DM patients in tirzepatide's Study GPGA-Parts B and C (1.26 h^{-1} vs. 1.03 h^{-1}, respectively). The values were also generally similar between healthy subjects in studies GPGA-Part B and GBCH (1.26 h^{-1} and 1.31 h^{-1}, respectively). However, it was noted that the baseline GE rate constant was higher (3.49 h^{-1}) in T2DM patients in dulaglutide's Study GBCD. The Applicant explored the baseline demographics between studies and no overt differences were noted. The reason for such a discrepancy remains unknown.

2. Description of PBPK models of the test drugs

A set of 8 drugs was included in this analysis as shown in Table 4. Since clinical data was available to address the effect of tirzepatide on the PK of ethinyl estradiol and norgestimate (Study GPGR), PBPK analyses of ethinyl estradiol and norgestimate were not included in this review. PBPK models of the tested drugs were developed in the population based PBPK software Simcyp® (V16, V17 and V18). Reviewer's analyses were conducted in Simcyp® V18.

Table 17 Selected biochemical and absorption characteristics of the tested drugs included in the PBPK analysis

	Drug	Food effect [a] (per USPI)	Obs. F	Obs. T_{max} (hour)	Dosage form in the model[#]	Peff (x e-4 cm/s)[b]	Fa[c]	Proposed BCS class[d]
1	Acetaminophen	Not available in over-counter label	~0.9	~1 hr	solution	5.39	1	BCS I
2	Metoprolol	Not significant	~0.5	~4hr	ER solid	1.3	0.7	BCS I
3	S-warfarin	Cation with Vitamin K rich food	~0.95	~2hr	solution	12	1	BCS I/II
4	Atorvastatin	Both AUC and C_{max}↓30%,	0.1-0.2	1-2hr	solution	4.49	1	BCS II
5	Ethinylestradiol	C_{max}↓30%, no effect on AUC	~0.6	~3hr	IR solid	5.76	0.95	BCS I/III
6	Norgestimate	Not available	~0.5	~2hr	IR solid	3.37	1	BCS I/III
7	Sitagliptin	Not significant	~0.87	1-4hr	IR solid	1.16	0.87	BCS I/III
8	Lisinopril	Not significant	~0.3	~7hr	solution	0.112	0.3	BCS III
9	Metformin	AUC ↓25%, C_{max}↓40%,	0.5-0.6	~ 7hr	solution	0.34	0.37	BCS III
10	Digoxin	Not available	0.7-0.8	~1hr	solution	1.44	0.8	BCS IV

Reference:

1 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022450Orig1s000ClinPharmR.pdf; https://pubmed.ncbi.nlm.nih.gov/2844083/
2 https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018704s025lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_017963.pdf; Applicant's clinical study #GBCO
3 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5702344/; https://d-nb.info/1184447233/34; Applicant's clinical study #GBCS
4 https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s057lbl.pdf; https://pubmed.ncbi.nlm.nih.gov/2844083/
5 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022573Orig1s000ClinPharmR.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-490_Norethindrone%20and%20Ethinyl%20Estradiol_BioPharmr.pdf; Applicant's clinical study #GBCQ
6 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022573Orig1s000ClinPharmR.pdf; https://pubmed.ncbi.nlm.nih.gov/2844083/; Applicant's clinical study #GBCQ
7 https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s019lbl.pdf; https://www.ema.europa.eu/en/documents/scientific-guideline/sitagliptin-film-coated-tablets-25-50-100-mg-product-specific-bioequivalence-guidance_en.pdf
8 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019777s076lbl.pdf; https://pubmed.ncbi.nlm.nih.gov/2844083/
9 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020357s037s039,021202s021s023lbl.pdf; https://pubmed.ncbi.nlm.nih.gov/2844083/
10 https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21648lbl.pdf; https://d-nb.info/1184447233/34; Applicant's clinical study #GBC

Note: [a] All tested drugs were recommended to be taken with or without food per USPI; [b] Human permeability (Peff) used as input parameter; [c]Estimated fraction absorbed (Fa) summarized from PBPK reports and submitted model output files; [d]Based on the literature cited in the reference, it may not reflect FDA's opinion

The Applicant developed PBPK models for acetaminophen, atorvastatin, lisinopril and sitagliptin. In-vitro apparent permeability (Papp) values was measured in MDCK assays for acetaminophen, metformin, metoprolol, sitagliptin, and S-warfarin to support the Papp in the corresponded PBPK models.

The acetaminophen model is based on a model published by Jiang et al.[3] (2013) and modified to include a description of acetaminophen absorption using the ADAM model. The Applicant's atorvastatin PBPK models described the interconversion between acid and lactone forms of atorvastatin and tracked the production and elimination of the active metabolite, o-hydroxyatorvastatin (OH-ATV). Atorvastatin is mainly metabolized by CYP3A4 to two active metabolites, OH-ATV and p-hydroxyatorvastatin. Given p-hydroxyatorvastatin is present in plasma at <10% of the total AUC, only OH-ATV is included in atorvastatin models. Following oral administration of atorvastatin, interconversion of acid and lactone forms can occur non-enzymatically, and this process is pH dependent. Lactone-atorvastatin can be converted back to atorvastatin or metabolized by CYP3A to active hydroxy metabolites. The Applicant's PBPK analysis for atorvastatin were conducted by running two independent models for atorvastatin and lactone-atorvastatin. The initial dose atorvastatin is divided as atorvastatin or lactone-atorvastatin form and used as the initial dose in two models. The allocation of initial dose as atorvastatin or lactone-atorvastatin is dose-dependent as presented in Table 5. The development of Applicant's atorvastatin PBPK models was detailed in Morse et al[4] (2019). The PBPK model for lisinopril includes an ADAM oral model and a full distribution PBPK model. In-vitro and in-vivo data from literature were used to inform its model parameters. The Applicant assumed that lisinopril is renally cleared. Sitagliptin PBPK model was built based on physicochemical and biological in vitro and in vivo data. It included an ADAM oral model and a full distribution PBPK model. Sitagliptin is cleared by CYP3A pathway and renal clearance.

For other compounds, the default compound files developed by Simcyp were utilized. Default models for metformin, metoprolol, and S-warfarin were modified to include ADAM models. For metformin, the Applicant modified the default model to include an ADAM oral model with solution formulation. The Applicant's rationale for selecting a solution formulation is that metformin exhibits high solubility and rapid dissolution profiles. For metoprolol, the ADAM oral model with a controlled release formulation was implemented. In-house Papp parameter was initially used and later refined to fit the clinical data. The dissolution profile for extended-release metoprolol was obtained from ANDA090615. For S-

[3] https://pubmed.ncbi.nlm.nih.gov/24132164/
[4] https://pubmed.ncbi.nlm.nih.gov/31250974/

warfarin, both immediate release (IR) formulation and a solution were included in the ADAM model. The Applicant stated that there is no difference between the C_{max} or T_{max} simulated using two formulations. Therefore, a solution was used in the model, and it was assumed precipitation would not occur in the stomach or the small intestine.

Reviewer's comments:

In order to describe the effect of a delay in the gastric residence time, a mechanistic absorption model is required. However, the absorption parameters such as permeability, solubility, diffusion coefficient and particle sizes were often derived from in-vitro data or in-silico predictions. The accuracy of these parameters may not always be informed by clinical PK data such as plasma concentration. Thus, FDA required sensitivity analysis between the key absorption parameters on the PK for the tested drugs. See Result section for more discussion.

Reviewer also noted that a less conventional approach was used for the development of atorvastatin PBPK model. Instead of one PBPK model, the PK profiles of atorvastatin and the active metabolite, OH-ATV, were simulated separately using two models. The PBPK model for atorvastatin acid tracked the biotransformation of atorvastatin acid and OH-ATV, and the model for atorvastatin lactone tracked the conversion of atorvastatin lactone to atorvastatin acid, and subsequently atorvastatin acid to OH-ATV. Finally, the PK profiles of atorvastatin and the active metabolite, OH-ATV, were computed by adding the outputs of atorvastatin and OH-ATV from two models. Reviewer noted that there were no changes in model inputs across different exposure scenarios, except for the fraction absorbed. Therefore, this model was considered acceptable to describe the dose-PK relationships. The ability of this model to simulate the PK profiles other than dosing differences, such as changes in metabolism activity, has not been verified.

Table 18. Dose-depended faction absorbed as atorvastatin acid or lactone in atorvastatin PBPK model

atorvastatin dose	0.1 mg	10 mg	20 mg	40 mg	80 mg
% dose absorbed as atorvastatin acid	8	12	20	25	41
% dose absorbed as lactone	92	88	80	75	59

Source PBPK report 8.6

3. *Incorporate GE effects in the PBPK model*

To assess the effect of tirzepatide on the absorption of concomitant drugs, the fold change in GE time estimated based on acetaminophen data was applied to the PBPK models of the tested drugs.

The fold changes in GE (i.e., ratios listed in Table 3) were applied to the gastric Mean Residence Time (MRT), a model parameter in the GI physiology section of Simcyp' s virtual health population. The baseline MRTs in the fasted and fed states are set as 0.27 and 1.18 hours, respectively. The Applicant assumed that the tirzepatide-mediated fold change in MRT is the same in the fasted and fed states.

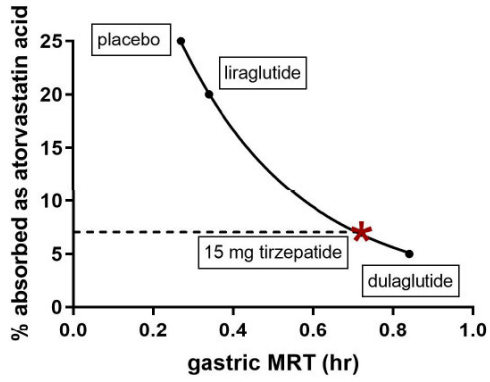
Reviewer's comments:

A similar modeling analysis was used to describe the dulaglutide-GE delayed effects on atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin in fasted condition and acetaminophen and S-warfarin in fed conditions. The PBPK analysis was used to describe the observed PK changes with and without dulaglutide. The PBPK analysis submitted for dulaglutide is considered exploratory. However, it provides some confidence on using fold-change in MRT to simulate both clinically significant and non-

significant[5] GED effects. The reviewer considers that Applicant's assumption that the fold-change in GE time is independent of prandial state has yet to be justified. Additional simulation was recommended to evaluate the effect of the GE delay on the substrate's PK parameters under both fasted and fed state. See discussion on model uncertainties and sensitivity analysis in Result section.

For atorvastatin, in addition to changes in gastric MRT, the fraction of atorvastatin absorbed as acid was estimated empirically based on the dose (MRT)-response (% absorbed) relationship derived using data observed from liraglutide and dulaglutide. An empirical relationship between fractions absorbed and MRT was first established using placebo data (25% absorbed, MRT of 0.27 hour) and dulaglutide (5% absorbed, MRT of 0.84 hour with 1.5 mg dulaglutide). The fractions of atorvastatin absorbed as acid when co-administered with dulaglutide was obtained by fitting to the observed data. A 38% and 5% decreased in C_{max} and AUC of atorvastatin was observed when coadministration with an escalation dosing of 0.6/1.2/1.8 mg of liraglutide at steady state (23 days). The magnitude of liraglutide-mediated GE delay at steady state is not known. A 31% and less than 5% decreased in C_{max} and AUC of acetaminophen was observed when coadministration with an escalation dosing of 0.6/1.2/1.8 mg of liraglutide at steady state (23 days). Thus, the liraglutide-mediated GE delay steady state is expected to be low. Reviewer concluded that due to limited clinical datapoint, the dose-response relationship between fractions absorbed and MRT for atorvastatin is considered exploratory. There is uncertainty in the predicted fractions absorbed of atorvastatin when administrated with 5 mg SD tirzepatide, and subsequently, the predicted GED effect. The dose-response relations of MRT and fraction absorbed was shown in Figure 2.

Figure 20. Relationship between observed effect GLP1RAs on gastric mean residence time (MRT) and estimated fraction atorvastatin absorbed as acid.



Assigned fraction absorbed in the PBPK models

Atorvastatin dose = 40 mg					
	Baseline	liraglutide	5/5/10/15 tirzepatide	1.5 mg dulaglutide	5 mg tirzepatide
MRT (fasted) used in the PBPK simulation (hour)	0.27	0.35	0.72	0.84	1.02
% dose absorbed as atorvastatin acid	25	20	7	5	0
% dose absorbed as lactone	75	80	93	95	100

Source: PBPK report figure 4.5, and extracted from PBPK outputs

4. Model validation

For each tested drug, the model validation of the model to describe the PK profiles was performed by comparing model predicted with observed PK profiles following single or multiple administration, as well as different dosing levels. The ability of PBPK analysis to capture the impact of GE on a drug's PK is demonstrated by comparing the predicted and observed PKs of acetaminophen after administration of tirzepatide by incorporating tirzepatide-mediated MRT value.

[5] Reviewer defined a non-clinically significant changes as less than 25% changes in PK parameters such as AUC and Cmax for a drug which is not NTI.

5. Sensitivity analysis

The Applicant conducted sensitivity analyses to evaluate the changes in the simulated PK of the tested drug around a range of gastric MRTs encompassing the range of gastric MRT following a single (5 mg SD) and multiple dosing (5/5/10/15 mg) of tirzepatide. On November 23, 2021, FDA issued an information request for additional simulations and sensitivity analyses to investigate the uncertainties regarding the modeling approaches used to estimate tirzepatide-mediate GE delay, potential food effect and absorption model parameters. Refer to Results and Discussion sections for more details.

C. RESULTS

1. Can the model describe the PK profiles of the tested compounds?

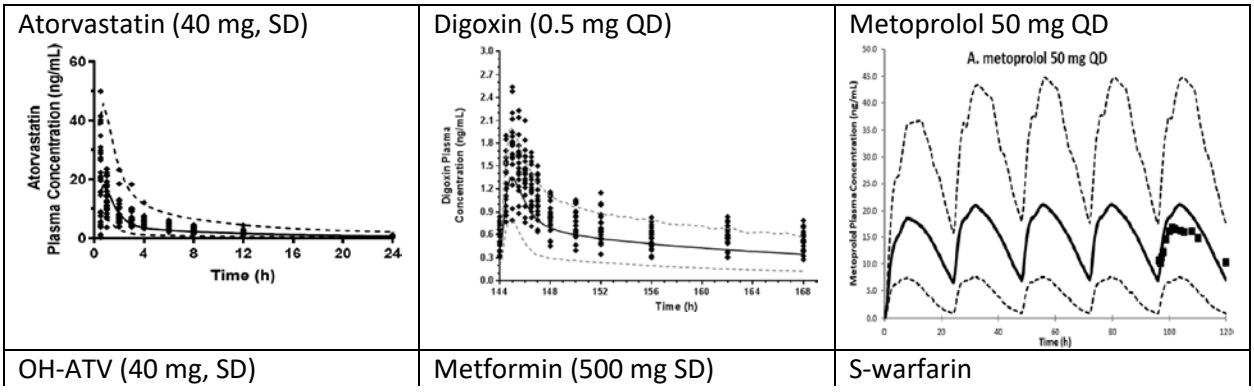
Yes. The Applicant's PBPK models for acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin reasonably described the respective clinical PK data following a single or multiple dose administration of each drug across different dosing levels. Table 6 and Figure 3 presented the selected PK verification of the tested drugs.

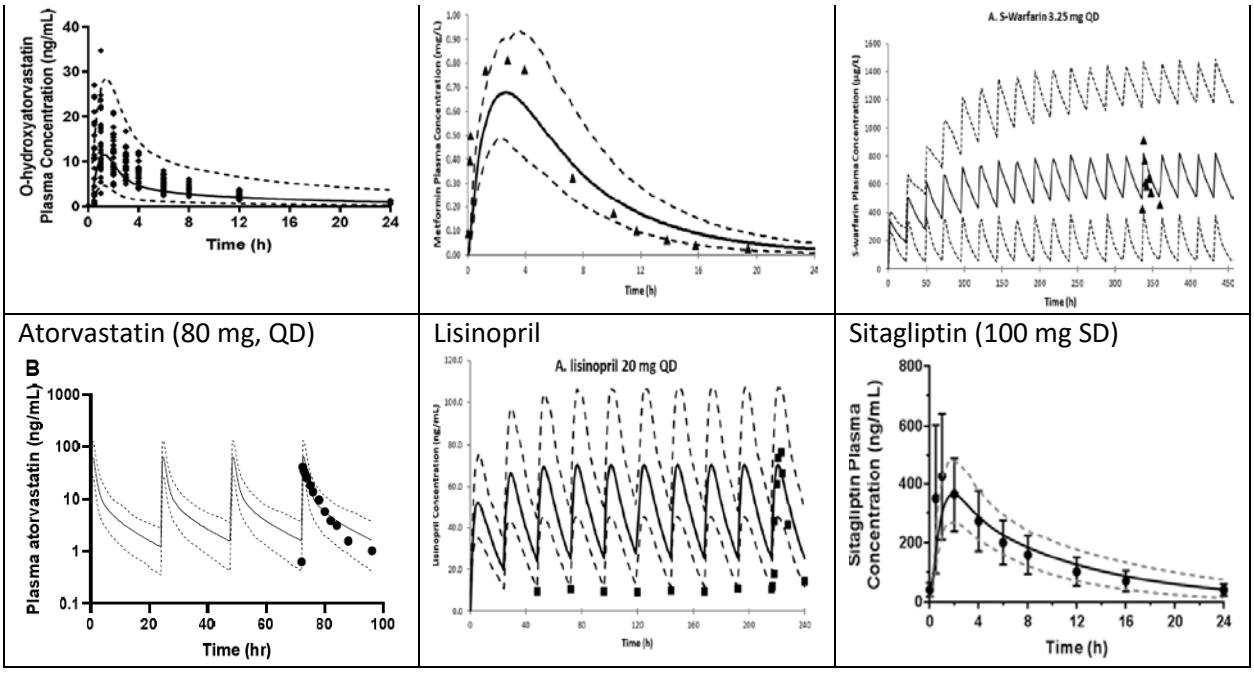
Table 19. Comparison of the observed and simulated PK parameters for acetaminophen under various dosing levels

Dose	500 mg SD (fasted)			500 mg SD (fed)			1000 mg QD (fasted)		
	AUC [a]	C_{max} [b]	T_{max} hour	AUC [a]	C_{max} [b]	T_{max} hour	AUC [a]	C_{max} [b]	T_{max} hour
Observed data	24.26	7.26	0.28	24.97	4.58	2.49	57	17.4	0.8
Pred/Obs ratio	1.03	0.64	0.43[d]	1.02	0.77	-0.35	0.89	0.73	0.13 [d]

Source Applicant's PBPK report Table 8.1 and 8.5. SD: single dose; QD: once daily dose; [a]AUCinf:µg·h/mL; [b]C_{max}: µg·h/mL; [c]AUC (0-t): µg·h/mL; [d]Difference of the predicted and the observed tmax values.

Figure 21. Comparison of the observed and simulated plasma concentration-time profiles for tested drugs





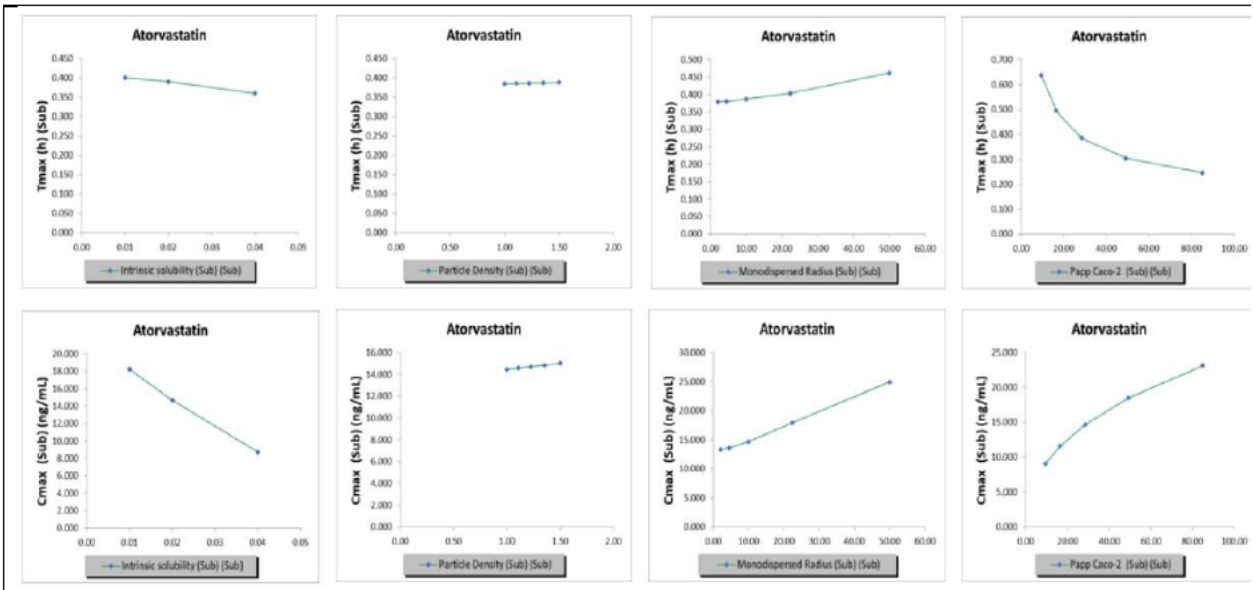
Source: PBPK report. Atorvastatin (Figure 4.3); OH-ATV (Figure 4.3); Digoxin (Figure 4.6); Metformin (Figure 8.29); Lisinopril (Figure 8.28); Metoprolol (Figure 8.37); S-warfarin (Figure 8.68); Sitagliptin (Figure 4.12). Solid points represent observed data, solid and dotted red represent medium, 5th and 95th percentiles of the simulated profiles.

Sensitivity analysis of the absorption parameters on the PK of the tested drugs

FDA recommended conducting a sensitivity analysis between the key absorption parameters and the simulated PK for the tested drugs. Applicant evaluated the sensitivity of solubility, particle size, permeability, and particle density values on the PK of digoxin, lisinopril, metformin, S-warfarin, and atorvastatin, and the sensitivity of the dissolution parameters on the PK of metoprolol and sitagliptin. In general, there was a lack of sensitivity associated with the selected parameters on the simulated PK of the tested compounds, except permeability. Increase permeability would lead to a higher C_{max} and lower T_{max} in digoxin, lisinopril, metformin, S-warfarin, and atorvastatin. In the case of atorvastatin, changes in solubility and permeability would impact the predicted C_{max} as shown in Figure 4.

Reviewer's independent analysis of key absorption parameters, which could describe the clinical PK of the respective drug, showed minimal or no impact of parameter uncertainties on the predicted effect of tirzepatide-mediated GE delay. Refer to Discussion Section for the example of lisinopril.

Figure 22. Sensitivity analyses of absorption inputs parameters on the PK of atorvastatin



Abbreviations: Cmax = maximum plasma concentration; Tmax = time at maximum plasma concentration.

Source: Applicant's response to FDA's IR Figure 4.9

2. Can the fold-change approach describe the impacted of GE delay on the PK of acetaminophen?

Yes, by incorporating the fold-change in MRT derived using population PK model, the Applicant was able to reproduce the changes in the PK of acetaminophen before and after single (Day 2) or multiple (Day 23) tirzepatide treatment as summarized in Table 7.

Table 20. Comparison of observed and simulated acetaminophen pharmacokinetic parameters before and after single or multiple tirzepatide treatment

		Observed PK ratio w/wo tirzepatide			Predicted PK ratio w/wo tirzepatide		
Dose	Sub.	C_{max}	T_{max} difference (hour)	AUC	C_{max}	T_{max} difference (hour)	AUC
0.5 QW [Day 2]	HV	0.95	0.17	0.97	0.98	0.08	1
0.5 QW [Day 23]	HV	1.11	-0.17	1.07	1	0.02	1
1.5 QW [Day 2]	HV	0.95	0	0.92	0.92	0.38	1
4.5 QW [Day 2]	HV	0.5	1	0.87	0.7	1.55	0.97
4.5 QW [Day 23]	HV	1.04	0.5	1.2	0.94	0.3	1
5/5/8/10 [Day 23]	HV	0.99	1	1.21	0.82	0.88	0.99
0.5 QW [Day 2]	T2M	1.1	0	1.11	1	0.02	1
0.5 QW [Day 23]	T2M	1.15	-0.17	1.09	1	1	1
5 QW [Day 2]	T2M	0.5	1	0.75	0.59	2.35	0.95
5 QW [Day 23]	T2M	0.92	0.83	1.05	0.97	0.15	1
5/5/10/15 [Day 23]	T2M	0.6	1	1.07	0.69	1.62	0.97

Source: Applicant's PBPK report

3. Is the PBPK analysis adequate to predict effects of GE delay in the tested drugs?

The model is adequate to provide qualitative assessment in term of PK charges in the test drug given the clinical experience with dulaglutide, and current understanding of the GE delay mechanism. Table 8 presented the predicted geometric mean C_{max} and AUC ratios for atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin following two tirzepatide exposure scenarios in the fasted state. The results suggested that for drugs with high permeability, high solubility, and fast dissolution (e.g., acetaminophen, digoxin, sitagliptin and S-warfarin), the absorption rates are limited by gastric emptying and an impact of tirzepatide on the C_{max} and T_{max} is expected. For the drugs where gastric emptying is not likely the rate limiting step in drug absorption (e.g., lisinopril and metformin) tirzepatide is predicted to have little impact on drug T_{max} and C_{max}. However, the predictability of this PBPK analysis to provide a quantitative estimation of the effects of GE delay on the PKs of tested drugs has not been fully established. Currently, this modeling approach has only been verified with one other GLP-1 RA, namely dulaglutide. Nevertheless, PBPK analysis suggested that tirzepatide-mediated delayed gastric emptying is not expected to result in clinically meaningful impact on the PK of acetaminophen, atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin.

Table 21. Simulated impact of GE delay on the PK parameters for tested drugs following a single or multiple administration of tirzepatide

a Predicted AUC and C_{max} Ratios for Drugs with and without a single dose of 5 mg Tirzepatide

Compound	Geometric Mean AUC Ratio (90% CI)	Geometric Mean C_{max} Ratio (90% CI)
Atorvastatin (0-inf)	0.69 (0.67 to 0.72)	0.14 (0.13 to 0.16)
o-Hydroxyatorvastatin (0-inf)	0.92 (0.89 to 0.95)	0.31 (0.28 to 0.34)
Total atorvastatin-related active species (0-inf)	0.83 (0.80 to 0.85)	0.23 (0.0.21 to 0.25)
Digoxin (0-24 h)	1.00 (0.91 to 1.09)	0.78 (0.73 to 0.83)
Lisinopril (0-24 h)	1.00 (0.92 to 1.07)	0.98 (0.92 to 1.04)
Metformin (0-24 h)	1.00 (0.94 to 1.07)	0.91 (0.86 to 0.96)
Metoprolol (0-24 h)	1.29 (1.12 to 1.48)	1.34 (1.18 to 1.52)
Sitagliptin (0-24 h)	1.00 (0.95 to 1.05)	0.89 (0.86 to 0.93)
S-warfarin (0-inf)	1.00 (0.85 to 1.17)	0.82 (0.78 to 0.86)

b Predicted AUC and C_{max} Ratios for Drugs with and without 5, 5, 10, and 15 mg of Tirzepatide (Day 23)

Compound	Geometric Mean AUC Ratio (90% CI)	Geometric Mean C_{max} Ratio (90% CI)
Atorvastatin (0-inf)	0.78 (0.76 to 0.80)	0.28 (0.27 to 0.29)
o-Hydroxyatorvastatin (0-inf)	0.95 (0.93 to 0.97)	0.41 (0.38 to 0.43)
Total atorvastatin-related active species (0-inf)	0.88 (0.86 to 0.90)	0.34 (0.32 to 0.35)
Digoxin (0-24 h)	1.00 (0.91 to 1.09)	0.85 (0.79 to 0.9)
Lisinopril (0-24h)	1.00 (0.93 to 1.08)	0.99 (0.93 to 1.06)
Metformin (0-24h)	1.00 (0.93 to 1.07)	0.95 (0.89 to 1.00)
Metoprolol (0-24h)	1.18 (1.03 to 1.36)	1.22 (1.08 to 1.39)
Sitagliptin (0-24h)	1.00 (0.95 to 1.05)	0.94 (0.9 to 0.98)
S-Warfarin (0-inf)	1.00 (0.85 to 1.17)	0.88 (0.84 to 0.92)

Source: Applicant's PBPK report Table 6.31, 6.32

D. DISCUSSION

1. What is the uncertainty in the predicted GE delay effects using different MRT values?

Alternative approach to estimate the tirzepatide-mediated GE delay

A semi-mechanist PK model was used to derive the fold-change in GE time induced by tirzepatide. In response to FDA' request for information dated 11/23/2021, the Applicant conducted additional analyses to evaluate the absolute (range) for GE delay from the clinical DDI data and its impact on the extent of predicted drug-drug interaction. Table 9 compared the values of gastric residence time derived using the absolute (range) values and those based on fold-change.

Table 22. Comparison of the values of gastric residence time derived using the absolute (range) values and those based on fold-change

	Absolute range approach			Fold-changes from the baseline approach		
Parameter	MRT (h)			MRT (h)		
	Control	tirzepatide 5 mg Day 2	tirzepatide 5/5/10/15 mg	Control	tirzepatide 5 mg Day 2	tirzepatide 5/5/10/15 mg
median	1.23	2.85	3.46	1.23	4.65	3.28
5% percentile	0.46	1.10	1.30	1.23	3.59	2.55
95 percentiles	2.59	7.11	6.42	1.24	6.86	4.63

Source: extract from IR response Table 4.3 and PBPK report Table 3.2

The Applicant compared the effects of tirzepatide on atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin using the median resident time derived using two different approaches. Except for acetaminophen and atorvastatin, the magnitude of changes in the PK (i.e., AUC and C_{max}) simulated using different RT values were less than 15%. Table 10 compared the predicted PK parameters for acetaminophen and atorvastatin using the different gastric residence time values. A more pronounced effect on C_{max} was seen in predicted acetaminophen and atorvastatin using fold-changes approach following 5 mg tirzepatide on day 2, but not on AUC. That is likely due to MRT value estimated using absolute range approach is higher than that with fold-change approach.

Table 23. Predicted PK parameters for acetaminophen and atorvastatin using the different gastric residence time values

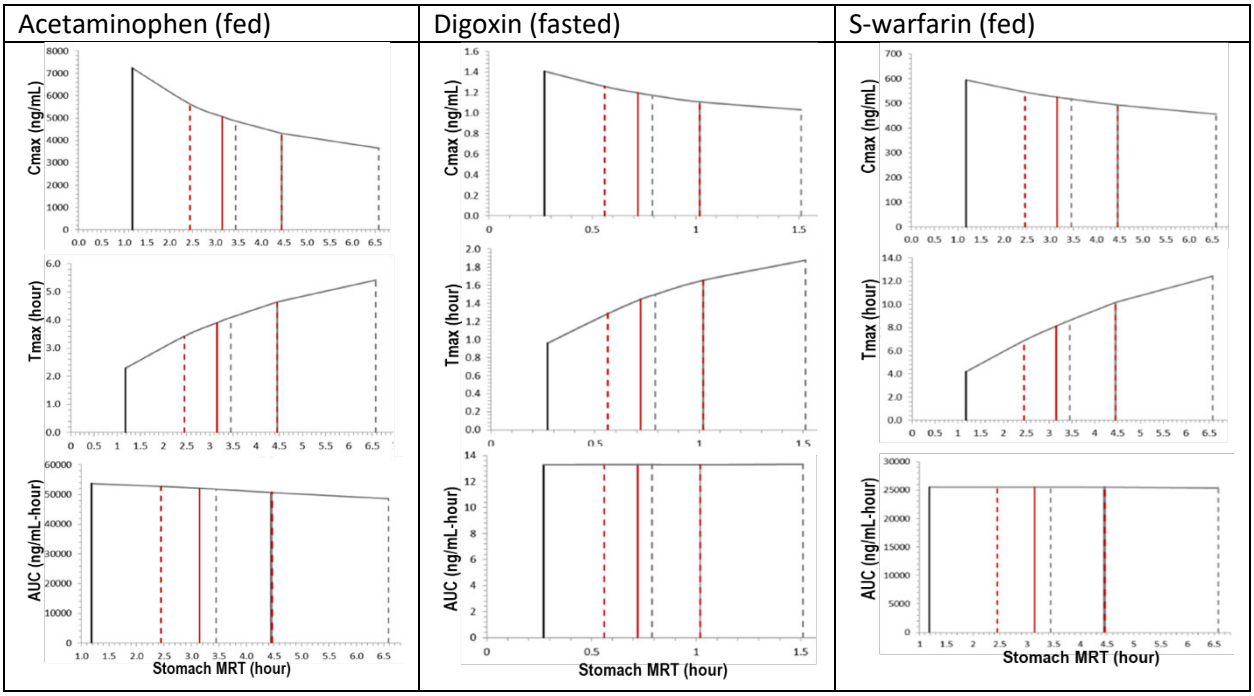
	Absolute range approach		Fold-change approach	
Drug	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio
5 mg Day 2				
Acetaminophen	0.98	0.73	0.95	0.59
Atorvastatin (total active species)	0.92	0.70	0.83	0.23
5-5-10-15 mg Day 23				
Acetaminophen	0.97	0.67	0.99	0.85
Atorvastatin (total active species)	0.91	0.40	0.88	0.34

Source: Fold-change approach: PBPK report Table 6.14, 6.28, 6.31, 6.32

Sensitivity of the simulated PK over a range of MRT

Applicant conducted sensitivity analysis of the MRT on the PK of the tested compounds. Figure 5 showed the results of SA for the selected compounds where steeper MRT-PK relationships in comparison to other tested drugs were simulated when MRT varies from 0.27-1.5 (fasted) and 1.18-6.5 (fed) hour. As shown in Figure 5, prolong MRT values results higher impact on C_{max} and T_{max} while minimal impact on drug's AUC were simulated.

Figure 23. Sensitivity analysis of MRT values on the PK of the tested drugs



PBPK report Figure 5.4, 5.5, 5.10. The vertical black line represents the median stomach MRT without tirzepatide. The grey solid line represents the median stomach MRT after a single 5 mg dose of tirzepatide and the grey dotted lines represent the 5th and 95th percentiles of the stomach MRT. The red solid line represents the median stomach MRT after 4 weeks of titration dosing (5 mg, 5 mg, 10 mg, and 15 mg) of tirzepatide and the dotted red lines represent the 5th and 95th percentiles of the stomach MRT.

2. What is the uncertainty regarding the food effect on the tirzepatide-mediated GE delay?

In the current DDI analysis, the clinical GE delay induced by tirzepatide under fasted state is not available. The Applicant assumed that the fold-change in GE time is independent of prandial state. In response to FDA's IR, Applicant acknowledges that there is no direct comparison of any single GLP-1 receptor agonist assessed with the same small molecule comedication in both the fed and fasted states. The Applicant noted that clinical studies suggested that gastric emptying delay is not an additive phenomenon that increases indefinitely. Currently, there is no data to suggest that the food induced delay in GE is lessened following the GLP-1 effect. Although indirect, it suggested GLP-1 effect and food effect occur via different mechanisms and would therefore be independent from each other.

Reviewer considers Applicant's assumption that the fold-change in GE time is independent of prandial state has yet to be justified. In response to FDA's IR, the Applicant conducted additional simulations which assumed that the effect of food and the GLP-1 receptor agonist on gastric mean residence time were additive. A deconvolution method was used to estimate the tirzepatide -mediated MRT by subtracting the baseline/control gastric mean residence time in fed state from the absolute gastric mean residence time in the presence of tirzepatide in the fed state. In the simulation, tirzepatide-mediated MRT (further adjusted with MRT ratio as shown in Table 3) was added' to the baseline of the fasted or fed state. Based on the Applicant's simulations (as shown in Table 11), the model suggested a modest change in the PK of tested drugs with and without food when assuming the effect of food and the tirzepatide-mediate GED are additive. This simulation only considered the effects of food on baseline MRT, without considering other factors such as changes in bile acid. There is no collective agreement on

whether there are other GLP-1 RA-induced physiological changes which might impact the drug absorption such as bile acid. Smits et al[6] reported that sitagliptin appears to increase hepatic bile acid production following 12 weeks of treatment, while liraglutide increased the serum CDCA concentration but did impact other bile acid species including CA, TCA, and LCA. Secondary bile acids are known to increase intestinal permeability and bile salts could increase the solubility of hydrophilic drugs.

Table 24. Predicted AUC and C_{max} Ratios for drugs in the fasted and fed state when co-administered with tirzepatide 5 mg on Day 2 using additive method

	Fasted		Fed		Fed/Fasted AUC ratio	Fed/Fasted C_{max} ratio
	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio		
Atorvastatin (total active species)	0.89	0.40	0.92	0.40	1.03	1.00
Digoxin	1.00	0.87	0.99	0.66	0.99	0.76
Lisinopril	1.00	0.99	1.00	0.93	1.00	0.94
Metformin	1.00	0.96	1.00	0.82	1.00	0.85
Metoprolol	1.02	1.07	1.00	1.01	0.98	0.94
Sitagliptin	1.00	0.95	1.00	0.83	1.00	0.87
S-warfarin	1.00	0.98	1.00	0.90	1.00	0.92

Source: Applicant's Response to FDA's IR Table 4.5 (fed) and Table 4.7 (fasted)

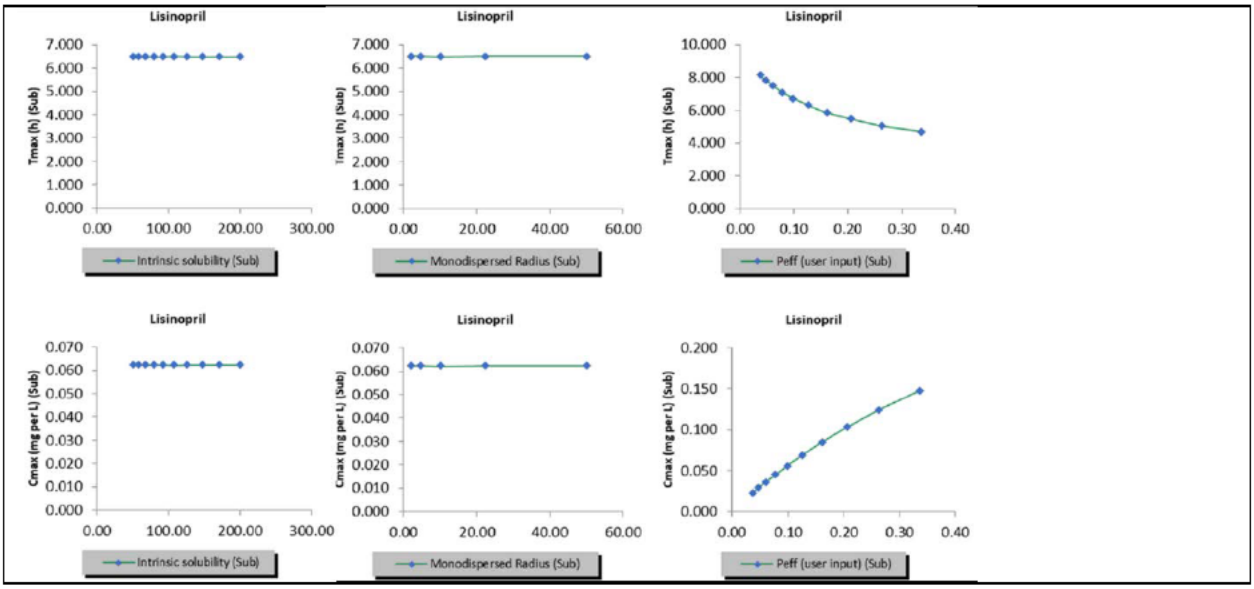
3. Sensitivity of absorption parameters on the effect of GLP-RA on the PK of the tested drugs

Based on the results of sensitivity analysis, a higher permeability would lead to a higher predicted C_{max} in digoxin, lisinopril, metformin, S-warfarin, and atorvastatin in the baseline condition (no GE delay). Additional sensitivity analyses were conducted by FDA reviewer to check the impact of permeability on the magnitude of impact of GE delay on the PK of tested drug (i.e., lisinopril).

As shown in Figure 6, simulated C_{max} and T_{max} values of lisinopril are sensitive to the permeability parameter used in the model. The Peff value of 0.112 x e-4 cm/s for lisinopril was estimated based on the clinical data to match the observed fraction absorbed in human.

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5129471/

Figure 24. Sensitivity analyses of absorption inputs parameters on the PK of lisinopril



Source: IR response figure 4.5

Two permeability values, 0.08 x e-4 cm/s and 0.18 x e-4 cm/s, were selected to provide a simulated AUC within 25% of that simulated using the Applicant's lisinopril PBPK model. The GE impacts were simulated using the alternative permeability parameters and the workspace files submitted by the Applicant. As shown in Table 12, the impact of GE delay (longer MRT) on PK of lisinopril is similar across simulations using different permeability parameters.

Table 25. Sensitivity analyses of permeability and GE delay on the PK of lisinopril

	Peff = 0.112 x e-4 cm/s			Peff = 0.08 x e-4 cm/s			Peff = 0.18 x e-4 cm/s		
MRT (hour)	AUC ratio	C_{max} ratio	T_{max} ratio	AUC ratio	C_{max} ratio	T_{max} ratio	AUC ratio	C_{max} ratio	T_{max} ratio
0.27 hr. (baseline)	1.00	1.00	1.00	0.78	0.76	1.01	1.29	1.38	0.95
1.51 hr. (w/ GED effect)	0.99	0.96	1.32	0.77	0.74	1.37	1.29	1.33	1.26

*The ratio is present as relative to the simulated PK values at baseline (MRT = 0.27, Peff = 0.112 x e-4 cm/s)

4. Previous clinical experience

Table 13 presents a summary of DDI dosing recommendation regarding the gastric emptying DDI for marketed GLP-1 RAs in US. There is no significant change (defined as 25% changes from the baseline) observed in the AUC of lisinopril or metformin (BCS class III) and/or atorvastatin (BCS Class II) following coadministration with dulaglutide[7] and liraglutide[8]. A 30-40% increase in the AUC of metformin and rosuvastatin was observed following the oral administration of semaglutide[9] at steady state. These changes were considered not clinically relevant for drugs where efficacy is AUC-mediated. For drugs dependent on threshold concentrations for efficacy or with narrow therapeutic index, the risk can be managed through labeling recommendations.

[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125469s044lbl.pdf
[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208583s014s015lbl.pdf
[9] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213051s006lbl.pdf

Table 26. Summary of gastric emptying DDI studies, mentioned in the FDA Label for GLP-1 RAs

	GLP-1 RA (Initial approved year)	Clinical data available to address GE delay[#]	FDA Dosing recommendation in section 7 regarding GED[*]
1	WEGOVY (semaglutide) (2017)	Digoxin, Oral Contraceptive, S-Warfarin, Lisinopril, Metformin, Atorvastatin, Furosemide, Levothyroxine	"… did not affect the absorption of orally administered medications";"...monitor the effects of oral medications concomitantly administered with (GLP-RA)"
2	ADLYXIN (lixisenatide) (2016)	Acetaminophen, Digoxin, Oral Contraceptive, S-Warfarin, Ramipril, Atorvastatin	"... oral contraceptives should be ... at least 1 hour before... or at least 11 hours after the dose of (GLP-RA)"; ". .. (for drugs) dependent on threshold concentrations for efficacy ... should be administered at least 1 hour before (GLP-RA)"
3	TANZEUM (albiglutide) (2014)	Digoxin, Oral Contraceptive, S-Warfarin, Simvastatin	"… did not affect the absorption of orally administered medications tested in clinical pharmacology studies to any clinically relevant degree" ; " Caution should be exercised when oral medications are concomitantly administered with (GLP-RA).
4	TRULICITY (dulaglutide) (2014)	Acetaminophen, Digoxin, Oral Contraceptive, S-Warfarin Lisinopril, Metoprolol, Metformin, Atorvastatin, Sitagliptin	"...did not affect the absorption of the tested orally administered medications to a clinically relevant degree (1.5 mg)"; "Monitor drug levels of oral medications with a narrow therapeutic index (e.g., warfarin) ..."
5	VICTOZA® (liraglutide) (2010)	Acetaminophen, Digoxin, Oral Contraceptive, Atorvastatin Lisinopril Griseofulvin	" .. did not affect the absorption of the tested orally administered medications to any clinically relevant degree"; "... caution should be exercised ..."
6	BYETTA® (exenatide) (2005)	Acetaminophen, Digoxin, S-Warfarin, Lisinopril, Lovastatin	".. used with caution ...(with) narrow therapeutic index or require rapid gastrointestinal absorption"; "... (for drug) dependent on threshold concentrations for efficacy ... should be administered at least 1 hour before (GLP-RA)"

[#]Source: Applicant's IR response Table 4.2
*Summarized from the USPI of the GLP-RA drugs
1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf
2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208471s004lbl.pdf
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125431s020lbl.pdf
4. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125469s044lbl.pdf
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022341s036lbl.pdf
6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021773s045lbl.pdf

4. Overall model risk assessment

Table 27.Overall model risk assessment

	Description	Applicant's position	FDA Assessment
Model influence	Describe the model influence, i.e., what is the weight of model predictions in decision-making considering the totality of evidence	Medium.	Initially: High. As the PBPK prediction will be used to waive the clinical studies. Final assessment: Medium. During the review process, the review team agreed that the clinical experience with dulaglutide and other GLP-1 receptor agonists (GLP-1 RAs) can provide quantitative evidence regarding the overall GED effect expected with GLP-1 RAs, including tirzepatide.
Decision consequence	Discuss your decision consequence based on all available evidence i.e., potential safety or efficacy risk to patients if an incorrect decision is made.	Low.	Low. Clinical studies showed the effect of delayed gastric emptying on small molecule PK is primarily a decrease in C_{max}. For most drugs where efficacy is driven by AUC exposure, there would therefore be low consequence. For drugs dependent on threshold concentrations for efficacy or with narrow therapeutic index, the risk could be managed with labeling recommendation.
Model Risk	Provide an assessment of overall risk of a wrong model prediction based on answers in 'Model influence' and 'Decision consequence'.	Low.	The overall model risk level is *low* when considering the clinical experience with other GLP-RAs, the effect of GE delay is mainly on C_{max}, and available risk mitigation strategy (i.e., labeling recommendations)

E. CONCLUSION

The Applicant's PBPK analysis provided a mechanistic interpretation of the effect of tirzepatide-induced GE delay. However, the predictability of this PBPK analysis to provide a quantitative estimation of the effects of GE delay on the PKs of the tested drugs has not been fully established. Currently, this modeling approach has only been applied with one other GLP-1 RA, namely dulaglutide. Nonetheless, the Reviewer considered the analysis adequate to provide a qualitative assessment in terms of PK changes for the test drugs taking into consideration the clinical experience with other GLP-1 RAs, and current understanding of the GE delay mechanism and possible impact on drug PK parameters. Therefore, the totality of evidence suggested that no clinically meaningful effect would be expected, and no dose modification would be needed for the tested drug(s) when concomitantly administered with tirzepatide. Labeling recommendations for drugs dependent on threshold concentrations for efficacy or with narrow therapeutic index will be implemented as part of a risk mitigation strategy.

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/s/

MOHAMAD M KRONFOL
03/18/2022 11:21:22 AM

ELYES DAHMANE
03/18/2022 11:25:32 AM

XINYUAN ZHANG on behalf of YUCHING N YANG
03/18/2022 12:17:43 PM
Proxy for Dr. Yuching Yang

MANUELA GRIMSTEIN
03/18/2022 12:21:36 PM

JUSTIN C EARP
03/18/2022 02:32:40 PM

JAYABHARATHI VAIDYANATHAN
03/18/2022 02:37:40 PM

SHIRLEY K SEO
03/18/2022 04:10:09 PM