

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**217806Orig1s000**

**CLINICAL PHARMACOLOGY**  
**REVIEW(S)**

# Office of Clinical Pharmacology Review

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|                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>NDA Number</b>               | 217806                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Link to EDR</b>              | <a href="\\CDSESUB1\evsprod\NDA217806\0001">\\CDSESUB1\evsprod\NDA217806\0001</a>                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Submission Date</b>          | 05/09/2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Submission Type</b>          | Priority review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Brand Name</b>               | Zepbound                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Generic Name</b>             | Tirzepatide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Dosage Form and Strength</b> | 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                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Route of Administration</b>  | Subcutaneous Injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Proposed Indication</b>      | As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: <ul style="list-style-type: none"> <li>• 30 kg/m<sup>2</sup> or greater (obesity) or</li> <li>• 27 kg/m<sup>2</sup> or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4) type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease)</li> </ul> |
| <b>Applicant</b>                | Eli Lilly and Company                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| <b>OCP Final Signatory</b>      | Edwin C Chow, Ph.D.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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## **1. EXECUTIVE SUMMARY**

The Applicant, Eli Lilly and Company, submitted NDA 217806 sequence 1 (S-0001) of a rolling submission on November 17, 2022, and a second and final sequence on May 8, 2023, seeking approval of tirzepatide (Zepbound) as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (CWM) in adults with an initial body mass index (BMI) of:

- 30 kg/m<sup>2</sup> or greater (obesity) or
- 27 kg/m<sup>2</sup> or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4) type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease).

Tirzepatide is an agonist at the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, developed for once-weekly CWM in adults with obesity or overweight in the presence of at least one weight-related comorbid condition. 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.

The to-be-marketed tirzepatide (Zepbound) is a solution for injection as pre-filled single-dose pen (SDP). The development program consists of population pharmacokinetics (popPK), pharmacodynamics (PD), tolerability, and pivotal efficacy and safety trials in adult patients. Tirzepatide (trade name, Mounjaro) is U.S. FDA-approved as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus (T2DM) under NDA 215866 in 2022. The strength, formulation, route of administration, and dosage regimen are identical between the T2DM and CWM phase 3 studies. Additional studies or reports that were submitted to the CWM NDA 217806 include a new gastric emptying study (GPHU), a counter regulation study (GPHG), a mechanistic study (GPGT), a PK study in Chinese participants (GPHT), and a new popPK and pharmacokinetic-pharmacodynamic (PK/PD) report in the indicated population.

The clinical pharmacology of tirzepatide is well characterized in the T2DM program and is cross referenced to this NDA. Please refer to OCP team primary reviews by Drs. Mohamad Kronfol, Elyes Dahmane, and Yuching Yang in Reference ID: 4954959 dated March 18, 2022, under NDA 215866.

### **1.1 Recommendations**

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/ DCEP) reviewed the clinical pharmacology data submitted in NDA 217806 and found it acceptable. The application is approvable from a clinical pharmacology perspective.

| Review Issue                                                             | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal or supportive evidence of effectiveness</b>                   | Two pivotal phase 3 trials GPHK (SURMOUNT-1) and GPHL (SURMOUNT-2) provide primary evidence of tirzepatide effectiveness and safety for CWM in adult patients. Patients treated with tirzepatide showed -14.7% to -20.9% significant reductions from baseline in bodyweight compared to -3.1% in those taking placebo.                                                                                                                                                                          |
| <b>General dosing instructions</b>                                       | <ul style="list-style-type: none"> <li>• Start at 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly</li> <li>• 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</li> <li>• Administer once weekly at any time of day, with or without meals</li> <li>• If a dose is missed administer within 4 days of missed dose</li> <li>• Inject subcutaneously in the abdomen, thigh, or upper arm</li> </ul> |
| <b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b>     | No dose adjustment to the proposed regimen is needed based on intrinsic factors like age (18 to 84 years), sex, race (71% white, 11% Asian, 9% American Indian, and 8% black), body weight, renal impairment, or hepatic impairment. Tirzepatide delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications.                                                                                                                 |
| <b>Labeling</b>                                                          | Refer to Section 2.4.                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Bridge between the to-be-marketed and clinical trial formulations</b> | The to-be-marketed formulation (preservative-free solution for subcutaneous injection) was used the pivotal CWM trials. There is no difference between the currently approved formulation under NDA 215866 and the to-be-marketed formulation used in pivotal CWM trials.                                                                                                                                                                                                                       |

## 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 insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Tirzepatide has affinity to both the GIP and GLP-1 receptors. The agonism is expected to result in decrease of 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 | <ul style="list-style-type: none"> <li>• PK is dose proportional in the dose ranging from 5-15 mg based on population PK (popPK) analysis</li> <li>• The time to reach maximum plasma concentration (<math>t_{max}</math>) ranges from 8 to 72 hours</li> <li>• Absolute bioavailability is approximately 80%<sup>a</sup></li> </ul> |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|              |                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Distribution | <ul style="list-style-type: none"> <li>Plasma Protein Binding is 99%<sup>a</sup></li> <li>Apparent Volume of Distribution at steady state (Vd<sub>ss</sub>) is 9.7 L</li> <li>Steady State is reached at 4 weeks after once-weekly administration</li> </ul>                                                                                                                                     |
| Metabolism   | <ul style="list-style-type: none"> <li>Proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis<sup>a</sup></li> </ul>                                                                                                                                                                                                                   |
| Elimination  | <ul style="list-style-type: none"> <li>Plasma Clearance (CL) is 0.056 L/h</li> <li>Terminal half-life (t<sub>1/2</sub>) is approximately 5 days<sup>a</sup></li> <li>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%)<sup>a</sup></li> </ul> |

<sup>a</sup>Data are reviewed under NDA 215866

## 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 (QW). 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. The recommended maintenance dosages of tirzepatide in adults are 5 mg, 10 mg, or 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                                                                                                                            |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 12.1 Mechanism of action | Removed (b) (4)                                                                                                                           |
| 12.2 Pharmacodynamics    | Consistent with labeling of approved GLP-1RA, reference to effects on calorie and food intake is moved from 12.1 to 12.2. Removed (b) (4) |
| 12.3 Pharmacokinetics    | Clarified central tendency measures for volume and clearance for proposed indication.                                                     |

### **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 a reduced-calorie diet and increased physical activity for chronic weight management (CWM) in adults. The regulatory background pertaining to Clinical Pharmacology included Type B Pre-NDA meetings as well as Type C written response with key discussion point including adequacy of Clinical Pharmacology study GPHU, popPK and exposure-response (E-R) analysis, and adequacy of the phase 3 studies dose and duration (see **APPEARS THIS WAY ON ORIGINAL**

**Table 3** in Appendix 4.1). The Clinical Pharmacology studies conducted under the T2DM NDA included Relative Bioavailability (BA), Single- and Multiple-Ascending Dose (SAD/MAD), Disposition of radioactivity, hepatic and renal impairment, DDI, and PD studies. Please refer to OCP team primary reviews by Drs. Mohamad Kronfol, Elyes Dahmane, and Yuching Yang in Reference ID: 4954959 dated March 18, 2022, under NDA 215866. Additional studies or reports that were submitted to the CWM NDA 217806 include a new gastric emptying study (GPHU), a counter regulation study (GPHG), a mechanistic study (GPGT), a PK study in Chinese participants (GPHT), and a new population PK and PK/PD report in the indicated population. The commercial formulation was used in both phase 3 CWM trials.

#### **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  $\beta$ -arrestin. Tirzepatide is expected to result in body weight reduction. 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 and calorie intake.

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients 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,  $t_{\max}$  (range) is 24 (8 to 72) hours. Mean (CV%) peak plasma concentration ( $C_{\max}$ ) ranges from 54.6 (28) to 1250 (20) ng/mL. Mean (CV%) area under the concentration time curve during dosing interval ( $AUC_{0-\tau}$ ) 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  $AUC_{0-\tau}$ .

Population PK analysis of PK data from one phase 3 study (SURMOUNT-1) shows that tirzepatide exposure increased dose-proportionally over the dose range of 5 to 15 mg. Following multiple dose administration of tirzepatide 15 mg in participants with obesity or overweight, the mean (CV%) steady-state  $C_{\max,ss}$  was 2120 ng/mL (19.7%) ng/mL. Following multiple dose administration of tirzepatide 15 mg, the mean (CV%) steady-state AUC was 266,000 ng\*hr/mL (20.4%). Mean accumulation ratio was 1.75.

### ***Distribution***

The mean (CV%) apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with obesity or overweight is approximately 9.7 L (28.5%). 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 mean (CV%) apparent population clearance of tirzepatide is 0.056 (20.9%) 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?*

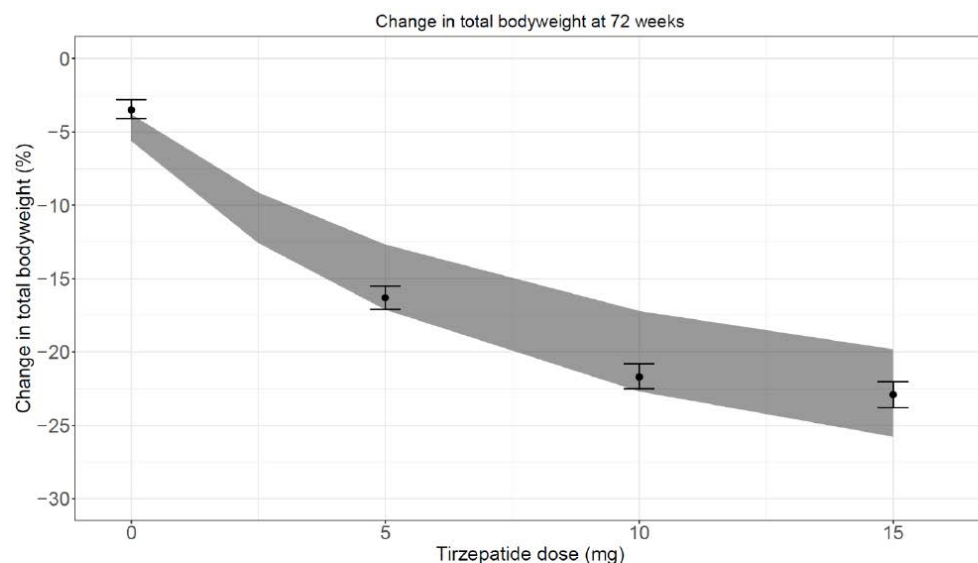
The Clinical Pharmacology data provide supportive evidence of effectiveness for tirzepatide as an adjunct to diet and exercise to improve body weight in adults. Refer to **Table 4** in Appendix 4.1, for the list of clinical pharmacology studies conducted under the T2DM NDA 215866 (for full review of those studies please refer to OCP team primary reviews by Drs. Mohamad Kronfol, Elyes Dahmane, and Yuching Yang in Reference ID: 4954959 dated March 18, 2022 under NDA 215866. Refer to **Table 5** in Appendix 4.1, for the list of clinical pharmacology studies conducted under this CWM NDA 217806.

In the Pharmacodynamic (PD) Study GPGT, the tirzepatide 15 mg weekly maintenance dosing regimen (QW) is shown to reduce calorie and food intake (see Appendix 4.2). In Study GPHU, tirzepatide delayed gastric emptying (GE) at doses of 5 mg and 15 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 55 % after the first 5 mg dose with no clinically relevant impact on AUC. The change in  $C_{max}$  of acetaminophen was decreased approximately 32% with no clinically relevant impact change on AUC when administered in the presence of 15 mg tirzepatide on Day 37 compared to when administered alone (see Appendix 4.2).

Longitudinal body weight data from two CWM phase 3 studies (Study I8F-MC-GPHK or SURMOUNT-1 in subjects without T2DM; I8F-MC-GPHL or SURMOUNT-2 in subjects with T2DM), were modeled separately to characterize the PK/PD relationships for safety and efficacy. The population body weight models adequately described body weight reduction from baseline over time. Additionally, the body weight model demonstrates a dose-dependent effect of tirzepatide on total body weight, fat mass, and fat free mass (**Figure 1** and **Figure 2** as representation from SURMOUNT-1) reduction with increasing tirzepatide doses of 5, 10, and 15 mg QW (see Appendix 4.3 Pharmacometrics Assessment). For clinical risk-benefit assessment, see Clinical review in DARRTS.

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 adverse events (AEs) and was adequately tolerated in participants with obesity or overweight. Changes to dose escalation scheme are not required from that of T2DM.

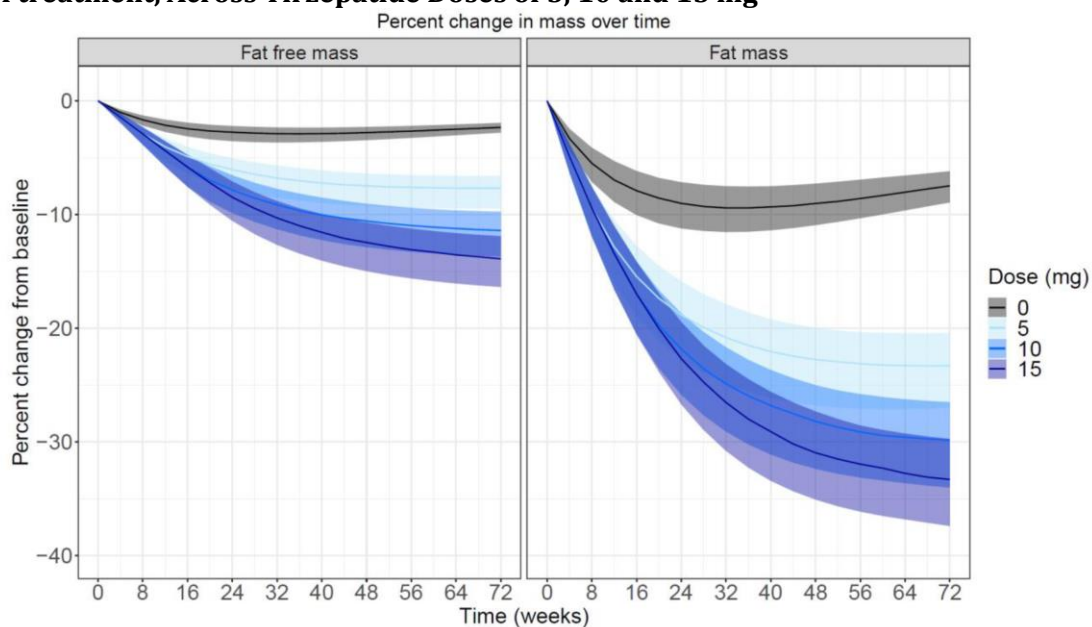
**Figure 1 Model-predicted Change from Baseline in Total Body Weight, Across Tirzepatide Doses of 5, 10 and 15 mg**



Note: The shaded area is the 95% confidence interval of model predictions. The points and error bars are the observed mean and 95% confidence interval, respectively.

(Dose-response based on SURMOUNT-1 data; source Applicant's CWM popPK report, Figure 10.4, page 63)

**Figure 2 Model-predicted Change from Baseline in Fat-free mass and fat mass after 72 weeks of treatment, Across Tirzepatide Doses of 5, 10 and 15 mg**



(Based on SURMOUNT-1 data; source Applicant's CWM popPK report, Figure 10.7, page 66)

### *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. The recommended maintenance dosages of tirzepatide in adults are 5 mg, 10 mg, or 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 cross-referenced data from the T2DM NDA (NDA 215866 S-0001) show that results of the phase 2 Study GPGB suggested that while promising efficacy (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 in 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 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. Dose-dependent changes in body weight were observed. For final efficacy and safety assessments on the data in pivotal phase 3 studies, refer to Clinical review in DARRTS.

In this NDA, the PK/PD analysis for safety characterized the effect of tirzepatide on the probability of occurrence of nausea, vomiting or diarrhea AEs. The PK/PD model was reasonable to describe the occurrence of nausea, vomiting, and diarrhea and the development of tolerance at 72 weeks. 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. Consistent with the T2DM development program under NDA 215866, the majority of nausea, vomiting, and diarrhea AEs were reported during the dose-escalation phase, and their incidence decreased with time once steady-state concentrations for the maintenance doses were attained (see Appendix 4.3 Pharmacometrics Assessment).

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. From the cross-referenced data from the T2DM NDA, 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 under NDA 215866.

Across two phase 3 clinical studies (SURMOUNT-1 and SURMOUNT-2), during the 72-week treatment period with ADA sampling in the chronic weight management studies, 64.5% (1591/2467) of tirzepatide-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 40.0% and 16.5% of tirzepatide -treated patients showed cross-reactivity to native GIP or native GLP 1, respectively. Of the tirzepatide -treated patients, 2.8% and 2.7% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP 1 receptors, respectively, and 0.8% and 0.1% developed cross-reactive neutralizing antibodies against native GIP or GLP 1, respectively. Refer to Immunogenicity review in DARRTS under NDA 217806 for additional details.

No clinically relevant effects on the PK of tirzepatide were observed based on age (range, 18-84 years), sex (67.5% females), race (71% white, 9% 10.9% Asian, American Indian, and 8% black), ADA titer, ADA status, renal function (estimated glomerular filtration rate range, 36-153 mL/min/1.73 m<sup>2</sup>), or hepatic impairment (see Appendix 4.3 Pharmacometrics Assessment).

From the cross-referenced data from the T2DM NDA, 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<sub>max</sub> 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.

## 4. APPENDICES

### 4.1 Summary of Bioanalytical Method Validation and Performance

No additional biopharmaceutical studies have been completed since the T2DM application of tirzepatide. Samples collected in the CWM program were analyzed for tirzepatide using the same method from the T2DM program over the course of clinical development. The LC/MS/MS method was developed and validated by (b) (4) Refer to OCP review for NDA 215866 for full details (Reference ID: 4954959 dated March 18, 2022). A LC/MS/MS assay used to measure tirzepatide concentrations in human plasma samples for studies GPHT, GPHO, and GPHK was validated at (b) (4) method for tirzepatide was successfully cross validated with the (b) (4) method for tirzepatide using spiked human plasma samples. The summary of the bioanalytical method validation is presented in **Table 2**.

Briefly, tirzepatide was extracted from human plasma using immunoaffinity in a 96-well format and LSN3316897 (stable isotope-labeled tirzepatide) as the internal standard. Next, tirzepatide and internal standard were identified and quantified using a Sciex API 6500+ spectrometer equipped with Positive Ionization and Multiple Reaction Monitoring detection over a standard curve range of 4.00 to 500 ng/mL. The concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using linear regression analysis employing a 1/x<sup>2</sup> weighting. The interassay accuracy (% relative error) during validation ranged from -3.4% to 2.7%. The interassay precision (% coefficient of variation) during validation was 1.8% to 8.9%. The inter-assay precision and interassay accuracy values passed all predefined acceptance criteria. 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 of 500 ng/mL were diluted up to a 100-fold dilution. ISR was conducted for the 3 clinical studies and the results indicated that the assay method performed according to established ISR acceptance criteria with  $\geq 2/3$  of ISR results within 20% difference.

**Table 2 Summary of method validation**

|                                                                           |                                                                                                                                                                                                                              |                |                                                                                                                                                                               |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bioanalytical method validation report name, amendments, and hyperlinks   | Report <a href="#">400008-191850-PMV-R1-R2</a>                                                                                                                                                                               |                |                                                                                                                                                                               |
| Method description                                                        | Quantification of LY3298176 in Human Plasma by LC/MS/MS                                                                                                                                                                      |                |                                                                                                                                                                               |
| Materials used for standard calibration curve and concentration           | Reference standard: tirzepatide lot # RS1058, expiration date 28-Oct-2020, overall correction factor 0.89 mg tirzepatide per mL.<br><br>Internal standard: LSN3316897 lot # BCA-BE03935-132, overall correction factor 0.80. |                |                                                                                                                                                                               |
| Validated assay range                                                     | 4.00 to 500 ng/mL                                                                                                                                                                                                            |                |                                                                                                                                                                               |
| Material used for quality controls (QCs) and concentration                | Tirzepatide lot # RS1058, expiration date 28-Oct-2020, overall correction factor 0.89 mg tirzepatide per mL.                                                                                                                 |                |                                                                                                                                                                               |
| 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              | 400008-191850- (b) (4) R1-R2<br>Section 5.3.1.4                                                                                                                               |
|                                                                           | Cumulative accuracy (%bias) from LLOQ to ULOQ<br>Tirzepatide                                                                                                                                                                 | -3.4% to 4.0%  | 400008-191850- (b) (4) R1-R2<br>Section 5.3.1.4                                                                                                                               |
|                                                                           | Cumulative precision (%CV) from LLOQ to ULOQ<br>Tirzepatide                                                                                                                                                                  | ≤5.8%          | 400008-191850- (b) (4) R1-R2<br>Section 5.3.1.4                                                                                                                               |
| Performance of QCs during accuracy and precision runs                     | Cumulative accuracy (%bias) in 3 QCs<br>QCs:<br>Tirzepatide                                                                                                                                                                  | -1.9% to 2.7%  | 400008-191850- (b) (4) R1-R2<br>Section 5.3.1.4                                                                                                                               |
|                                                                           | Inter-batch %CV<br>QCs:<br>Tirzepatide                                                                                                                                                                                       | ≤8.9%          | 400008-191850- (b) (4) R1-R2<br>Section 5.3.1.4                                                                                                                               |
|                                                                           | Total error (TE)<br>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 for selectivity. Response was 0.0% of LLOQ. Matrix effect was tested at 3 concentrations and not matrix effects testing passed criteria. |

|                                      |                                                                                                                                                                                                                                                                                                |                                                                                   |
|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Interference & specificity           | Number of total lots tested. Range of observed bias. State any issue                                                                                                                                                                                                                           | Interference was evaluated in all batches. No interference effects were observed. |
| Hemolysis effect                     | Number of total lots tested. Range of observed bias. State any issue                                                                                                                                                                                                                           | Six lots of 2% hemolytic plasma were tested. Response was 1.7% of LLOQ.           |
| Lipemic effect                       | Number of total lots tested. Range of observed bias. State any issue                                                                                                                                                                                                                           | Six lots of lipemic plasma were tested. Response was 2.4% of LLOQ.                |
| Dilution linearity & hook effect     | 100-fold dilution validated. Hook effect not applicable.                                                                                                                                                                                                                                       |                                                                                   |
| Bench-top/process stability          | Plasma: 24 hours at room temperature<br>Extracted plasma: 179 hours at 6°C                                                                                                                                                                                                                     |                                                                                   |
| Freeze-Thaw stability                | 5 freeze-thaw cycles at -20°C and -70°C                                                                                                                                                                                                                                                        |                                                                                   |
| Long-term storage                    | 804 days at -20°C and 49 days at -70°C                                                                                                                                                                                                                                                         |                                                                                   |
| Parallelism                          | Not applicable                                                                                                                                                                                                                                                                                 |                                                                                   |
| Carry over                           | There was no significant carryover.                                                                                                                                                                                                                                                            |                                                                                   |
| <b>Method performance in Studies</b> |                                                                                                                                                                                                                                                                                                |                                                                                   |
| Assay passing rate                   | GPHO: 85 out of 95 runs passed (89%)<br>GPHT: 15 out of 19 runs passed (79%)<br>GPHK: 7 out of 7 runs passed (100%)                                                                                                                                                                            | GPHO (b) (4)<br>GPHT (b) (4)<br>GPHK (b) (4)                                      |
| Standard curve performance           | <ul style="list-style-type: none"> <li>Cumulative bias range:<br/>GPHO: -0.9% to 1.1%<br/>GPHT: -1.7% to 1.4%<br/>GPHK: -1.5% to 1.8%</li> <li>Cumulative precision:<br/>GPHO: <math>\leq 5.2\%</math> CV<br/>GPHT: <math>\leq 8.3\%</math> CV<br/>GPHK: <math>\leq 5.7\%</math> CV</li> </ul> | GPHO (b) (4)<br>GPHT (b) (4)<br>GPHK (b) (4)                                      |
| QC performance                       | <ul style="list-style-type: none"> <li>Cumulative bias range:<br/>GPHO: -0.1% to 3.3%<br/>GPHT: -0.5% to 2.1%<br/>GPHK: -0.6% to 1.5%</li> <li>Cumulative precision:<br/>GPHO: <math>\leq 5.6\%</math> CV<br/>GPHT: <math>\leq 5.1\%</math> CV<br/>GPHK: <math>\leq 3.7\%</math> CV</li> </ul> | GPHO (b) (4)<br>GPHT (b) (4)<br>GPHK (b) (4)                                      |
| Method reproducibility               | GPHO: 8% of samples were tested in the ISR and 99% passed acceptance criteria.<br>GPHT: 11% of samples were tested in the ISR and 100% passed acceptance criteria.<br>GPHK: 11% of samples were tested in the ISR and 96% passed acceptance criteria.                                          | GPHO (b) (4)<br>GPHT (b) (4)<br>GPHK (b) (4)                                      |
| Study sample analysis/stability      | Samples were kept at -70°C for up to 718 days. Stability was established for 804 days at -70°C.                                                                                                                                                                                                | GPHO (b) (4)<br>GPHT (b) (4)<br>GPHK (b) (4)                                      |

|                                                           |                                                                                                                                                                               |                                           |
|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Bioanalytical method validation report name and hyperlink | Report <a href="#">LY3298176_CVR_</a> (b) (4)                                                                                                                                 |                                           |
| Changes in method                                         | Cross validation for preparation of spiked QC samples of LY3298176 in human plasma between validations 151682VKM_EII and 400008-192387. (b) (4)                               |                                           |
| New validated assay range if any                          | Not applicable.                                                                                                                                                               |                                           |
| Validation parameters                                     | Cross-validation performance                                                                                                                                                  | Source location                           |
| Cross-validation                                          | 6 replicates of 4 spiking levels, plus 4 aliquots of blank serum were analyzed, and the % differences ranged from -36.7% to -4.6%. 88% of the spiked samples were within 20%. | LY3298176_CVR_ (b) (4)<br>Section 5.3.1.4 |
| List other parameters                                     | Not applicable.                                                                                                                                                               |                                           |

Abbreviation: QC = quality control.

**Table 3 Regulatory background pertaining to Clinical Pharmacology**

| Date       | Meeting or Communication – key discussion points                                                                                                                                                                            |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10/30/2019 | Under IND 139721, the Applicant submitted protocol for Study GPHK: a phase 3 study in patients with obesity or overweight without T2DM (SURMOUNT1)                                                                          |
| 06/26/2019 | Type C meeting, nonclinical program, dose-response relationship, adequacy of Clinical Pharmacology study GPHU, PopPK and Exposure-Response (E-R) analysis, 36-Item Short Form Health Survey, Version 2 (SF-36v2) acute form |
| 10/08/2020 | Type C WRO – phase 3 studies GPHL, GPHM, GPHN design, dose, duration, endpoints                                                                                                                                             |
| 04/21/2022 | Type C meeting, Clinical development plan; CVOT design, safety monitoring, stats, and endpoints.                                                                                                                            |
| 08/11/2022 | Type B Pre-NDA meeting – adequacy of the content to support NDA from CMC, Clinical and Clinical Pharmacology; product name; integrated summary of efficacy and safety                                                       |
| 05/08/2023 | NDA 217806 submitted                                                                                                                                                                                                        |

**Table 4 Index of Studies and Analyses in the Clinical Pharmacology Program under Type 2 Diabetes Mellitus NDA 215866**

| Study                                                       | Description                                  | Population                                                         | SC Dosing Regimen                                                                                                                                                                                                                           |
|-------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Disposition and Metabolism Study</b>                     |                                              |                                                                    |                                                                                                                                                                                                                                             |
| GPHX                                                        | Disposition of radioactivity and PK          | Healthy males                                                      | Single 2.9-mg dose <sup>a</sup> [ <sup>14</sup> C-TZP 100 µCi]                                                                                                                                                                              |
| <b>Healthy Participant PK, PD, and Tolerability</b>         |                                              |                                                                    |                                                                                                                                                                                                                                             |
| 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<br>[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 |
| <b>PK and/or PD in Patients with T2DM, and Tolerability</b> |                                              |                                                                    |                                                                                                                                                                                                                                             |
| 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           |
| <b>Effect of Intrinsic Factors</b>                          |                                                                                 |                                                                                                            |                                                                                                                                                                                                                     |
| 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                                                                                                                                                                                                     |
| <b>Effect of tirzepatide on PK and/or PD of other drugs</b> |                                                                                 |                                                                                                            |                                                                                                                                                                                                                     |
| GPGR                                                        | Effect on combined OC                                                           | Healthy women eligible to use OC                                                                           | Single 5 mg TZP                                                                                                                                                                                                     |
| <b>Mechanistic Pharmacodynamic Study</b>                    |                                                                                 |                                                                                                            |                                                                                                                                                                                                                     |
| GPGT                                                        | Effect on pancreatic $\alpha$ and $\beta$ cell function and insulin sensitivity | T2DM [diet/ exercise control and metformin $\pm$ 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 <sup>b</sup> or Placebo |

Abbreviations: BMI = body mass index; MAD = multiple ascending dose; OC = oral contraceptive; OAM = oral antihyperglycemic medication; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; SAD = single-ascending dose; SC = subcutaneous; T2DM = type 2 diabetes mellitus; TZP = tirzepatide administered SC. <sup>a</sup> Planned dose 4.1 mg; actual dose 2.9 mg; however, 100  $\mu$ Ci 14C was administered per plan. <sup>b</sup> 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.

(Source: page 32 Table 12 of Clinical Pharmacology Review NDA 215866)

**Table 5 Index of Studies and Analyses in the Clinical Pharmacology Program under CWM NDA 217806**

| Study                                    | Description                                              | Population                                 | SC Dosing Regimen                                                                                                                                                                                                                                                    |
|------------------------------------------|----------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PK and/or PD in patients</b>          |                                                          |                                            |                                                                                                                                                                                                                                                                      |
| GPHU                                     | Impact of TZP on gastric emptying                        | Obesity or overweight with or without T2DM | Total dosing duration: 6 weeks Dose-escalation scheme: TZP QW: 5 mg (2 weeks), 10 mg (3 weeks), 15 mg (1 week) Acetaminophen dosing: Days -1, 2, and 37                                                                                                              |
| <b>Effect of Intrinsic Factors</b>       |                                                          |                                            |                                                                                                                                                                                                                                                                      |
| GPHT                                     | Multiple dose safety, PK, PD                             | Native Chinese with T2DM                   | Total dosing duration: 16 to 24 weeks TZP QW dose range: 2.5 to 15 mg [1] 2.5 mg (4 weeks), 5 mg (4 weeks), 7.5 mg (4 weeks), 10 mg (4 weeks) [2] 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 (4 weeks) Or Placebo |
| <b>Mechanistic Pharmacodynamic Study</b> |                                                          |                                            |                                                                                                                                                                                                                                                                      |
| GPHG                                     | Effect on the Counterregulatory response to hypoglycemia | T2DM                                       | Total dosing duration: 12 weeks Dose-escalation scheme: TZP QW: 2.5 mg (2 weeks), 5 mg (2 weeks), 10 mg (4 weeks), 15 mg (4 weeks) or Placebo                                                                                                                        |

Abbreviations: BMI = body mass index; MAD = multiple ascending dose; OC = oral contraceptive; OAM = oral antihyperglycemic medication; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; SAD = single-ascending dose; SC = subcutaneous; T2DM = type 2 diabetes mellitus; TZP = tirzepatide administered SC. Note: Tirzepatide dose-escalation scheme for CWM 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.

(Source: page 14 Table 2.7.2.3. of Summary of Clinical Pharmacology NDA 217806)

## 4.2 Clinical PK and/or PD Assessments

### ***Study GPHU: The Impact of Tirzepatide on Gastric Emptying (GE) in Overweight/Obese Non-diabetic Subjects and in Overweight/Obese Subjects with Type 2 Diabetes Mellitus***

The Applicant conducted Study GPHU, open-label, fixed-sequence study to assess the effect of multiple doses of tirzepatide (5 to 15 mg) on the PK parameters of acetaminophen to determine the impact on GE, PD, safety, and tolerability of tirzepatide in participants with obesity or overweight with or without T2DM when administered using a prefilled syringe.

Thirty-six participants with obesity or overweight (18 with T2DM and 18 without T2DM) between the ages of 28 and 65 years, inclusive, with a body mass index of 27.12 to 44.87 kg/m<sup>2</sup>, inclusive, received at least 1 dose of study treatment, and 30 participants (15 T2DM participants and 15 non-T2DM participants) completed the study. All 36 participants were of Hispanic or Latino ethnicity. Subjects received tirzepatide SC alone once weekly for 6 weeks on Days 1 (5 mg), 8 (5 mg), 15 (10 mg), 22 (10 mg), 29 (10 mg), and 36 (15 mg), and received oral acetaminophen 1 g on Days -1, 2, and 37. GE was assessed by comparing the PK profiles of acetaminophen between treatment groups on Day -1, Day 2, and Day 37. Blood was collected to assess tirzepatide PK before and up to 168 hours. Tirzepatide PK parameters were calculated using noncompartmental analysis and included  $C_{max}$ ,  $AUC_{0-\infty}$ ,  $t_{max}$ , and  $t_{1/2}$ .

Tirzepatide delayed gastric emptying (GE) at doses of 5 mg and 15 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 55 % after the first 5 mg dose with no clinically relevant impact on AUC. The  $C_{max}$  of acetaminophen was decreased approximately 32% with no clinically relevant impact on AUC when administered in the presence of 15 mg tirzepatide on Day 37 compared to when administered alone. This delay in gastric emptying (GE) was greatest following the first tirzepatide dose and the delay in GE was less evident following repeated tirzepatide doses within the study duration. The maximum effect of tirzepatide on GE was studied under conservative clinical conditions, i.e., this approach was conservative, because it evaluated maximum possible effect of tirzepatide on GE. These conditions included escalation to tirzepatide doses of 10 and 15 mg within 6 weeks via 5/5/10/10/10/15 mg scheme, thereby attaining the highest doses within 6 weeks, which is appreciably faster than the time required to attain these doses in the phase 3 studies 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, and 12.5 QW on gastric emptying is unknown.

The reviewer's conclusion agrees with that of the Applicant. In patients with and without T2DM, tirzepatide QW dosing delays GE consistent with GLP-1 pharmacology. Similar results were shown in the T2DM GE study of  $C_{max}$  reduction by 50%, however, the Applicant proposed a labeling change from the T2DM labeling to include the observed effect to account for the difference in population and the new  $C_{max}$  reduction of 55%. This labeling change to section 12.3 is acceptable.

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

Study GPGT results pertaining to CWM NDA 217806 are presented here. For full review of Study GPGT please see OCP review for NDA 215866 Reference ID: 4954959 dated March 18, 2022, under NDA 215866.

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 study allowed enrollment of subjects with BMI between 25 kg/m<sup>2</sup> and 45 kg/m<sup>2</sup>, inclusive. The 15 mg tirzepatide dose was attained via the same stepwise escalation used in phase 3 studies. Subjects received an ad libitum meal served buffet style. Ad libitum food intake was assessed during a 45-min buffet meal at noon by measuring the food intake as the grams of macronutrients (protein, fat, carbohydrate) consumed during that period. The Applicant presented data of macronutrient composition of the meals in the addendum. At week 28, the change from baseline in food intake was assessed.

The Applicant concludes that at week 28 tirzepatide lowered food intake by -309.8 kcal (95%CI -423.0, -196.6) from baseline vs placebo. The Applicant concludes that at week 28 tirzepatide lowered carbohydrate, protein, and fat intake by -117.8 kcal (95% CI -172.8, -62.9), -59.9 kcal (-84.0, -35.7), and -142.5 kcal (-207.2, -77.8) respectively from baseline vs placebo.

The reviewer's conclusion agrees with that of the Applicant. This study demonstrated reductions in measures of food and calorie intake with tirzepatide compared to placebo and semaglutide.

Study I8F-MC-GPHT and Study I8F-MC-GPHG were submitted under this NDA and were conducted in patients with T2DM and did not have any impact on labeling of the CWM indication. Therefore, these studies were not reviewed and not discussed in this review. For completeness only, study I8F-MC-GPHT is a Multiple Dose Titration Study in Chinese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Tirzepatide, while Study I8F-MC-GPHG A Randomized, Placebo-Controlled, Crossover Study to Investigate the Effect of Once-Weekly Tirzepatide on the Counter-Regulatory Response to Hypoglycemia in Patients with T2DM.

## 4.3 Pharmacometrics Review

### 4.3.1 Population PK analysis

#### 4.3.1.1 Review Summary

Tirzepatide was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (under NDA 215866) in 2022. The current NDA package seeks approval of tirzepatide as an adjunct therapy to a reduced-calorie diet and increased physical activity for chronic weight management (CWM) in adults with obesity or overweight.

From a pharmacometric analysis perspective, data from the SURMOUNT-1 and SURMOUNT-2 studies support pharmacokinetic (PK) modeling and pharmacokinetic-pharmacodynamic (PK/PD) analyses for efficacy and safety; however, SURMOUNT-2 study enrolled T2DM subjects while SURMOUNT-1 enrolled subjects without T2DM. In the context of CWM in the target population, this review focuses on results from SURMOUNT-1 PK and PK/PD analyses.

Additionally, SURMOUNT-2 PK and PK/PD analysis results are briefly provided for comparison (when specified). For details of the pharmacometrics assessment of tirzepatide effect on weight management and safety and tolerability in the context of T2DM, refer to the Office of Clinical Pharmacology Review by Drs. Kronfol, Dahmane, Earp, and Vaidyanathan (NDA 215866, dated 8MAR2022).

In general, the population PK (popPK) and PK/PD analyses adequately capture the population data and are considered acceptable for descriptive labeling purposes. Specifically, the developed model was used to support the current submission as outlined in **Table 6**.

**Table 6. Specific Comments on Applicant's Final Population PK model**

| Utility of the final model                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Reviewer's Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Support applicant's proposed labeling statements about intrinsic and extrinsic factors</b> | <b>Intrinsic factor</b>                                                                                                                                                                                                                                                                                                                                                                                                                          | <p><b>Section 8.6</b><br/>"No dosage adjustment of ZEPBOUND is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed."</p> <p><b>Section 8.7</b><br/>"No dosage adjustment of ZEPBOUND is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed."</p> <p>Similar states regarding renal impairment and hepatic impairment having no impact on ZEPBOUND PK in <b>Section 12.3</b>.</p> | <p>These statements are acceptable as body weight was the only statistically significant covariate identified on tirzepatide PK. Yet, weight-based dose adjustment is not warranted due to the moderate impact on PK and the proposed titration dosing approach.</p> <p>Additionally, age, sex, race, renal impairment, hepatic impairment, antidrug antibody (ADA) status, or ADA titer were not found to significantly impact tirzepatide PK, and no dosing adjustment is warranted based on these factors in obese or overweight subjects.</p> |
| <b>Derive exposure metrics and population PK parameters</b>                                   | <p>The popPK model (based on SURMOUNT-1) was used to the characterize the PK profile of ZEPBOUND for the CWM indication and quantify clinically relevant covariate effects.</p> <p>The popPK model was used to derive population PK parameters for labeling purposes (i.e., absorption, distribution, elimination).</p> <p>Using the individual PK parameters, exposures were derived for the sequential PK/PD efficacy and safety analyses.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p>The popPK model adequately captured tirzepatide PK and is acceptable in deriving individual exposures for PK/PD modeling for CWM.</p>                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Derive exposure metrics for Exposure-response analyses</b>                                 | <p>Posterior-predicted exposures were derived based on the final popPK model for the PK/PD analyses for: body weight loss model, nausea and vomiting, and diarrhea Markov models (mild, moderate, or severe).</p>                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p>The final PK/PD models adequately described the effect of tirzepatide in lowering body weight, tolerability, and the aforementioned safety events to tirzepatide in CWM.</p>                                                                                                                                                                                                                                                                                                                                                                   |

#### 4.3.1.2 Introduction

The primary objectives of applicant's analysis were to:

- characterize tirzepatide PK in adults with obesity or overweight following weekly subcutaneous (SC) injections of tirzepatide

- identify covariates that may impact tirzepatide PK in the study population
- derive individual PK parameters and exposure metrics for exposure-response analyses
- describe the exposure-weight-loss relationships
- describe the exposure-safety relationships for nausea, vomiting, and diarrhea

#### 4.3.1.3 Model Development

##### Data

Data from two studies is available for analysis, SURMOUNT-1 and SURMOUNT 2. **Table 7** provides a summary of the study data, and **Table 8** summarizes the baseline demographics for SUMROUNT-1. The final dataset of SURMOUNT-1 included 14317 PK observations from 1880 unique subjects across tirzepatide treatment groups.

**Table 7. Summary of Study**

| Study Alias and Treatment Duration  | Study Description                                                                                                                                                                         | Participant Type (N)                                                                             | Treatment Regimen/ Formulation                                                                                                                                                                                             |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I8F-MC-GPHK (SURMOUNT-1) (72 weeks) | A multicenter, randomized, placebo-controlled, double-blinded study in participants with obesity, or overweight with at least one weight-related comorbidity                              | Obesity/Overweight with at least one weight-related comorbidity (without T2DM) (2539 randomized) | All SC route of administration QW <ul style="list-style-type: none"> <li>• TZP 5 mg titrated</li> <li>• TZP 10 mg titrated</li> <li>• TZP 15 mg titrated</li> <li>• Placebo</li> </ul> All with solution formulation in AI |
| Study Alias and Treatment Duration  | Study Description                                                                                                                                                                         | Participant Type (N)                                                                             | Treatment Regimen/ Formulation                                                                                                                                                                                             |
| I8F-MC-GPHL (SURMOUNT-2) (72 weeks) | Efficacy and Safety of Tirzepatide Once Weekly in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-2) | Obesity/Overweight with T2DM (938 randomized)                                                    | All SC route of administration QW <ul style="list-style-type: none"> <li>• TZP 10 mg titrated</li> <li>• TZP 15 mg titrated</li> <li>• Placebo</li> </ul> All with solution formulation in AI                              |

*Abbreviations: AI = autoinjector; N = number of subjects; QW = once weekly; SC = subcutaneous; T2DM = type 2 diabetes mellitus; TZP = tirzepatide; N/V/D = nausea, vomiting, diarrhea*

*Source: Applicant's CWM popPK report, Table 7.1, page 15; Applicant's popPK and PK/PD report for SURMOUNT-2, Table 6.1, page 8.*

**Table 8. Summary of Baseline Characteristics of SUMROUND-1 Subjects in the PopPK and PK/PD Analyses**

|                                            | N,<br>Arithmetic Mean $\pm$ SD<br>Median (Minimum – Maximum) |                                                        |                                                        |                                                         |                                                         |                                                      |
|--------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|------------------------------------------------------|
|                                            | Placebo                                                      | Tirzepatide<br>5 mg QW                                 | Tirzepatide<br>10 mg QW                                | Tirzepatide<br>15 mg QW                                 | Overall<br>PK Analysis <sup>a</sup>                     | Overall<br>PK/PD Analysis <sup>a</sup>               |
| <b>Age<br/>(years)</b>                     | 643, 44.4 $\pm$ 12.5,<br>44 (18 - 78)                        | 630, 45.6 $\pm$ 12.7,<br>46 (18 - 79)                  | 636, 44.7 $\pm$ 12.4,<br>45 (18 - 75)                  | 630, 44.9 $\pm$ 12.3,<br>45 (18 - 84)                   | 1880, 45 $\pm$ 12.4,<br>45 (18 - 84)                    | 2539, 44.9 $\pm$ 12.5,<br>45 (18 - 84)               |
| <b>BMI<br/>(kg/m<sup>2</sup>)</b>          | 643, 38.2 $\pm$ 6.89,<br>36.4 (26.9 - 69.9)                  | 630, 37.4 $\pm$ 6.63,<br>36 (27 - 68.9)                | 636, 38.2 $\pm$ 7.01,<br>36.5 (27.2 - 67.7)            | 630, 38.1 $\pm$ 6.69,<br>36.9 (27.1 - 67.5)             | 1880, 37.9 $\pm$ 6.79,<br>36.5 (27 - 68.9)              | 2539, 38 $\pm$ 6.81,<br>36.5 (26.9 - 69.9)           |
| <b>Body Weight<br/>(kg)</b>                | 643, 105 $\pm$ 21.4,<br>101 (67.6 - 202)                     | 630, 103 $\pm$ 20.7,<br>98.8 (64 - 199)                | 636, 106 $\pm$ 23.3,<br>101 (60.1 - 206)               | 630, 106 $\pm$ 22.9,<br>102 (65.7 - 214)                | 1880, 105 $\pm$ 22.4,<br>101 (60.1 - 214)               | 2539, 105 $\pm$ 22.1, 101<br>(60.1 - 214)            |
| <b>Fat Mass<sup>b</sup><br/>(kg)</b>       | 643, 47.4 $\pm$ 15.2,<br>44.3 (20 - 117)                     | 630, 46 $\pm$ 14.6,<br>43.1 (19.5 - 113)               | 636, 47.9 $\pm$ 15.5,<br>44.6 (17.9 - 116)             | 630, 47.7 $\pm$ 14.8,<br>45.5 (19.8 - 112)              | 1880, 47.2 $\pm$ 15,<br>44.3 (17.9 - 116)               | 2539, 47.3 $\pm$ 15.1,<br>44.2 (17.9 - 117)          |
| <b>Fat Free Mass<sup>c</sup><br/>(kg)</b>  | 643, 57.3 $\pm$ 11.4,<br>54.2 (38.9 - 97.3)                  | 630, 56.9 $\pm$ 11.2,<br>53.8 (36.6 - 90.7)            | 636, 57.9 $\pm$ 12.4,<br>54.3 (35.8 - 93.2)            | 630, 57.9 $\pm$ 12.6,<br>53.8 (36.5 - 103)              | 1880, 57.5 $\pm$ 12,<br>53.9 (35.8 - 103)               | 2539, 57.5 $\pm$ 11.9, 54.2<br>(35.8 - 103)          |
| <b>Waist<br/>Circumference (cm)</b>        | 643, 114 $\pm$ 14.9,<br>112 (80 - 178)                       | 629, 113 $\pm$ 14.2,<br>112 (82 - 177)                 | 636, 115 $\pm$ 15.8,<br>113 (80 - 191)                 | 630, 114 $\pm$ 15.6,<br>112 (76.1 - 169)                | 1879, 114 $\pm$ 15.2,<br>112 (76.1 - 191)               | 2538, 114 $\pm$ 15.2, 112<br>(76.1 - 191)            |
| <b>Waist to Height<br/>Ratio</b>           | 643,<br>0.689 $\pm$ 0.0869,<br>0.679 (0.485 -<br>1.08)       | 629,<br>0.684 $\pm$ 0.0839,<br>0.673 (0.488 -<br>1.04) | 636,<br>0.691 $\pm$ 0.0881,<br>0.679 (0.506 -<br>1.09) | 630,<br>0.689 $\pm$ 0.0864,<br>0.679 (0.491 -<br>0.993) | 1879,<br>0.688 $\pm$ 0.0862,<br>0.677 (0.488 -<br>1.09) | 2538,<br>0.688 $\pm$ 0.0863, 0.678<br>(0.485 - 1.09) |
| <b>HbA1c<br/>(%)</b>                       | 643, 5.57 $\pm$ 0.375,<br>5.6 (4.5 - 7.0)                    | 630, 5.56 $\pm$ 0.362,<br>5.6 (3.6 - 6.6)              | 636, 5.55 $\pm$ 0.367,<br>5.5 (4.4 - 6.7)              | 630, 5.55 $\pm$ 0.403,<br>5.5 (4.4 - 8.9)               | 1880, 5.55 $\pm$<br>0.378, 5.5 (3.6 -<br>8.9)           | 2539, 5.56 $\pm$ 0.377,<br>5.6 (3.6 - 8.9)           |
| <b>eGFR<br/>(mL/min/1.73m<sup>2</sup>)</b> | 643, 98.1 $\pm$ 18.3,<br>99 (44 - 150)                       | 630, 97.6 $\pm$ 17.9,<br>98 (44 - 151)                 | 636, 98.3 $\pm$ 18.3,<br>101 (36 - 146)                | 630, 98.2 $\pm$ 17.7,<br>99 (36 - 153)                  | 1880, 98.1 $\pm$ 17.9,<br>99 (36 - 153)                 | 2539, 98.1 $\pm$ 18,<br>99 (36 - 153)                |
| <b>AST<br/>(IU/L)</b>                      | 642, 22.3 $\pm$ 10.2,<br>20 (5 - 92)                         | 630, 21.8 $\pm$ 9.64,<br>20 (5 - 140)                  | 636, 22.1 $\pm$ 11.4,<br>20 (7 - 197)                  | 630, 22.4 $\pm$ 11,<br>20 (8 - 142)                     | 1880, 22.1 $\pm$ 10.7,<br>20 (5 - 197)                  | 2538, 22.1 $\pm$ 10.5,<br>20 (5 - 197)               |
| <b>ALT<br/>(IU/L)</b>                      | 643, 27.6 $\pm$ 18.5,<br>22 (7 - 179)                        | 630, 26.7 $\pm$ 16.4,<br>22 (7 - 116)                  | 636, 27.3 $\pm$ 17.7,<br>22 (4 - 161)                  | 629, 27.8 $\pm$ 19.3,<br>22 (6 - 170)                   | 1879, 27.3 $\pm$ 17.9,<br>22 (4 - 170)                  | 2538, 27.4 $\pm$ 18,<br>22 (4 - 179)                 |
| <b>Albumin<br/>(g/dL)</b>                  | 643, 44.7 $\pm$ 2.77,<br>45 (35 - 55)                        | 630, 44.7 $\pm$ 2.69,<br>45 (37 - 55)                  | 636, 44.6 $\pm$ 2.73,<br>45 (33 - 56)                  | 630, 44.7 $\pm$ 2.64,<br>45 (37 - 53)                   | 1880, 44.7 $\pm$ 2.68,<br>45 (33 - 56)                  | 2539, 44.7 $\pm$ 2.71,<br>45 (33 - 56)               |

|                    | N,<br>Percent of Participants (%) |                        |                         |                         |                                     |                                        |
|--------------------|-----------------------------------|------------------------|-------------------------|-------------------------|-------------------------------------|----------------------------------------|
|                    | Placebo                           | Tirzepatide<br>5 mg QW | Tirzepatide<br>10 mg QW | Tirzepatide<br>15 mg QW | Overall<br>PK Analysis <sup>a</sup> | Overall<br>PK/PD Analysis <sup>a</sup> |
| <b>Sex</b>         |                                   |                        |                         |                         |                                     |                                        |
| Female             | 436 (67.8)                        | 426 (67.6)             | 427 (67.1)              | 425 (67.5)              | 1272 (67.7)                         | 1714 (67.5)                            |
| Male               | 207 (32.2)                        | 204 (32.4)             | 209 (32.9)              | 205 (32.5)              | 608 (32.3)                          | 825 (32.5)                             |
| <b>Ethnicity</b>   |                                   |                        |                         |                         |                                     |                                        |
| Hispanic           | 310 (48.2)                        | 308 (48.9)             | 297 (46.7)              | 299 (47.5)              | 895 (47.6)                          | 1214 (47.8)                            |
| Not Hispanic       | 281 (43.7)                        | 276 (43.8)             | 286 (45.0)              | 280 (44.4)              | 835 (44.4)                          | 1123 (44.2)                            |
| Not Reported       | 52 (8.1)                          | 46 (7.3)               | 53 (8.3)                | 51 (8.1)                | 150 (8)                             | 202 (8.0)                              |
| <b>Race</b>        |                                   |                        |                         |                         |                                     |                                        |
| American Indian    | 58 (9)                            | 56 (8.9)               | 58 (9.1)                | 59 (9.4)                | 173 (9.2)                           | 231 (9.1)                              |
| Asian              | 71 (11)                           | 68 (10.8)              | 71 (11.2)               | 66 (10.5)               | 205 (10.9)                          | 276 (10.9)                             |
| Black              | 55 (8.6)                          | 48 (7.6)               | 47 (7.4)                | 51 (8.1)                | 142 (7.6)                           | 201 (7.9)                              |
| Multi-racial       | 7 (1.1)                           | 9 (1.4)                | 6 (0.9)                 | 8 (1.3)                 | 23 (1.2)                            | 30 (1.2)                               |
| Pacific Islander   | 2 (0.3)                           | 2 (0.3)                | 2 (0.3)                 | 3 (0.5)                 | 7 (0.4)                             | 9 (0.4)                                |
| White              | 450 (70)                          | 447 (71)               | 452 (71.1)              | 443 (70.3)              | 1330 (70.7)                         | 1792 (70.6)                            |
| <b>Alcohol Use</b> |                                   |                        |                         |                         |                                     |                                        |
| No                 | 308 (47.9)                        | 291 (46.2)             | 297 (46.7)              | 282 (44.8)              | 863 (45.9)                          | 1178 (46.4)                            |
| Yes                | 335 (52.1)                        | 339 (53.8)             | 339 (53.3)              | 348 (55.2)              | 1017 (54.1)                         | 1361 (53.6)                            |
| <b>Tobacco Use</b> |                                   |                        |                         |                         |                                     |                                        |
| No                 | 574 (89.3)                        | 536 (85.1)             | 561 (88.2)              | 543 (86.2)              | 1625 (86.4)                         | 2214 (87.2)                            |
| Yes                | 69 (10.7)                         | 94 (14.9)              | 75 (11.8)               | 87 (13.8)               | 255 (13.6)                          | 325 (12.8)                             |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; BMI = body mass index; BW = body weight; cm = centimeters; FFM = fat free mass; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; N = number of participants; PD = pharmacodynamic; PK = pharmacokinetic; PK/PD = pharmacokinetics/pharmacodynamics; QW = once weekly; SD = standard deviation.

<sup>a</sup> The PK analysis included participants randomized to tirzepatide treatment. The PK/PD analyses included participants randomized to either placebo or tirzepatide treatment; <sup>b</sup> Fat Mass = BW – FFM (Janmahasatian et al. 2005); <sup>c</sup> FFM, female =  $(9270 \times BW) / (8780 + 244 \times BMI)$ ; FFM, male =  $(9270 \times BW) / (6680 + 216 \times BMI)$  (Janmahasatian et al. 2005)

Source: Applicant's CWM popPK report, Table 7.5, pages 19-20

### Base model

The base model was informed by the structural popPK model from tirzepatide T2DM development program. The base model was a two-compartment PK model with first order absorption and linear elimination. Mean absolute bioavailability was fixed to 80% (previous study data). Time-dependent body weight was modeled on clearance and volume of distribution parameters. Between-subject variability (IIV) was included on absorption rate constant (Ka), clearance (CL), central volume of distribution (Vc), and proportional residual error model. Allometric scaling was included (fixed) on CL, intercompartmental clearance (Q), Vc, and peripheral volume of distribution (Vp).

Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), prior PK information, successful model convergence, acceptable parameter shrinkage, and diagnostic plots.

### Covariate analysis

Covariates were screened for the final popPK model, and the inclusion result are summarized in **Table 9**. Additionally, the final tirzepatide popPK model included the relationships between fat-free mass (FFM) and fat mass and CL and Vd. FFM was calculated based on subject's total body weight, sex, and body mass index. Fat mass is also derived subsequently using the following relationships (Janmahasatian S, et al. *Clin Pharmacokinet.* 2005; 44(10): 1051-1065):

$$\text{Eq 1. FFM (male)} = 9270 \times \text{BW} / (6680 + 216 \times \text{BMI})$$

$$\text{Eq 2. FFM (female)} = 9270 \times \text{BW} / (8780 + 244 \times \text{BMI})$$

$$\text{Eq 3. Fat Mass} = \text{BW} - \text{FFM}$$

**Table 9. Covariates Assessed for PopPK Model**

| Covariate                          | Included in Final Model | Influence on PK Parameters |
|------------------------------------|-------------------------|----------------------------|
| Injection site <sup>a</sup>        | No                      | --                         |
| Age <sup>b</sup>                   | No                      | --                         |
| Albumin                            | No                      | --                         |
| AST, ALT                           | No                      | --                         |
| Body size                          | Yes <sup>c</sup>        | CL, Vd                     |
| eGFR <sup>d</sup>                  | No                      | --                         |
| Race <sup>e</sup>                  | No                      | --                         |
| Sex                                | No <sup>c</sup>         | --                         |
| Titer of anti-tirzepatide antibody | No                      | --                         |

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CL = clearance; eGFR = estimated glomerular filtration rate; FFM = fat free mass; N = number of participants; PK = pharmacokinetics; SC = subcutaneous; Vd = volume of distribution.

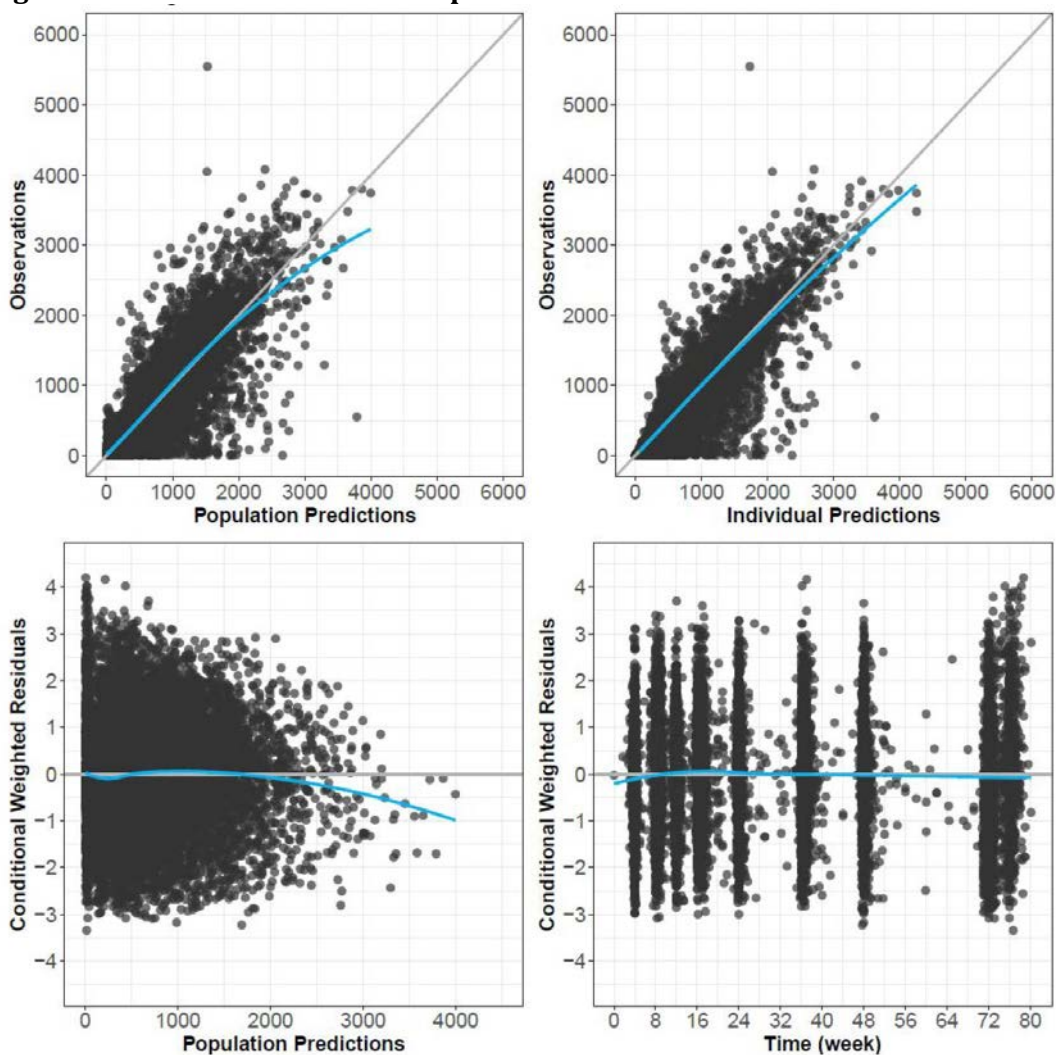
<sup>a</sup> Approximately 91% of observed tirzepatide concentrations were associated with SC administration in the abdomen. The other potential administration sites were the arms and the thighs; <sup>b</sup> In the SURMOUNT-1 population PK analysis, the majority of participants were <65 years old. There were 112 participants who were at least 65 years old and less than 75 years old, and 5 participants who were at least 75 years old; <sup>c</sup> Body weight, BMI, and sex were factors in the calculation of FFM (Janmahasatian et al. 2005). FFM and fat mass were included as covariates on CL and Vd; <sup>d</sup> In the SURMOUNT-1 population PK analysis, the majority of participants had a baseline eGFR greater than 90 mL/min/1.73m<sup>2</sup>, N=1241 (66%). There were 603 (32%) participants with a baseline eGFR at least 60 and less than 90 mL/min/1.73m<sup>2</sup> and there were 36 (2%) participants with a baseline

eGFR at least 30 and less than 60 mL/min/1.73m<sup>2</sup>; <sup>e</sup> In the SURMOUNT-1 population PK analysis, the most common race categories of participants were White (71%), Asian (11%), American Indian (9%), and Black (8%)  
Source: Applicant's CWM popPK report, Table 9.1, pages 32-33

### Final model

The parameter estimates and bootstrap results (1000 replicates) for the final covariate model are listed in **Table 10** Error! Reference source not found.. Pooled T2DM popPK model (an established model from the T2DM development program) parameter estimates are also provided for comparison. The goodness-of-fit (GoF) and prediction-corrected VPC plots for the final covariate model are shown in **Figure 3** and **Figure 4**, respectively.

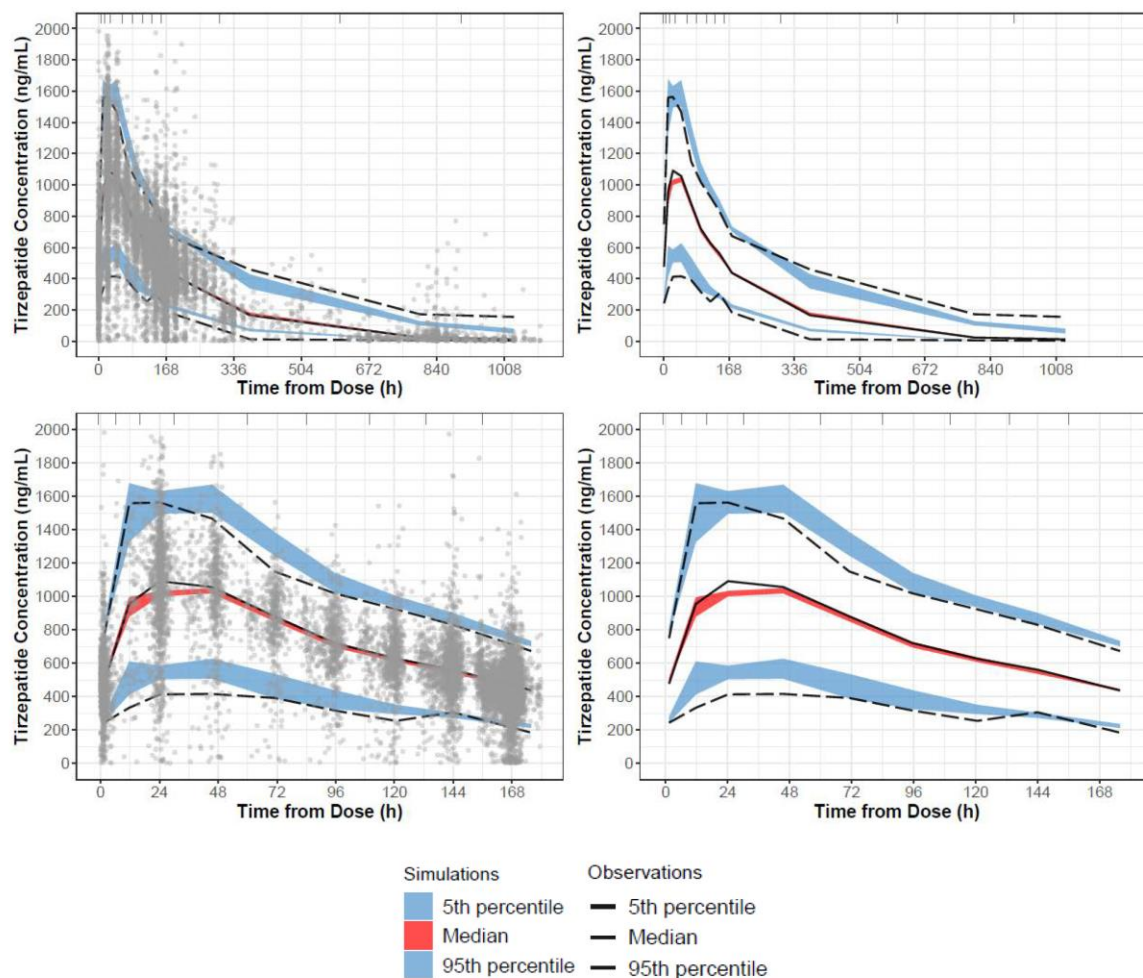
**Figure 3. GoF Plots for the Final PopPK Model**



Abbreviations: Observations = tirzepatide concentration, ng/mL; PK = pharmacokinetics; Time = time from first dose

Source: Applicant's CWM popPK report, Figure ATT.4.2, page 182

**Figure 4. Prediction-corrected VPC for the Final PopPK Model**



Abbreviations: pcVPC = prediction-corrected visual predictive check; PK = pharmacokinetics.

Note: Solid circles denote individual values, shaded areas denote 95% confidence interval of simulation percentiles, and the dashed lines denote the observation percentiles.

Source: Applicant's CWM popPK report, Figure 9.4, page 39

**Table 10. Parameter Estimates for SURMOUNT-2 Final PopPK Model (and previously reported T2DM model outputs)**

| Parameter                                                                                                       | T2DM Pooled Analysis<br>Population Estimate<br>Bootstrap Median<br>(95% CI) <sup>a</sup> | SURMOUNT-1<br>Population Estimate<br>Bootstrap Median<br>(95% CI) <sup>a</sup> | SURMOUNT-2<br>Population Estimate<br>Bootstrap Median<br>(95% CI) <sup>a</sup> |
|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Bioavailability<br>(F, fraction)                                                                                | 0.8 fixed                                                                                | 0.8 fixed                                                                      | 0.8 fixed                                                                      |
| Absorption rate<br>( $k_a$ , 1/h)                                                                               | 0.0373<br>0.0370 (0.0289, 0.0460)                                                        | 0.0318<br>0.0321 (0.0280, 0.0395)                                              | 0.0373 fixed                                                                   |
| Clearance<br>(CL, L/h/70 kg)                                                                                    | 0.0329<br>0.0329 (0.0313, 0.0342)                                                        | 0.0371<br>0.0371 (0.0359, 0.0382)                                              | 0.0406<br>0.0408 (0.0392, 0.0431)                                              |
| Intercompartmental<br>clearance<br>(Q, L/h/70 kg)                                                               | 0.126<br>0.125 (0.101, 0.144)                                                            | 0.0934<br>0.0930 (0.0851, 0.101)                                               | 0.121<br>0.120 (0.104, 0.138)                                                  |
| Central volume of<br>distribution<br>( $V_c$ , L/70 kg)                                                         | 2.47<br>2.46 (2.05, 2.92)                                                                | 2.88<br>2.90 (2.45, 3.74)                                                      | 3.48<br>3.51 (3.11, 3.93)                                                      |
| Peripheral volume of<br>distribution<br>( $V_p$ , L/70 kg)                                                      | 3.98<br>3.98 (3.56, 4.21)                                                                | 4.05<br>4.03 (3.62, 4.31)                                                      | 4.33<br>4.33 (3.90, 4.73)                                                      |
| <b>Covariate Effects</b>                                                                                        |                                                                                          |                                                                                |                                                                                |
| <i>Effect on <math>F_b</math></i><br>Relative study effect                                                      | -0.181<br>-0.181 (-0.220, -0.147)                                                        | NA <sup>g</sup>                                                                | NA <sup>g</sup>                                                                |
| <i>Effect on CL and <math>Q_c</math></i><br>Body weight (kg)<br>Fraction of fat mass                            | 0.8 fixed <sup>f</sup><br>1 fixed                                                        | 0.8 fixed <sup>f</sup><br>0.711<br>0.712 (0.638, 0.800)                        | 0.8 fixed <sup>f</sup><br>0.888<br>0.880 (0.707, 0.993)                        |
| <i>Effect on <math>V_c</math> and <math>V_p</math></i> <sup>d</sup><br>Body weight (kg)<br>Fraction of fat mass | 1 fixed <sup>f</sup><br>0.482<br>0.483 (0.447, 0.524)                                    | 1 fixed <sup>f</sup><br>0.417<br>0.416 (0.315, 0.526)                          | 1 fixed <sup>f</sup><br>0.527<br>0.519 (0.356, 0.686)                          |
| <i>Effect on <math>k_a</math></i> <sup>e</sup><br>Lyophilized<br>formulation                                    | -0.161<br>-0.161 (-0.207, -0.107)                                                        | NA <sup>h</sup>                                                                | NA <sup>h</sup>                                                                |
| <b>Interindividual<br/>variability CV%</b>                                                                      |                                                                                          |                                                                                |                                                                                |
| $k_a$                                                                                                           | 22.5%<br>22.1 (14.9, 28.7)                                                               | 15.2%<br>15.2 (14.4, 16.3)                                                     | 22.5% fixed                                                                    |
| CL                                                                                                              | 14.2%<br>14.2 (13.7, 14.7)                                                               | 12.3%<br>12.3 (11.6, 13.0)                                                     | 13.5%<br>13.5 (12.1, 15.0)                                                     |
| $V_c$                                                                                                           | 49.0%<br>49.5 (38.3, 62.3)                                                               | 61.5%<br>61.1 (47.5, 71.2)                                                     | 81.5%<br>81.0 (65.4, 96.7)                                                     |
| Proportional residual                                                                                           | 58.1%<br>58.0 (56.1, 60.0)                                                               | 65.2%<br>65.1 (62.0, 68.3)                                                     | NA                                                                             |
| <b>Residual variability</b>                                                                                     |                                                                                          |                                                                                |                                                                                |

| Parameter        | T2DM Pooled Analysis<br>Population Estimate<br>Bootstrap Median<br>(95% CI) <sup>a</sup> | SURMOUNT-1<br>Population Estimate<br>Bootstrap Median<br>(95% CI) <sup>a</sup> | SURMOUNT-2<br>Population Estimate<br>Bootstrap Median<br>(95% CI) <sup>a</sup> |
|------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Proportional (%) | 20.6%<br>20.6 (20.3, 21.0)                                                               | 20.6%<br>20.6 (20.0, 21.3)                                                     | 29.2%<br>29.2 (27.6, 30.9)                                                     |

Abbreviations: CI = bootstrap-derived confidence interval; CL = clearance; CV = coefficient of variation; F = bioavailability; FFM = fat-free mass (kg);  $k_a$  = absorption rate constant; N/A = not applicable; PK = pharmacokinetic; Q = intercompartmental clearance; SURMOUNT-1 = Study I8F-MC-GPHK; SURMOUNT-2 = Study I8F-MC-GPHL; T2DM = type 2 diabetes mellitus;  $V_c$  = central volume of distribution;  $V_d$  = volume of distribution;  $V_p$  = peripheral volume of distribution.

<sup>a</sup> Median and 95% CI derived from bootstrap analysis.

<sup>b</sup>  $F = \Theta_1 * (1 + \Theta_{10})$  where  $\Theta_1$  is the bioavailability value from Study I8F-MC-GPGE and  $\Theta_{10}$  is the relative fraction.

<sup>c</sup>  $iCL = pCL * [(FFM + \text{fat mass} * \Theta_8)/70]^{0.8}$  where  $iCL$  is an individual's CL,  $pCL$  is the population CL, FFM is an individual's FFM, and  $\Theta_8$  is a fraction. The described structure was applied to CL and Q.

<sup>d</sup>  $iV_d = pV_d * [(FFM + \text{fat mass} * \Theta_9)/70]^1$  where  $iV_d$  is an individual's  $V_d$ ,  $pV_d$  is the population  $V_d$ , FFM is an individual's FFM, and  $\Theta_9$  is a fraction. The described structure was applied to  $V_c$  and  $V_p$ .

<sup>e</sup>  $ik_a = pk_a * (1 + \Theta_{11})$  where  $ik_a$  is an individual's  $k_a$ ,  $pk_a$  is the population  $k_a$ , and  $\Theta_{11}$  is a fraction.

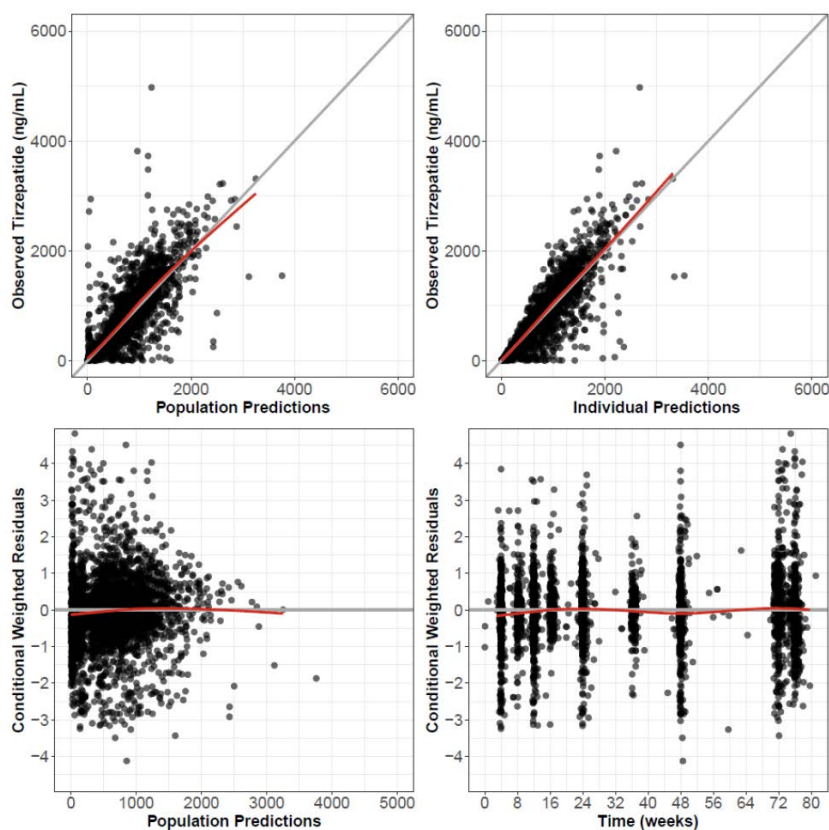
<sup>f</sup> Holford 1996, Mordenti et al. 1991. Wang and Prueksaritanont 2010.

<sup>g</sup> A scalar for F relative to 0.8 was tested and did not have a statistically significant impact on the objective function in the analysis of SURMOUNT-1 or SURMOUNT-2.

<sup>h</sup> The solution formulation of tirzepatide was administered in SURMOUNT-1 and SURMOUNT-2.

Source: Applicant's response to FDA information request dated 05JUNE2023

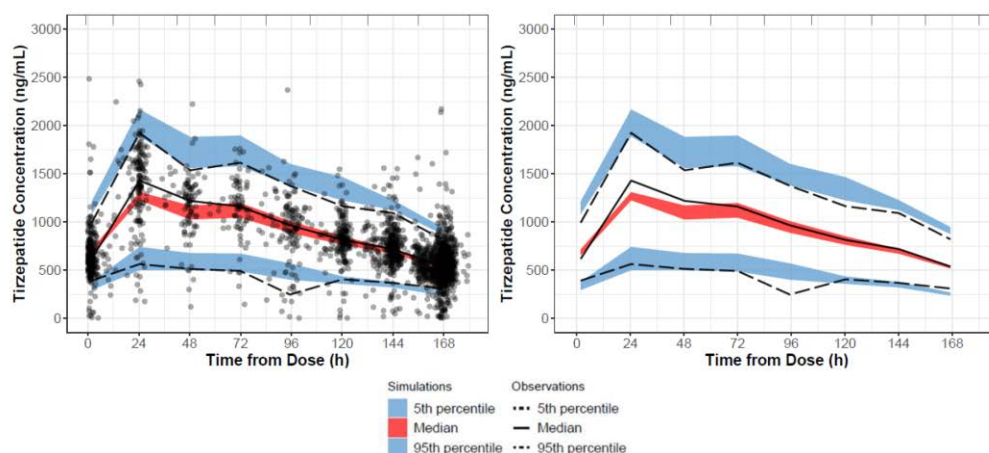
**Figure 5. GoF Plots for SURMOUNT-2 Final PopPK Model**



Abbreviations: PK = pharmacokinetics; SURMOUNT-2 = Study I8F-MC-GPHL.

Source: Applicant's response to FDA information request dated 05JUNE2023

**Figure 6. Prediction-corrected VPC for SURMOUNT-2 Final PopPK Model**



Abbreviations: pcVPC = prediction corrected visual predictive check; PK = pharmacokinetics; SURMOUNT-2 = Study I8F-MC-GPHL.

Source: Applicant's response to FDA information request dated 05JUNE2023

*Reviewer comments: the final popPK model is acceptable for descriptive labeling of tirzepatide disposition in adults with obesity or overweight. The model parameters were estimated with good precision (<14.8% relative standard error), and this is also evident from the bootstrap analysis. The IIV were low to moderate for Ka and CL (15.2% and 12.3%, respectively) but were high for Vc and proportional error term (61.5% and 65.2%, respectively). The latter is not unexpected given the prior model from T2DM development program (demonstrated high IIV for Vc and proportional error term). ETA Shrinkage were 68%, 12% and 19% for Ka, CL, and Vc, respectively, and the relatively high shrinkage for Ka is consistent with the pooled T2DM popPK model. This likely is due to the number of PK observations available in the absorption phase. GoF plots of the final model demonstrated that the model described the data reasonably well without obvious model bias or misspecification. Prediction-corrected VPC demonstrated that the final model captured the variability and central tendency of tirzepatide PK profile. Overall, the model adequately described the PK of tirzepatide in adults with obesity or who are overweight and is acceptable for deriving ADME parameters (absorption, distribution, metabolism, and elimination) for labeling statements and exposure metrics for subsequent PK/PD analyses.*

*Model output of the SURMOUNT-2 popPK model is summarized in **Table 10** and diagnostic plots are shown **Figure 5** and **Figure 6**. Briefly, the 95% CIs of the SURMOUNT-2 PK model parameters derived from bootstrap analysis showed reasonable precision in parameter estimation (RSE <17.1%). The ETA shrinkage parameters on CL and Vc were 25% and 19%, respectively, and were comparable with the values reported in the previous population PK analyses; however, ETA shrinkage for Ka was high (80.3%). Generally, GoF and diagnostic plots indicate that the model adequately describes the SURMOUNT-2 data without obvious bias.*

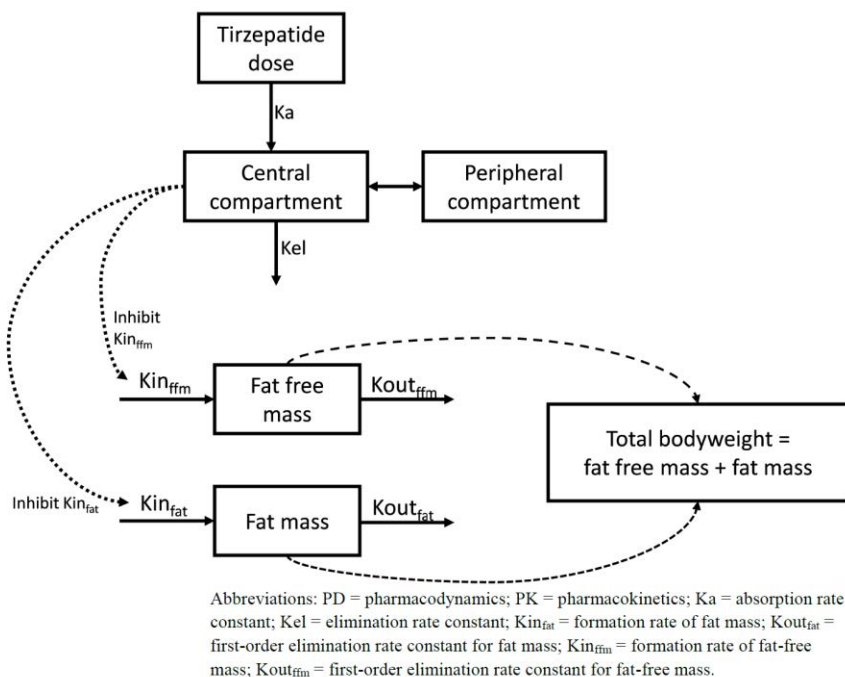
#### 4.3.2 Body Weight Model

The Applicant quantified the exposure-weight-loss relationship through a body weight PK/PD model using an established model from the T2DM development program. In this submission for CWM, the final PK/PD dataset for body weight model development included 54804 observations from 2523 subjects from SURMOUNT-1.

A sequential approach was used to characterize the effect of tirzepatide on body weight reduction in the study population. The Applicant utilized an indirect response model to account for the delay effect of tirzepatide in body weight reduction. A schematic of the structural model is shown in **Figure 7**. Model evaluation was conducted using standard goodness-of-fit plots, bootstrap, and visual prediction checks. The Applicant developed the PK/PD model using 50% of randomly selected data (i.e., training data), and the remaining 50% was used for external evaluation to increase confidence in the model. The final model estimates are summarized in **Table 11**. Based on the Applicant's analysis, sex was a significant covariate and was included in the final model. Females had a 31% lower baseline FFM than males. Females also had a 5% higher baseline fat mass than males. Females had a higher  $I_{max}$  and  $IC_{50}$  relative to males. Asian race was also a significant covariate in the model, with Asian patients being estimated to have 11% lower and 25% lower FFM and fat mass at baseline, respectively.

Using the body weight model, the Applicant performed simulation to demonstrate dose-response relationship (**Figure 10**) at 72 weeks and to compare changes in body composition (i.e., FFM and fat mass) (**Table 12, Figure 11**) over time across dose levels at 72 weeks. Overall, the Applicant's simulations demonstrated that the subjects (obese or overweight) lose more fat mass than FFM over time.

**Figure 7. Schematic of the Body Weight Model**



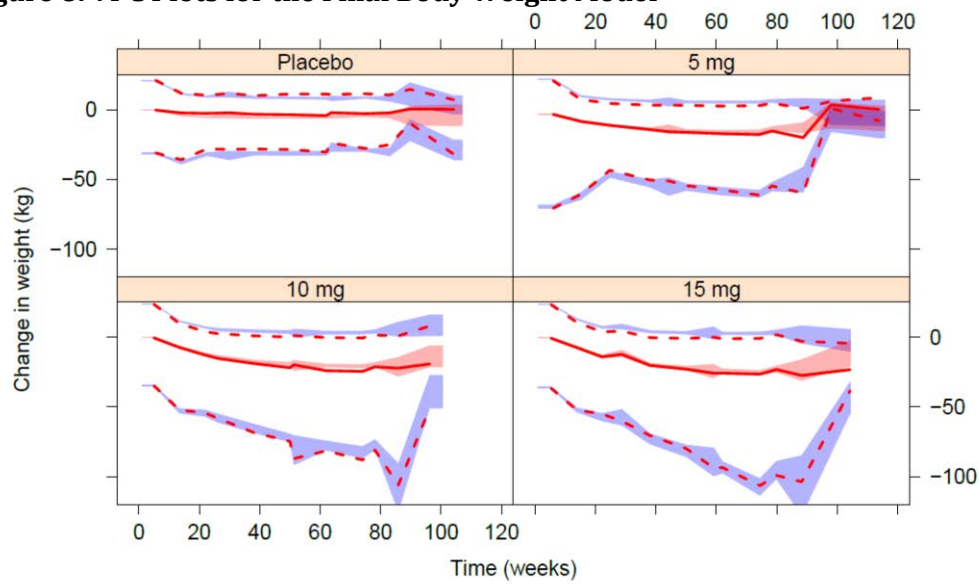
Source: Applicant's CWM popPK report, Figure 8.1, page 26

**Table 11. Parameter Estimates for the Final Body Weight Model**

| <b>Population Parameter</b>                                                | <b>Estimate (95% CI)<sup>a</sup></b> |
|----------------------------------------------------------------------------|--------------------------------------|
| Baseline fat-free mass (kg)                                                | 73.5 (72.6, 74.3)                    |
| Baseline fat mass (kg)                                                     | 45.0 (43.4, 46.3)                    |
| First-order elimination rate constant, Kout (week <sup>-1</sup> )          | 0.0314 (0.0295, 0.0348)              |
| Maximum effect for drug inhibiting formation of fat free mass              | 0.144 (0.119, 0.176)                 |
| Maximum effect for drug inhibiting formation of fat mass                   | 0.319 (0.266, 0.385)                 |
| IC50 for drug inhibiting formation of fat free mass (ng/mL)                | 1760 (1490, 2030)                    |
| IC50 for drug inhibiting formation of fat mass (ng/mL)                     | 518 (390, 678)                       |
| Placebo fractional reduction in fat-free mass Kin                          | 0.0658 (0.0594, 0.0698)              |
| Placebo fractional reduction in fat mass Kin                               | 0.213 (0.192, 0.228)                 |
| Half life of waning placebo effect (weeks)                                 | 40.3 (34.6, 54.4)                    |
| <b>Covariate Effects</b>                                                   |                                      |
| Fractional change in baseline fat-free mass in females                     | -0.312 (-0.322, -0.302)              |
| Fractional change in fat mass in females                                   | 0.0539 (0.0170, 0.0994)              |
| Fractional change in drug maximum effect for fat-free mass in females      | 1.78 (1.37, 2.33)                    |
| Fractional change in drug maximum effect for fat mass in females           | 0.809 (0.528, 1.12)                  |
| Fractional change in drug IC50 effect for fat-free mass in females         | 1.14 (0.836, 1.55)                   |
| Fractional change in drug IC50 effect for fat mass in females              | 2.05 (1.31, 3.19)                    |
| Fractional change in baseline fat-free mass in Asians                      | -0.110 (-0.128, -0.0905)             |
| Fractional change in baseline fat mass in Asians                           | -0.254 (-0.291, -0.214)              |
| <b>Interindividual variability (CV%)</b>                                   |                                      |
| Baseline fat-free mass                                                     | 11.0 (10.5, 11.5)                    |
| Baseline fat mass                                                          | 29.3 (28.1, 30.4)                    |
| Correlation between the random effects for baseline fat and fat-free mass  | 0.851 (0.835, 0.864)                 |
| Correlation between the random effects for baseline fat-free mass and Kout | -0.140 (-0.212, -0.0667)             |
| Correlation between the random effects for baseline fat mass and Kout      | -0.172 (-0.246, -0.0936)             |
| First-order elimination rate constant, Kout                                | 124 (110, 140)                       |
| Maximum drug effect on fat-free mass                                       | 84.5 (68.4, 102)                     |
| Maximum drug effect on fat mass                                            | 69.6 (54.4, 85.1)                    |
| Correlation between the random effects for maximum effect (IMAX)           | 0.993 (0.988, 0.994)                 |
| IC50 for drug inhibiting formation of fat free mass                        | 25.7 (19.4, 34.7)                    |
| IC50 for drug inhibiting formation of fat mass                             | 47.4 (35.3, 66.1)                    |
| Correlation between the random effects for IC50                            | 0.9994 (0.9986, 0.9998)              |
| Placebo effect for fat-free mass                                           | 96.6 (87.5, 107)                     |
| Placebo effect on fat mass                                                 | 94.7 (86.3, 106)                     |
| Correlation between the random effects for placebo                         | 0.977 (0.972, 0.985)                 |
| <b>Residual error</b>                                                      |                                      |
| Proportional for fat-free mass (%)                                         | 0.985 (0.910, 1.04)                  |
| Proportional for fat mass (%)                                              | 3.35 (3.08, 3.54)                    |
| Correlation between residual error (%)                                     | 98.4 (98.4, 98.6)                    |

Source: Applicant's CWM popPK report, Table 9.3, page 41

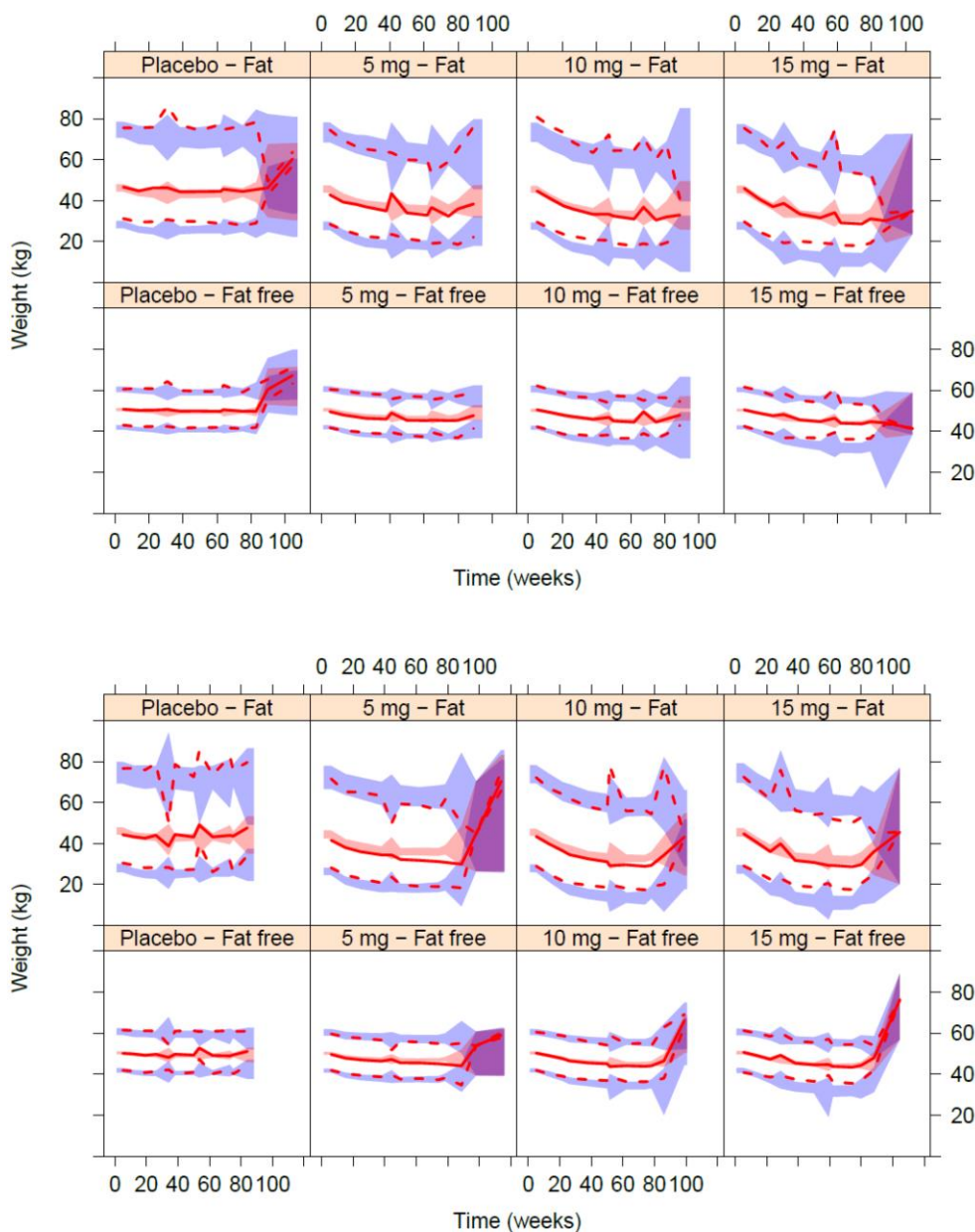
**Figure 8. VPC Plots for the Final Body Weight Model**



*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.*

*Source: Applicant's CWM popPK report, Figure 9.7, page 46*

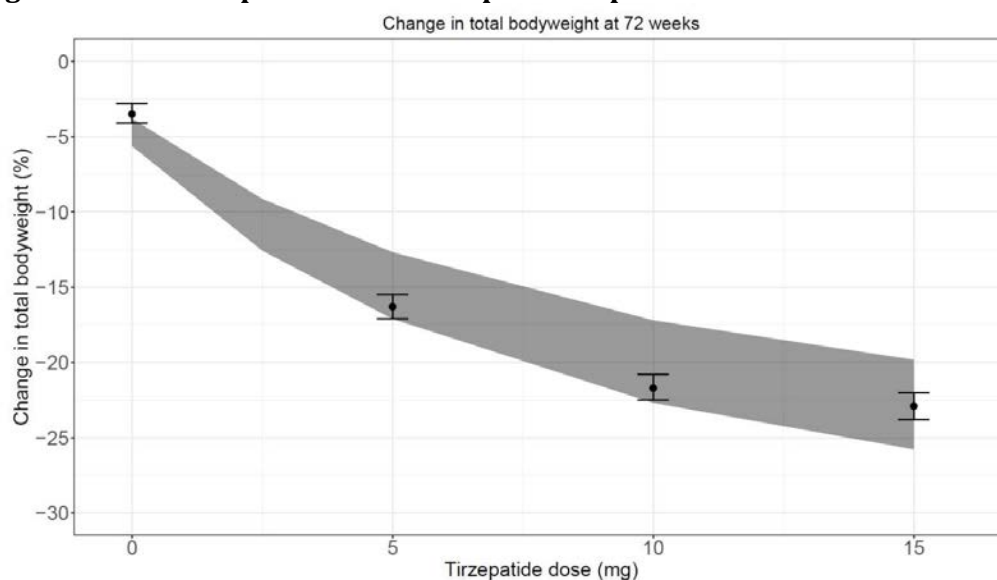
**Figure 9. VPC Plots for the Final Body Weight Model by Fat Mass and FFM**



*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. The top 4 panels are for the training dataset. The bottom 4 panels are for the external evaluation dataset.*

*Source: Applicant's CWM popPK report, Figure 9.6, page 45*

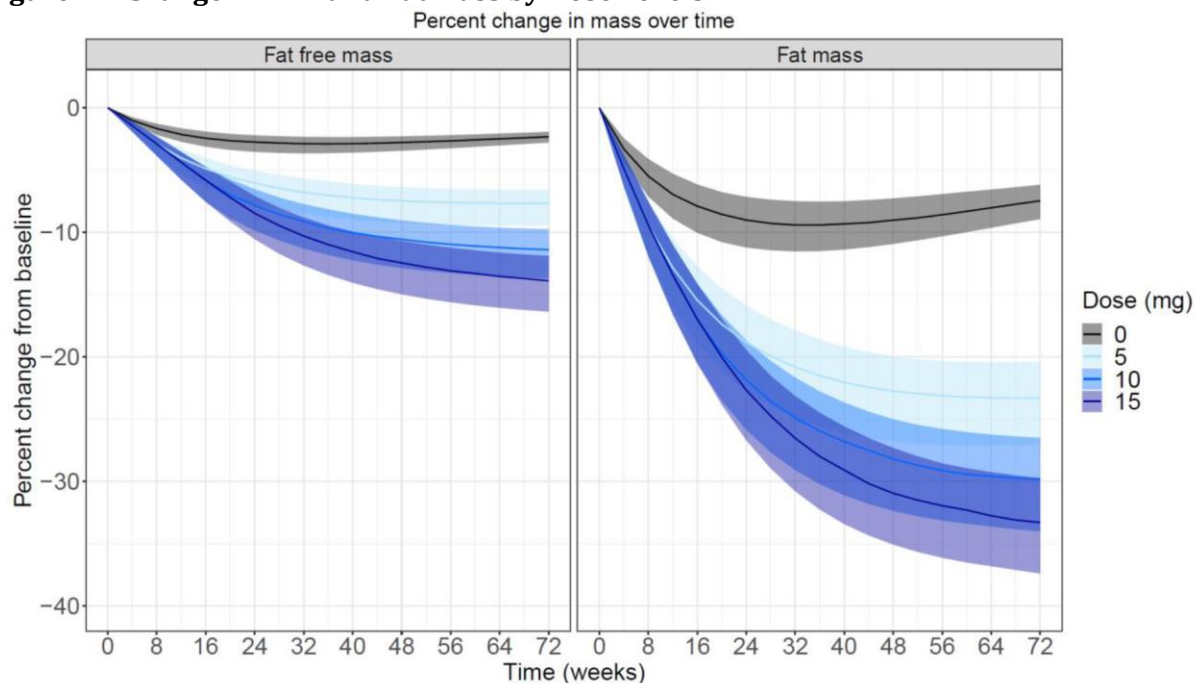
**Figure 10. Dose-response Relationship of Tirzepatide at 72 Weeks**



The shaded area is the 95% confidence interval of model predictions; the points and error bars are the observed mean and 95% confidence interval respectively

Source: Applicant's CWM popPK report, Figure 10.4, page 63

**Figure 11. Change in FFM and Fat Mass by Dose Levels**



Simulation included the dose escalation approach; the continuous line is the mean prediction; the shaded area is the 95% confidence interval.

Source: Applicant's CWM popPK report, Figure 10.7, page 66

**Table 12. Model-predicted and Observed Change in Body Composition after 72 Weeks**

|                          | Weight Reduction (Percent Change from Baseline) at 72 weeks<br>Mean (95% CI) |                          |                         |                          |                         |                          |                         |                          |
|--------------------------|------------------------------------------------------------------------------|--------------------------|-------------------------|--------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
|                          | Placebo                                                                      |                          | Tirzepatide 5 mg QW     |                          | Tirzepatide 10 mg QW    |                          | Tirzepatide 15 mg QW    |                          |
|                          | PK/PD Model                                                                  | SURMOUNT -1 <sup>a</sup> | PK/PD Model             | SURMOUNT -1 <sup>a</sup> | PK/PD Model             | SURMOUNT -1 <sup>a</sup> | PK/PD Model             | SURMOUNT -1 <sup>a</sup> |
| <b>Total body weight</b> | -4.62<br>(-5.62, -3.80)                                                      | -2.4<br>(0.40)           | -14.6<br>(-17.1, -12.7) | -16.0<br>(0.39)          | -19.7<br>(-22.7, -17.2) | -21.4<br>(0.39)          | -22.5<br>(-25.8, -19.8) | -22.5<br>(0.39)          |
| <b>Fat-free mass</b>     | -2.34<br>(-2.79, -1.94)                                                      | NR                       | -7.68<br>(-9.47, -6.60) | NR                       | -11.4<br>(-13.7, -9.75) | NR                       | -13.9<br>(-16.4, -11.9) | NR                       |
| <b>Fat mass</b>          | -7.48<br>(-8.94, -6.19)                                                      | NR                       | -23.3<br>(-27.0, -20.4) | NR                       | -29.8<br>(-34.0, -26.5) | NR                       | -33.3<br>(-37.4, -29.7) | NR                       |

Abbreviations: CI = confidence interval; NR = not reported; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PK/PD Model = exposure-response weight reduction model; QW = once weekly; SURMOUNT-1 = Study I8F-MC-GPHK; T2DM = type 2 diabetes mellitus.

<sup>a</sup> Shown least-square means and standard error from SURMOUNT-1 efficacy analysis set.

Source: Applicant's response to FDA information request dated 20JUNE2023

**Table 13. Model-predicted and Observed Change in Body Composition after 72 Weeks (SURMOUNT-2)**

|                          | Weight Reduction (Percent Change from Baseline) at 72 weeks<br>Mean (95% CI) |                         |                         |                         |                         |                         |
|--------------------------|------------------------------------------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                          | Placebo                                                                      |                         | Tirzepatide 10 mg QW    |                         | Tirzepatide 15 mg QW    |                         |
|                          | PK/PD Model                                                                  | SURMOUNT-2 <sup>a</sup> | PK/PD Model             | SURMOUNT-2 <sup>a</sup> | PK/PD Model             | SURMOUNT-2 <sup>a</sup> |
| <b>Total body weight</b> | -4.04<br>(-5.34, -3.03)                                                      | -3.29<br>(0.49)         | -11.5<br>(-14.3, -9.44) | -13.43<br>(0.48)        | -14.7<br>(-18.8, -12.1) | -15.65<br>(0.49)        |
| <b>Fat free mass</b>     | -1.87<br>(-2.25, -1.43)                                                      | NR                      | -5.75<br>(-6.63, -5.12) | NR                      | -7.50<br>(-8.70, -6.51) | NR                      |
| <b>Fat mass</b>          | -7.18<br>(-8.80, -5.81)                                                      | NR                      | -19.8<br>(-22.7, -17.5) | NR                      | -25.5<br>(-29.9, -22.5) | NR                      |

Abbreviations: CI = confidence interval; NR = not reported; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PK/PD Model = exposure-response weight reduction model; QW = once weekly; SURMOUNT-2 = Study I8F-MC-GPHL; T2DM = type 2 diabetes mellitus.

<sup>a</sup> Shown least-square means and standard error from SURMOUNT-2 efficacy analysis set.

Source: Applicant's response to FDA information request dated 20JUNE2023

*Reviewer comments: the body weight model appropriately describes the effect of tirzepatide on body weight reduction from baseline in adults with obesity or who are overweight, supporting the proposed dosing regimen for CWM. The final model parameters were estimated with reasonable precision (highest RSEs are 35.8% and 30.8% while others are below 21.4%). Shrinkage on IIVs ranged from low to high (0.2% to 45.7%) with the highest for IIVs for IC50 of drug inhibition formation on both fat mass and FFM, and other shrinkage values are below 28.2%. The Applicant's weight loss model overall adequately describes the total body weight observations and reasonably predicts "new" data based on VPC plots stratified by dose levels and fat mass and FFM (Table 10, Figure 8 and Figure 9).*

The simulation results show that the model appropriately captures the effect of tirzepatide on weight loss and reduction in FFM and fat-mass across dose levels (including dose escalation scheme) to Week 72.

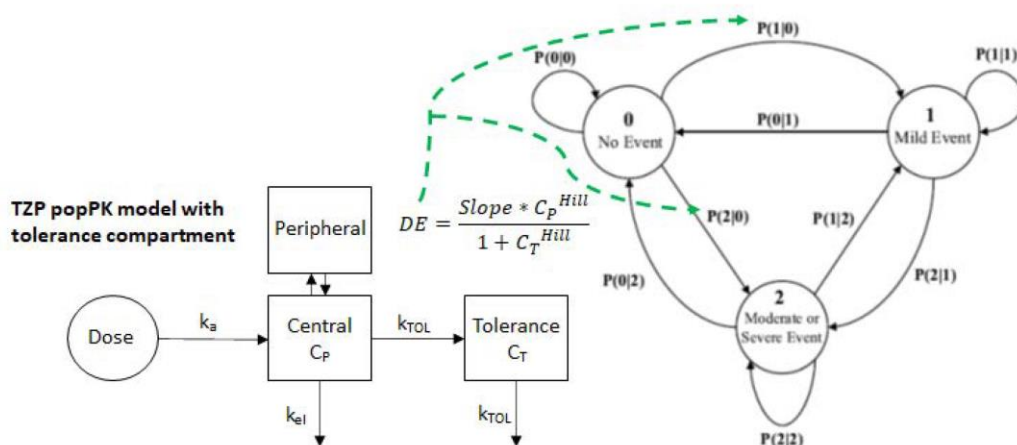
Model-predicted weight loss (SURMOUNT-2) by body composition in the T2DM population is summarized in **Table 13**. Refer to Applicant's response to FDA information requested dated 05JUNE2023 for additional diagnostic plots of the PK/PD model based on the SURMOUNT-2 data in this submission. Details of the pharmacometrics assessment in the context of T2DM is discussed in the Office of Clinical Pharmacology Review by Drs. Kronfol, Dahmane, Earp, and Vaidyanathan (NDA 215866, dated 8MAR2022).

#### 4.3.3 Nausea, Vomiting and Diarrhea Models

The Applicant performed PK/PD analysis to characterize the effect of tirzepatide on safety and tolerability adverse events (AEs) (i.e., any category of nausea, vomiting, and diarrhea or N/V/D). The final model that describes the events in obese or overweight subjects in SURMOUNT-1 study was informed by the PK/PD model from the T2DM development program. The endpoints modeled are probability of transitioning from no AE to mild AE and no AE to moderate or severe AE. The final dataset for N/V/D includes approximately 1194000 (x3) daily observations from 2523 subjects from SURMOUNT-1.

Using the PK/PD model developed previously (for T2DM development program), a sequential modeling approach was used to estimate the PD parameters (i.e., estimation of transition probabilities of AEs using a discrete-time Markov chain model accounting for covariates). A schematic of the structural model is depicted in **Figure 12**. The analysis demonstrated that females have a decrease in the nausea and vomiting tolerance rate constant (KTOL) relative to males. Therefore, females will develop tolerance slower than men resulting in a higher and more persistent probability of nausea and vomiting. Caucasian patients had an increase in baseline probability of mild nausea relative to non-Caucasians. The final model parameters of the nausea-vomiting model and the diarrhea model are summarized in **Table 14** and **Table 15**. The VPC plot for the final N/V/D model is shown in **Figure 13**.

**Figure 12. Schematic of N/V/D Model**



Abbreviations: AE = adverse event;  $k_a$  = absorption rate constant;  $k_{el}$  = 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; KTOL = 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. 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 CWM popPK report, Figure 8.2, page 29

**Table 14. Parameter Estimates for the Final N/V Model**

| Population Parameter                                                                                                                 | Estimate (95% CI) <sup>a</sup> |
|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Baseline transition probability from no to mild nausea, NP10 (logit)                                                                 | -9.70 (-10.2, -9.23)           |
| Baseline transition probability from no to moderate/severe nausea, NP20 (logit)                                                      | -10.6 (-11.6, -9.92)           |
| Baseline transition probability from mild to no nausea and from moderate/severe to no nausea, NP01 & NP02 (logit)                    | -4.05 (-4.29, -3.75)           |
| Baseline transition probability from mild to moderate/severe nausea and from moderate/severe to mild nausea, NP21 & NP12 (logit)     | -7.71 (-8.33, -7.37)           |
| Baseline transition probability from no to mild vomiting, VP10 (logit)                                                               | -12.1 (-13.4, -11.5)           |
| Baseline transition probability from no to moderate/severe vomiting, VP20 (logit)                                                    | -13.0 (-14.1, -12.1)           |
| Baseline transition probability from mild to no vomiting and from moderate/severe to no vomiting, VP01 & VP02 (logit)                | -3.33 (-3.68, -2.94)           |
| Baseline transition probability from mild to moderate/severe vomiting and from moderate/severe to mild vomiting, VP21 & VP12 (logit) | -30 FIX                        |
| Slope of drug effect with tolerance on NP10, SLPN10                                                                                  | 1.33 (0.856, 1.78)             |
| Slope of drug effect with tolerance on NP20, SLPN20                                                                                  | 1.21 (0.784, 1.69)             |
| Slope of drug effect on NP01 and NP02, SLPN012 (log)                                                                                 | -8.65 (-87.5, -7.35)           |
| Slope of drug effect with tolerance on VP10, SLPV10                                                                                  | 1.56 (1.01, 2.95)              |
| Slope of drug effect with tolerance on VP20, SLPV20                                                                                  | 1.60 (0.971, 2.715)            |
| Power model exponent for nausea drug effects with tolerance, HILLN (log)                                                             | -0.889 (-0.989, -0.770)        |
| Power model exponent for vomiting drug effects with tolerance, HILLV (log)                                                           | -0.973 (-1.18, -0.825)         |
| Tolerance rate constant, $K_{TOL}$ (log) ( $h^{-1}$ )                                                                                | -8.21 (-8.81, -7.77)           |
| First event effect on NP10 & NP20                                                                                                    | -0.226 (-0.257, -0.185)        |
| First event effect on VP10 & VP20                                                                                                    | -0.271 (-0.302, -0.233)        |
| Current nausea effect on VP10 & VP20                                                                                                 | -0.182 (-0.216, -0.147)        |
| <b>Covariate Effects</b>                                                                                                             |                                |
| Hispanic ethnicity effect on $K_{TOL}$                                                                                               | -0.175 (-0.351, 0.154)         |
| Japanese subrace effect on $K_{TOL}$                                                                                                 | 0 FIX                          |
| Gender effect on $K_{TOL}$                                                                                                           | -0.413 (-0.603, -0.175)        |
| Caucasian race effect on NP10                                                                                                        | -0.425 (-0.680, -0.177)        |
| Japanese subrace effect on NP20                                                                                                      | -30 FIXED                      |
| Japanese subrace effect on VP10                                                                                                      | 0 FIXED                        |
| Japanese subrace effect on VP20                                                                                                      | -30 FIXED                      |

Abbreviation: CI = confidence interval.

<sup>a</sup> CI obtained from a bootstrap analysis.

The previous N/V/D PK/PD model from the T2DM program identified and included Hispanic ethnicity and Japanese sub-race as significant covariates on  $K_{TOL}$ . In this submission, the Japanese differences (on  $K_{TOL}$ )

were not estimable as there were no moderate/severe AEs and very few reported AE in general. Therefore, the transitions and differences to non-Japanese were fixed to low probability values or no differences.

Source: Applicant's CWM popPK report, Table 9.4, pages 52-53

**Table 15. Parameter Estimates for the Diarrhea Markov Model**

| Population Parameter                                                                                                                 | Estimate (95% CI) <sup>a</sup> |
|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Baseline transition probability from no to mild diarrhea, DP10 (logit)                                                               | -9.63 (-10.8, -9.20)           |
| Baseline transition probability from no to moderate/severe diarrhea, DP20 (logit)                                                    | -11.0 (-11.3, -9.42)           |
| Baseline transition probability from mild to no diarrhea and from moderate/severe to no diarrhea, DP01 & DP02 (logit)                | -3.40 (-4.36, -3.64)           |
| Baseline transition probability from mild to moderate/severe diarrhea and from moderate/severe to mild diarrhea, DP21 & DP12 (logit) | -8.44 (-60.9, -8.09)           |
| Slope of drug effect with tolerance on DP10, SLPD10                                                                                  | 0.352 (0.0411, 1.14)           |
| Slope of drug effect with tolerance on DP20, SLPD20                                                                                  | 0.365 (0.0323, 1.08)           |
| Power model exponent for diarrhea drug effects with tolerance, HILLD (log)                                                           | -0.580 (-0.875, -0.101)        |
| Tolerance rate constant, K <sub>TOL</sub> (log) (h <sup>-1</sup> )                                                                   | -10.4 (-11.2, -8.58)           |
| First event effect on DP10 & DP20                                                                                                    | -0.230 (-0.278, -0.164)        |
| <b>Covariate Effects</b>                                                                                                             |                                |
| Japanese subrace effect on DP20                                                                                                      | -30 FIX                        |

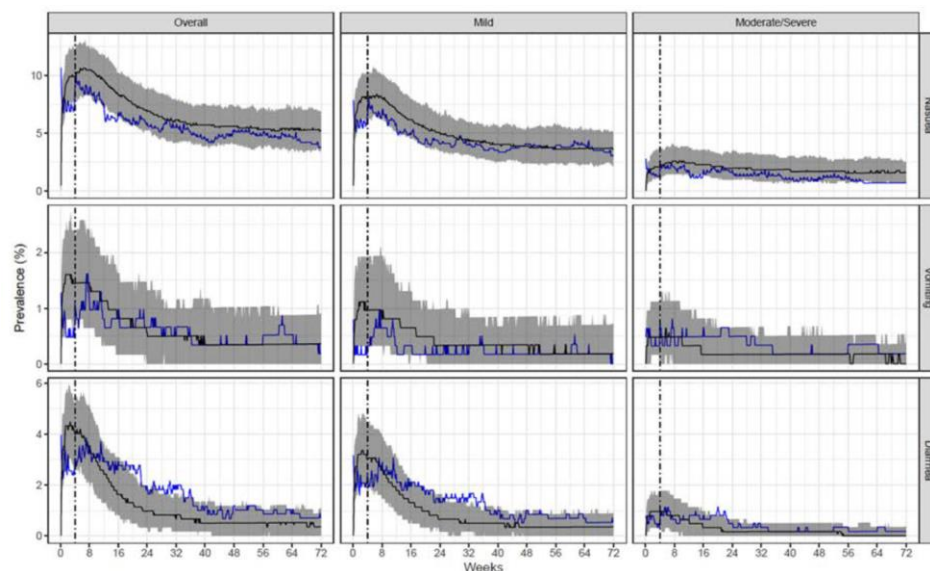
Abbreviation: CI = confidence interval.

<sup>a</sup> CI obtained from a bootstrap analysis.

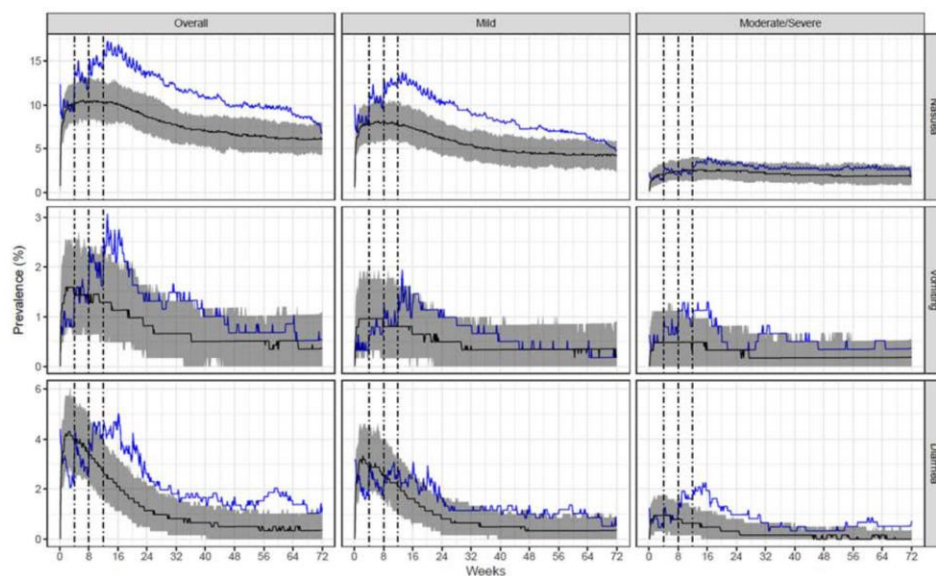
Source: Applicant's CWM popPK report, Table 9.5, page 54

**Figure 13. VPC of the Final N/V/D Model with Overlaid Observed Daily Prevalence for 5 mg, 10 mg, and 15 mg Tirzepatide**

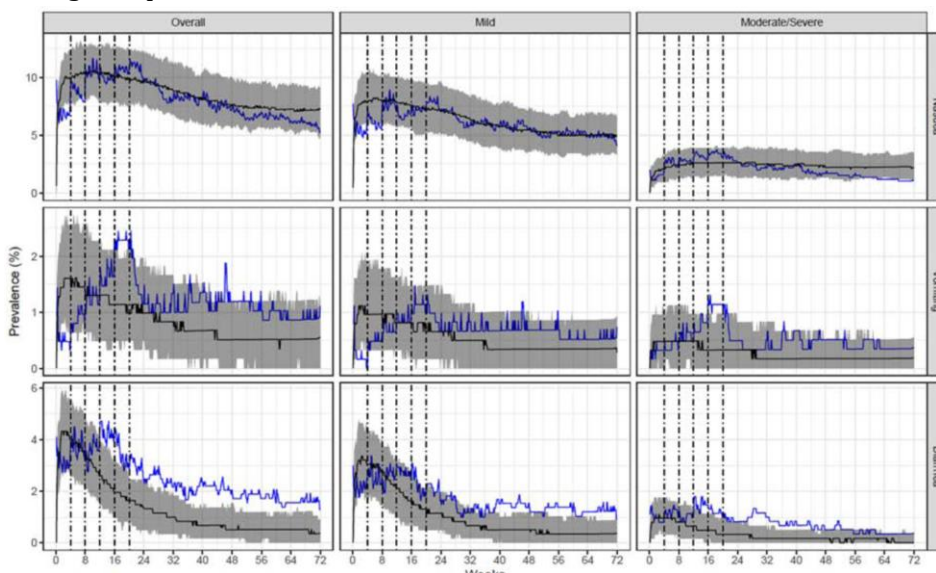
5 mg tirzepatide treatment arm



10 mg tirzepatide treatment arm



### 15 mg tirzepatide treatment arm



Black lines, median of model predictions; gray bands, 90% confidence intervals; blue lines, observed prevalence of event; black dashed lines, dose escalation

Source: Applicant's CWM popPK report, Table 9.5, page 54

*Reviewer comments: the Applicant's nausea-vomiting and diarrhea Markov models reasonably describe the observed safety events during tirzepatide treatment, including dose escalation scheme in adults with obesity or overweight. The model parameters for nausea-vomiting model were generally precise with the highest RSE at 33.1% and  $\leq 22.3\%$  for other parameters. For the diarrhea model, parameters were estimated with good precision (RSE  $< 28.0\%$ ). The 95% CI from bootstrap analysis also demonstrated the precision of the parameter estimates from the N/V/D models. Similar to the previously established models, the models summarized above are average models without accounting for IIV on relevant PK parameters and modeled probabilities.*

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