2.7.2. Summary of Clinical Pharmacology Studies

Tirzepatide (LY3298176)

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Abbreviations

Acronym or Term	Definition
AUC	area under the concentration versus time curve
AUC(0-t_{last})	AUC from time zero to time t, where t is the last time point with a measurable concentration
$AUC_{(0\text{-}tau)}$	AUC over one dosing interval, where 168 hour is the dose interval for QW tirzepatide
AUC(0-∞)	AUC from time zero to infinity
CI	confidence interval
C_{max}	maximum observed drug concentration
FG	fasting glucose
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLSM	geometric least square mean
HbA1c	glycated hemoglobin
Ka	absorption rate constant
LS	least squares
PD	pharmacodynamics
PFP	prefilled pen
PFS	prefilled syringe
PK	pharmacokinetics
QW	once weekly
RA	receptor agonist
SC	subcutaneous
SDP	single-dose prefilled pen
$t_{1/2}$	half-life
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event

2.7.2. Summary of Clinical Pharmacology Studies

2.7.2.1. Background and Overview

Tirzepatide is a long-acting GIP receptor and GLP-1receptor agonist. It is an amino acid molecule including a C20 fatty di-acid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1. It is administered QW through SC injection.

Tirzepatide is approved as an adjunct to diet and exercise to treat adults with insufficiently controlled T2DM in the US, EU, and Japan, with other applications either approved or under review. Applications for the indication of chronic weight management have been submitted in some markets.

The present application comprises one Phase 1 Study I8F-MC-GPIP (GPIP) using prespecified bioequivalence criteria to investigate the PK of the tirzepatide preserved formulation administered via fixed, multi-dose, single-patient use prefilled pen, hereafter termed multi-dose PFP, and the non-preserved formulation administered via single-dose prefilled pen hereafter termed SDP.

2.7.2.1.1. Conclusions from the Clinical Pharmacology Program

Overall exposures as measured using PK parameters, $AUC_{(0\text{-}tlast)}$ and $AUC_{(0\text{-}\infty)}$, following a 5-mg dose of tirzepatide using the preserved formulation administered through the multi-dose PFP (test) compared to the non-preserved formulation administered through an SDP (reference) met the prespecified criteria, as the GLSM ratio and associated 90% CIs of the GLSM ratios were contained within the prespecified limits of 0.80 and 1.25.

Peak exposure as measured using C_{max} following a 5-mg dose of tirzepatide using the preserved formulation administered through the multi-dose PFP (test) compared to the non-preserved formulation administered through an SDP (reference) did not meet the prespecified criteria. While the GLSM ratio of 0.809 and the upper bound of the 90% CIs of 0.838 were within the prespecified limits of 0.80 and 1.25, the lower bound of 90% CI was 0.780 and thereby was just outside the prespecified criteria.

Administration of 5-mg doses of tirzepatide using the preserved formulation administered through the multi-dose PFP or the non-preserved formulation administered through an SDP was generally well tolerated in healthy participants, consistent with the established safety profile.

More details can be found in the GPIP CSR.

Comparison of noncompartmental PK parameters across clinical pharmacology studies alongside an evaluation of exposure-response relationships across studies (Section 2.7.2.3) supports the following conclusions:

- Tirzepatide AUC and C_{max} for multi-dose PFP were comparable to SDP based on

  - overlapping values for test treatment, multi-dose PFP in Study GPIP when compared with the SDP and PFS device evaluated in similarly designed clinical pharmacology studies.
  - the difference between the population PK model-estimated ka associated with multi-dose PFP versus SDP had minimal impact on the metrics of tirzepatide exposure (AUC and C_{max}).
- Projected steady-state exposures (AUC and C_{max}) from Study GPIP for both multi-dose PFP and SDP delivery are expected to reside well within the model-predicted range of exposures after 40 weeks of treatment with 5, 10, and 15 mg QW tirzepatide in Phase 3 studies and these exposures were associated with significant observed and model-predicted glycemic and body weight reduction efficacy.
- The proposed multi-dose PFP is expected to result in comparable efficacy to SDP while not resulting in any additional concerns over safety and tolerability and continuing to maintain a favorable benefit.
- Tirzepatide exposure (AUC) drives clinical efficacy, and small differences in C_{max} observed when comparing the multi-dose PFP with the SDP in the crossover Study GPIP are not clinically meaningful for QW tirzepatide.

2.7.2.2. Summary of Results of Individual Studies

2.7.2.2.1. Clinical Pharmacology Study GPIP

Study GPIP contributed to the summary of clinical pharmacology of tirzepatide administration via multi-dose PFP. Details of the study are provided in Section 2.7.1.2 of the Summary of Biopharmaceutic Studies and Associated Analytical Methods.

The bioequivalence of the tirzepatide PK profiles of the test formulation delivered using multi-dose PFP, compared to the reference formulation delivered using SDP, was evaluated by comparing the ratios of GLSMs for test versus reference, and the 90% CIs for the ratios for

- area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration ($AUC_{[0\text{-}tlast]}$),
- area under the concentration versus time curve from time zero to infinity ($AUC_{[0\text{-}\infty]}$), and
- maximum observed drug concentration (C_{max}).

The GLSM ratios of multi-dose PFP:SDP were 0.943 and 0.948 for the $AUC_{(0\text{-}tlast)}$ and $AUC_{(0\text{-}\infty)}$, respectively, and the 90% CIs for the ratios were completely contained within the prespecified criteria (0.80, 1.25). The GLSM ratio for C_{max} was 0.809 with the 90% CI upper bound of 0.838 residing within (0.8, 1.25) and the lower bound just outside the 0.80 limit (0.780). The median difference of time to C_{max} (t_{max}) of tirzepatide was 12 hours between multi-dose PFP and SDP. t_{max} was attained later when tirzepatide was administered through a multi-dose PFP versus when administered through SDP.

Refer to GPIP CSR for complete details of the study and associated results.

2.7.2.3. Comparison and Analyses of Pharmacokinetics and Exposure-Response Relationships across Studies

The PK parameters and exposure metrics for administration of tirzepatide with multi-dose PFP and SDP in Study GPIP were compared to the results from the biopharmaceutic Phase 1 studies (I8F-MC-GPGS [GPGS]) and I8F-MC-GPHI [GPHI]) supporting the T2DM program.

The potential efficacy and tolerability associated with multi-dose PFP usage in individuals with T2DM were evaluated by comparing the exposure from Study GPIP to previously established exposure-response relationships for reduction in FG and HbA1c, reduction in body weight, and prevalence of nausea in participants with T2DM.

2.7.2.3.1. Comparison of Pharmacokinetics by Device in Biopharmaceutic Studies

The 3 biopharmaceutic studies listed below with a brief description of study design and key findings were included in the comparison and analysis of tirzepatide PK and exposure across devices. The study settings, conduct, and conditions were similar between the Phase 1 studies included in the comparison. A single SC dose of tirzepatide 5 mg was administered by study personnel to healthy study participants. The protocol schedule for serial sampling collected for tirzepatide concentrations was the same across all 3 studies. The scope of this comparison included only administration of tirzepatide at the abdomen injection site.

Study I8F-MC-GPIP: A Bioequivalence Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by a Multi-dose Prefilled Pen Versus Single-Dose Pen in Healthy Participants

Study Design: Study GPIP was a multicenter, open-label, randomized, 2-period, 2-sequence, crossover study with healthy participants and compared the PK of a single dose of tirzepatide 5 mg administered SC through multi-dose PFP (termed PFP for this comparison analysis) versus SDP.

Results Summary: The extent of total tirzepatide exposure following administration of a 5-mg dose using PFP was similar to that following SDP as indicated by the AUC GLSM ratio, and the associated 90% CIs were within the interval of 0.8 to 1.25.

The shape of the PK profile for tirzepatide delivered through PFP was characterized by a slightly lower peak exposure compared to SDP such that the GLSM ratio for C_{max} was within the prespecified interval of 0.8 to 1.25 and the lower bound of the 90% CI (0.78) was just outside the interval.

Administration of tirzepatide was generally well tolerated and similar incidence of TEAEs was observed with PFP and SDP delivery of tirzepatide. The most common TEAEs were GI disorders consistent with the known safety profile of the GLP-1-RA class and previous tirzepatide data.

Further details are summarized in Section 2.7.1.2 of the Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Study I8F-MC-GPGS: A Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by an Autoinjector Versus Prefilled Syringe in Healthy Subjects

Study Design: Study GPGS was a single-center, open-label, randomized 2-period, 2-sequence, crossover study with healthy participants and compared the PK of a single dose of tirzepatide 5 mg administered SC through autoinjector (SDP) versus PFS.

Results Summary: Tirzepatide exposure following administration of a 5-mg dose using SDP was similar to that following PFS, as demonstrated by AUC and C_{max} GLSM ratios and 90% CI within the interval of 0.80 to 1.25.

Generally, tirzepatide administration was well tolerated with both SDP and PFS delivery devices. The most common TEAEs were GI disorders consistent with the known safety profile of the GLP-1-RA class and previous tirzepatide data.

Further details are summarized in the initial Module 2.7.1 of the T2DM application.

Study I8F-MC-GPHI: Effect of Injection Site on the Relative Bioavailability of a Single Dose of Tirzepatide in Subjects with Low and High Body Mass Indices

Study Design: Study GPHI was a single-center, open-label, 3-period, 3-sequence, randomized, crossover study with healthy participants in 2 body mass index groups (low [18.5 to 27.0 kg/m^2] and high [27.1 to 45.0 kg/m^2]) and investigated administration of tirzepatide with the SDP device at the abdomen, thigh, and upper arm injection sites.

Results Summary: Tirzepatide exposure, defined as $AUC_{(0-\infty)}$ and C_{max}, following administration of a 5-mg dose to the upper arm or thigh injection site was similar to that attained following administration to the abdomen injection site, i.e., the 90% CI for the GLSM ratios of each comparison fell within the interval of 0.80 to 1.25.

Tirzepatide administration was generally well tolerated by participants in all study periods. The most common TEAEs were GI disorders consistent with the known safety profile of the GLP-1-RA class and previous tirzepatide data.

Further details are summarized in the initial Module 2.7.1 of the T2DM application.

2.7.2.3.1.1. Comparison of Noncompartmental PK Analysis Exposure Parameters from Studies GPIP, GPGS, and GPHI

Methods: Data on the tirzepatide concentrations over time from Studies GPIP, GPGS, and GPHI were analyzed using standard noncompartmental methods of analysis implemented in the software Phoenix WinNonlin.

Results Summary: Figure 2.7.2.1 shows the mean tirzepatide concentration over time profiles grouped by study and device. Compared with the curves associated with SDP or PFS administration, the shape of the tirzepatide concentration versus time curve associated with PFP delivery appears to have slightly lower concentrations in the initial time after dosing, i.e., within the time interval up to 48 hours postdose and higher concentrations, thereafter, suggesting that

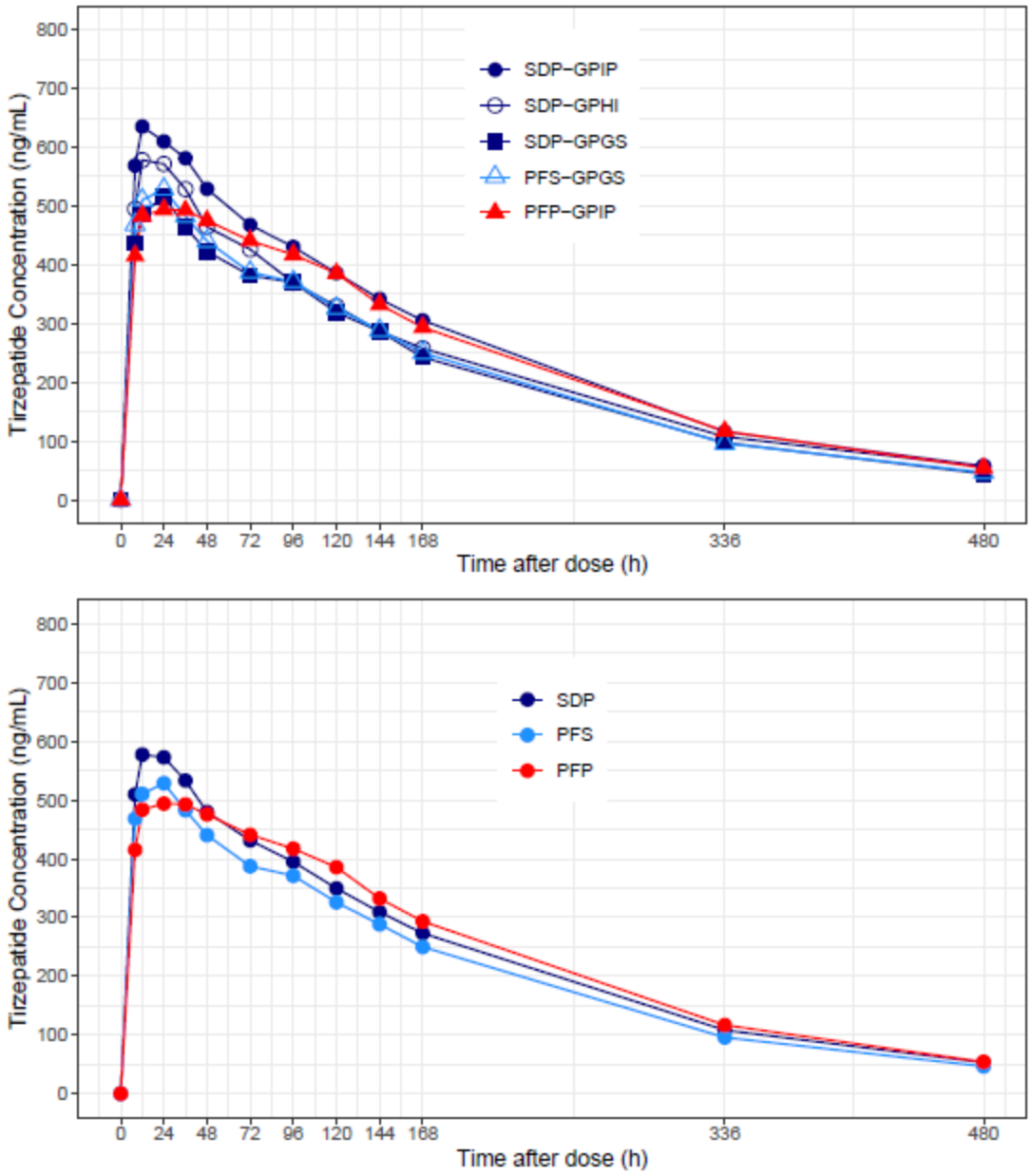
the total extent of exposure is similar and only the rate of absorption may be slightly lower with PFP delivery.

Table 2.7.2.1 presents a summary of the exposure parameters $AUC_{(0-\infty)}$ and C_{max} calculated from noncompartmental PK analysis.

The reported PK parameters from Study GPIP were within the range of values reported for Studies GPGS and GPHI.

When evaluating by device, the tirzepatide AUC and C_{max} were comparable between:

- PFP in Study GPIP and SDP in Studies GPIP, GPGS, and GPHI.
- PFP in Study GPIP and PFS in Study GPGS.



Abbreviations: GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; PFP = fixed, multi-dose prefilled pen; PFS = prefilled syringe; SDP = single-dose pen.

Figure 2.7.2.1. Arithmetic mean tirzepatide plasma concentration versus time curve stratified by device and study (top) and by device alone (bottom).

Table 2.7.2.1. Summary of Exposure Parameters from Noncompartmental Analysis of a Single Dose of Tirzepatide 5 mg SC in Healthy Participants in Studies GPIP, GPGS, and GPHI

	Geometric mean (CV%)					
Study[a]	**GPIP**	**GPIP**	**GPGS**	**GPGS**	**GPHI (low BMI)[b]**	**GPHI (high BMI)[b]**
Device	**PFP**	**SDP**	**SDP**	**PFS**	**SDP**	**SDP**
N	62	65	42	44	27	27
$AUC_{(0-\infty)}$ (ng·h/mL)	119000[c] (22%)	126000 (22%)	101000 (18%)	104000[c] (18%)	126000 (15%)	100000 (27%)
C_{max} (ng/mL)	524 (27%)	647 (31%)	530 (25%)	556 (22%)	670 (19%)	544 (26%)
$t_{1/2}$[d] (hours)	126[e] (81.5 – 186)	122[f] (39.0 – 178)	122 (96.8 – 152)	121[g] (97.9 – 153)	132 (109 – 155)	125 (103 – 168)

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve from time 0 to infinity; BMI = body mass index; C_{max} = maximum observed drug concentration; CV = coefficient of variation; GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; N = number of participants; PFP = fixed, multi-dose prefilled pen; PFS = prefilled syringe; SC = subcutaneous; SDP = single-dose pen; $t_{1/2}$ = half-life.

[a] The arithmetic mean (standard deviation) baseline body weight was 71.2 kg (11.3) [GPIP], 72.0 kg (11.5) [GPGS], 73.8 kg (8.39) [GPHI, low BMI], and 96.5 kg (17.0) [GPHI, high BMI].

[b] Participants with BMI 27 kg/m^2 and BMI > 27 kg/m^2 were grouped as low BMI and high BMI, respectively.

[c] N = 61.

[d] Geometric mean (minimum – maximum).

[e] N = 60.

[f] N = 64.

[g] N = 42.

2.7.2.3.1.2. Population PK Analysis of the Influence of Device on Tirzepatide PK

Methods: A population PK analysis focusing on the tirzepatide concentrations from the biopharmaceutic Studies GPIP, GPGS, and GPHI was performed to evaluate the influence of PFP device on tirzepatide PK.

Previously, a robust population PK model was developed using the nonlinear mixed effects modeling software, NONMEM, and pooled data from Phase 1, 2, and 3 studies supporting the initial T2DM application (5802 participants, 39644 observations). Module 5.3 (Section 5.3.3.5) of the initial T2DM application summarizes further details of the population PK model development. The impact of delivery devices on tirzepatide PK was evaluated as part of the covariate screening within the T2DM population PK model development. No statistically or clinically significant differences in PK were detected between the devices used to support the T2DM program (SDP and PFS) and these results were consistent with noncompartmental analysis results from Study GPGS.

The established population PK model supporting the initial T2DM application was used as the base model for the analysis of Studies GPIP, GPGS, and GPHI. The base model has 2 compartments with first-order absorption and interindividual variability on ka, clearance (CL), and central volume of distribution (Vc). The bioavailability parameter was fixed to 0.8 based on

the results from the Phase 1 bioavailability Study (I8F-MC-GPGE). Body weight-based allometric parameters were included as fixed values on clearance and volume of distribution parameters based on the previously established tirzepatide population PK model.

Results Summary:

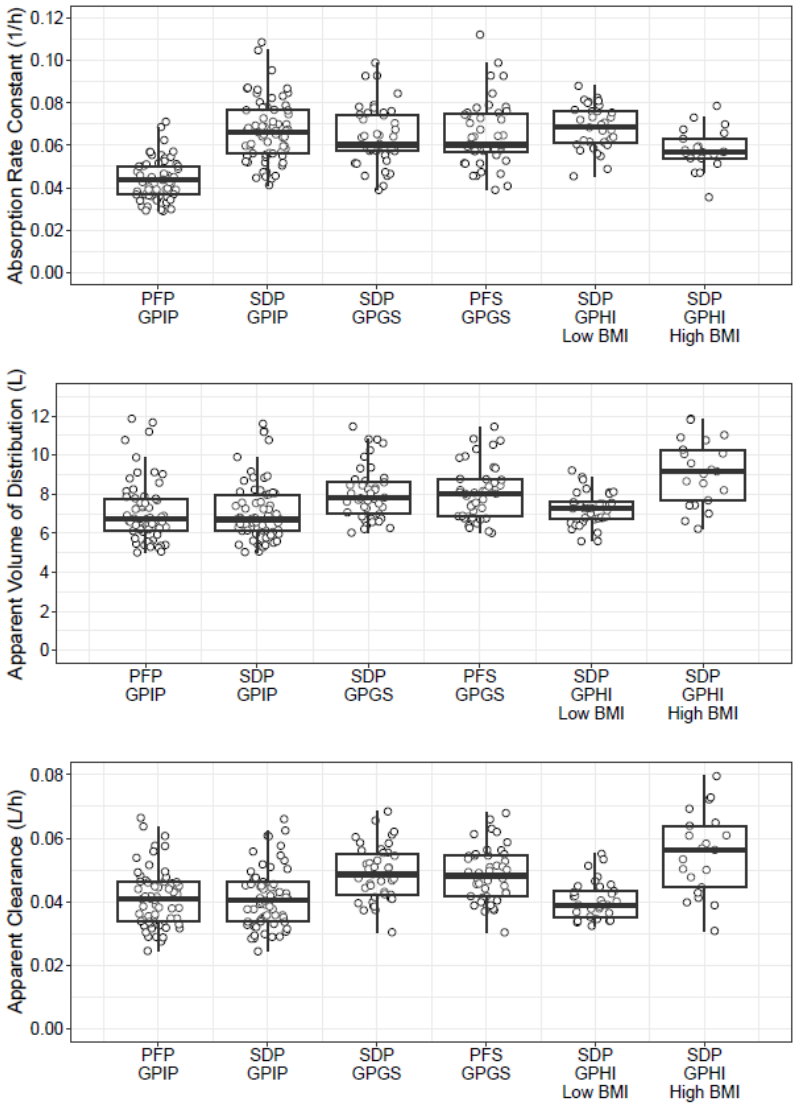
PFP was a statistically significant covariate on the absorption rate constant (ka). The estimate of ka following administration of tirzepatide with PFP was 35% lower than the estimate of ka following administration with SDP.

No difference between delivery through PFP versus SDP or PFS was detected for the PK parameters of bioavailability, clearance, or volume of distribution in the population PK model, and these findings were consistent with the comparison of noncompartmental analysis results that showed comparable extent of exposure (AUC) between delivery devices.

The tirzepatide PK parameter estimates from the population PK analysis of Studies GPIP/GPGS/GPHI were consistent with the T2DM population PK model parameter estimates (Table 2.7.2.2).

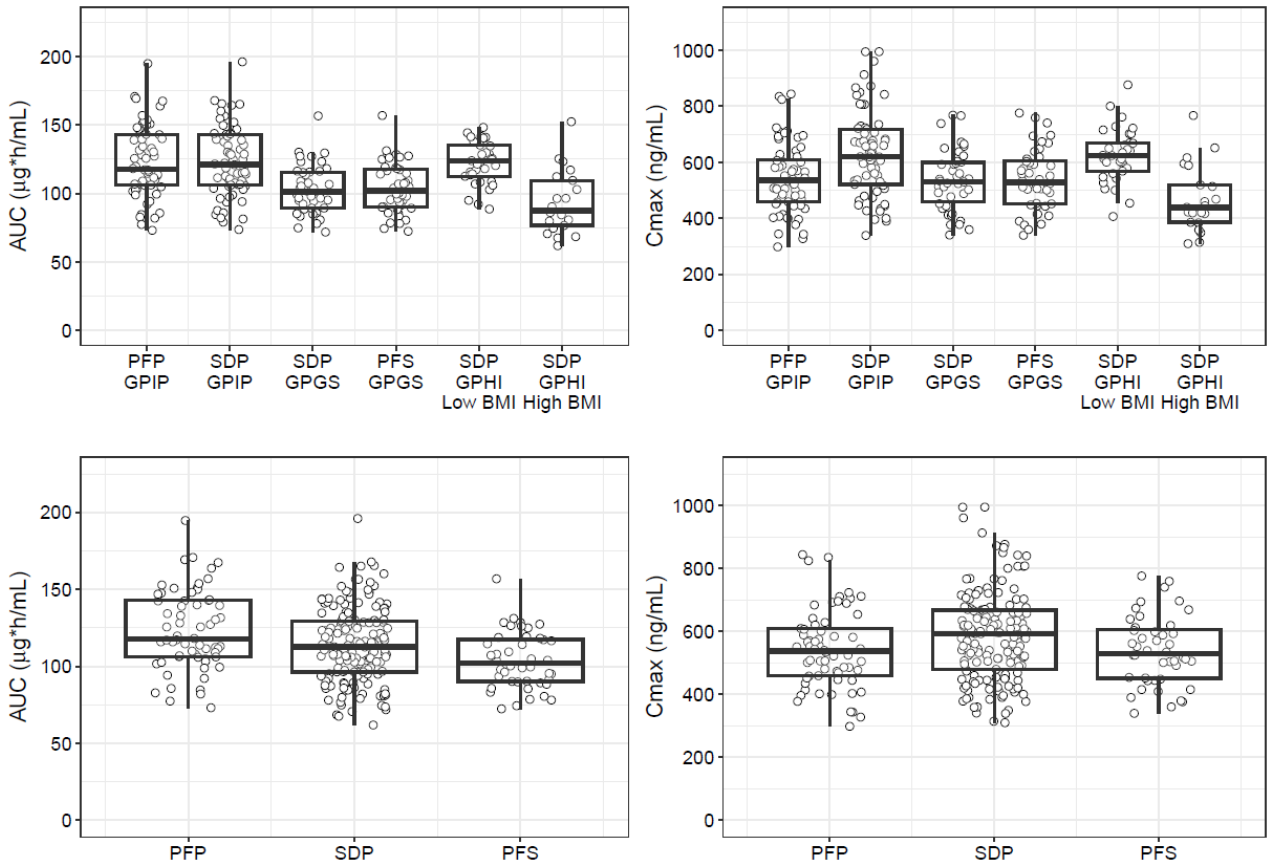
Figure 2.7.2.2 and Figure 2.7.2.3 show a summary of the model-based post hoc PK and exposure parameters for Studies GPIP, GPGS, and GPHI. The range of values for tirzepatide exposure overlap between studies and devices.

The difference between the model-estimated ka associated with PFP versus SDP delivery has minimal impact on the metrics of tirzepatide exposure (AUC and Cmax).



Abbreviations: BMI = body mass index; GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; High BMI = participants with BMI >27 kg/m^2; low BMI = participants with BMI ≤27 kg/m^2; PFP = fixed, multi-dose prefilled pen; PFS = prefilled syringe; PK = pharmacokinetic(s); SDP = single-dose pen.
Note: The middle line in each boxplot represents the median; the top and bottom margins of the boxplot represent the 75th and 25th percentiles; the whiskers extend up to ±1.5 times the interquartile range. The open symbols represent the individual post hoc PK parameter values.

Figure 2.7.2.2. Population model-based post hoc PK parameters stratified by study and device.



Abbreviations: AUC = area under the concentration versus time curve; BMI = body mass index; C_{max} = maximum observed drug concentration; GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; High BMI = participants with BMI >27 kg/m^2; Low BMI = participants with BMI ≤27 kg/m^2; PFP = fixed, multi-dose prefilled pen; PFS = prefilled syringe; PK = pharmacokinetics; SDP = single-dose pen.

Note: The middle line in each boxplot represents the median; the top and bottom margins of the boxplot represent the 75th and 25th percentiles; the whiskers extend up to ±1.5 times the interquartile range. The open symbols represent the individual post hoc PK parameter values.

Figure 2.7.2.3. Population model-based post hoc AUC (left) and C_{max} (right) stratified by study and device (top) and device alone (bottom).

Table 2.7.2.2. Tirzepatide Population PK Model Parameters

Parameter	GPIP/GPGS/GPHI Model Estimate Median (95% CI)[a]	T2DM Model Estimate Median (95% CI)[a]
	N =164 , nobs = 3517	N = 5802, nobs = 39644
Bioavailability (F, fraction)	0.8 fixed	0.8 fixed
Absorption rate constant[b] (ka, 1/h)	0.0434 [PFP] 0.0433 (0.0339, 0.0550) 0.0664 [SDP] 0.0661 (0.0565, 0.0770)	0.0373 0.0370 (0.0289, 0.0460)
Clearance[c] (CL, L/h/70 kg)	0.0337 0.0337 (0.0328, 0.0345)	0.0329 0.0329 (0.0313, 0.0342)
Intercompartmental clearance[c] (Q, L/h/70kg)	0.254 0.252 (0.227, 0.284)	0.126 0.125 (0.101, 0.144)
Central volume of distribution[d] (Vc, L/70kg)	2.07 2.06 (1.62, 2.50)	2.47 2.46 (2.05, 2.92)
Peripheral volume of distribution[d] (Vp, L/70kg)	4.55 4.55 (4.19, 4.90)	3.98 3.98 (3.56, 4.21)
Interindividual variability (CV%)		
Ka	20.6% 20.3 (17.3, 23.3)	22.5% 22.1 (14.9, 28.7)
CL	15.8% 15.7 (14.1, 17.4)	14.2% 14.2 (13.7, 14.7)
Vc	49.6% 49.5 (40.4, 63.1)	49.0% 49.5 (38.3, 62.3)
Residual variability		
Proportional (%)	11.6% 11.5 (11.0, 12.1)	20.6% 20.6 (20.3, 21.0)

Abbreviations: BW = body weight; CI = bootstrap-derived confidence interval; CL = clearance; CV = coefficient of variation; GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; N = number of participants; nobs = number of observations; PFP = fixed, multi-dose prefilled pen; PK = pharmacokinetics; SDP = single-dose pen; T2DM = type 2 diabetes mellitus; Vd = volume of distribution.

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

[b] ika = tvka * (BW/70)^-0.558 where ika is an individual's ka, tvka is the population ka, and BW is an individual's BW. The described structure was used only in the GPIP/GPGS/GPHI model.

[c] iCL = tvCL * (BW/70)^0.8 where iCL is an individual's CL, tvCL is the population CL, and BW is an individual's BW. The described structure was applied to CL and Q in both the GPIP/GPGS/GPHI and T2DM models.

[d] iVd = tvVd * [(fat free mas + fat mass * Θ_9)/70]^1 where iVd is an individual's Vd, tvVd is the population Vd, fat free mass is an individual's fat free mass, fat mass is an individual's fat mass, and Θ_9 is a fraction. The estimate of Θ_9 was 0.482 in the T2DM model and this value was used in the GPIP/GPGS/GPHI model. The described structure was applied to Vc and Vp in both the GPIP/GPGS/GPHI and T2DM models.

2.7.2.3.2. *Assessment of Device Impact on Efficacy and Tolerability Based on Exposure-Response Relationships*

The pharmacology of GLP-1 analogs for the treatment of T2DM uses a prolonged $t_{1/2}$ approach relative to the short $t_{1/2}$ (approximately 2 minutes) of native GLP-1 (Nauck 2016). Tirzepatide is a QW administered dual GIP and GLP-1-RA with a mean $t_{1/2}$ of approximately 5 days, which enables sustained therapeutic exposure during treatment. In the understanding of the clinical pharmacology of tirzepatide, the extent of exposure with repeated dosing (steady-state $AUC_{[0\text{-}tau]}$) was related to the efficacy responses (HbA1c and body weight).

Peak concentrations during the initiation and the early period of treatment were related to GI tolerability, a known tolerability concern of the incretin class of agents. Starting treatment on lower doses and escalating dose levels in smaller increments reduced the incidence and severity of GI events. Doses higher than 5 mg were poorly tolerated in Phase 1 Study GPGA, resulting in a 5-mg dose being considered as the maximum tolerated dose when administered as a single dose. Subsequently in Phase 2 Study, GPGB, doses higher than 5 mg were attained only by dose escalation with a starting dose of 5 mg.

Robust PK/PD models describing the relationship between tirzepatide concentrations and the key efficacy endpoints of HbA1c and body weight and the tolerability index of nausea prevalence were developed to support the initial T2DM application (Module 5.3, Section 5.3.3.5).

To evaluate the potential impact of tirzepatide exposure on efficacy and tolerability, the tirzepatide exposure metrics observed after a single 5-mg SC dose in Study GPIP were scaled to steady-state values.

The $AUC_{(0\text{-}\infty)}$ after a single dose is equivalent to the $AUC_{(0\text{-tau})}$ at steady state where tau is the dosing interval in the multiple dosing regimen. For QW administration of tirzepatide, the value of tau is 168 hours.

To project steady-state C_{max}, the value reported for a single dose was multiplied by the accumulation index to account for the accumulation of drug with repeated dosing.

$$Accumulation\ index = \frac{1}{1 - e^{-(\ln(2)/t_{1/2})*\mathrm{tau}}}$$

Since the tirzepatide $t_{1/2}$ in Study GPIP was consistent with the estimate from the robust population PK analysis of pooled T2DM studies, it was deemed appropriate to utilize the accumulation index value, 1.7, derived from the T2DM population PK analysis.

Table 2.7.2.3 presents a summary of the single-dose exposure metrics and projected steady-state exposure metrics for Study GPIP.

Table 2.7.2.3. Predicted Steady-State Exposure Metrics Based on Observed Exposure after a Single Dose of Tirzepatide 5 mg in Study GPIP

Parameter	Device	Single Dose 5 mg	Steady-State 5 mg QW
AUC[a] (ng·h/mL)	PFP	119000	119000
	SDP	126000	126000
C_{max}[b] (ng/mL)	PFP	524	891
	SDP	647	1100

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{(0-\infty)}$ = AUC from time 0 to infinity; $AUC_{(0\text{-tau})}$ = AUC over one dosing interval where 168 hour is the dose interval for QW tirzepatide; C_{max} = maximum observed drug concentration; PFP = fixed, multi-dose prefilled pen; QW = once weekly; SDP = single-dose pen.

[a] The $AUC_{(0-\infty)}$ after a single dose is equivalent to the $AUC_{(0\text{-tau})}$ at steady state for tirzepatide QW administration.

[b] The C_{max} after a single dose is scaled to steady state by multiplying by 1.7, the accumulation index for tirzepatide QW administration.

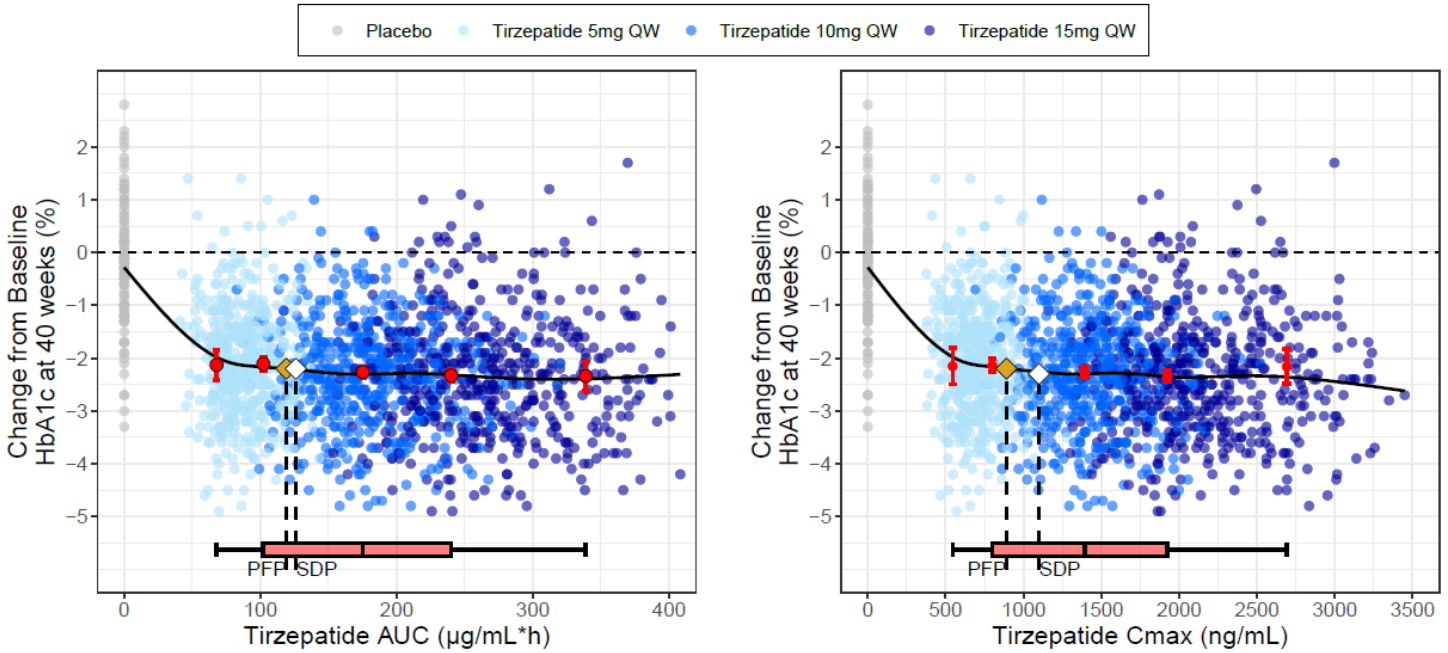
2.7.2.3.2.1. Exposure-Response Relationships for Efficacy

Fasting Glucose (FG)-HbA1c

FG and HbA1c data from multiple Phase 2 and 3 studies were used to characterize the PK/PD relationship. The initial Module 5.3 (Section 5.3.3.5) of the T2DM application summarizes a comprehensive description of the development of the FG-HbA1c PK/PD model3.

The time course of HbA1c was driven by the effect of tirzepatide on FG concentration through a linked concentration-response model that fitted both FG and HbA1c data jointly. The estimated $t_{1/2}$ turnover of HbA1c was 3 weeks, which corresponded to the attainment of steady state after 3 to 4 months of glucose and drug exposure, and this was consistent with generally accepted understanding of hemoglobin physiology. Average steady-state tirzepatide concentrations following maintenance doses of 5, 10, and 15 mg QW ranged from 491 to 1470 ng/mL (approximately equivalent to $AUC_{[0\text{-tau}]}$ of 82500 to 247000 ng/mL·h) and resulted in 74% to 89% of maximal glycemic effect.

The projected steady-state exposures (AUC and C_{max}) from Study GPIP for both PFP and SDP delivery (Table 2.7.2.3) fall within the model-predicted range of exposures after 40 weeks of treatment with 5, 10, and 15 mg QW tirzepatide in Phase 3 Studies GPGI, GPGK, and GPGM and these exposures were associated with significant observed and model-predicted glycemic efficacy (Figure 2.7.2.4).



Abbreviations: AUC = area under the concentration versus time curve; CFB = change from baseline; C_{max} = maximum observed drug concentration; HbA1c = glycated hemoglobin; PFP = prefilled pen; Phase 3 studies = Study I8F-MC-GPGI, Study I8F-MC-GPGK, and Study I8F-MC-GPGM; QW = once weekly; SDP = single-dose prefilled pen.

Note: The circles represent the individual observed CFB HbA1c and the corresponding model-predicted AUC or C_{max} after 40 weeks of treatment with placebo or tirzepatide 5, 10, and 15 mg QW in Phase 3 studies. The solid black line represents the loess fit of the observed CFB HbA1c in Phase 3 studies. The red circles represent the mean model-predicted CFB HbA1c and 95% confidence interval at the 5th, 25th, 50th,75th, and 95th percentiles of the overall model-predicted AUC or C_{max} in Phase 3 studies. At the bottom of each plot, the middle line in the boxplot represents the median; the left and right margins of the boxplot represent the 25th and 75th percentiles; the whiskers extend to the 5th and 95th percentiles of Phase 3 exposure across dose groups. The horizontal dashed line is a reference line at 0. The vertical dashed lines and the yellow and white diamond symbols represent the projected mean steady-state exposure based on tirzepatide 5 mg PFP and SDP from Study GPIP and the expected CFB HbA1c associated with the exposure.

Figure 2.7.2.4. Tirzepatide exposure and change from baseline HbA1c after 40 weeks of tirzepatide 5, 10, and 15 mg QW – AUC (left) and C_{max} (right).

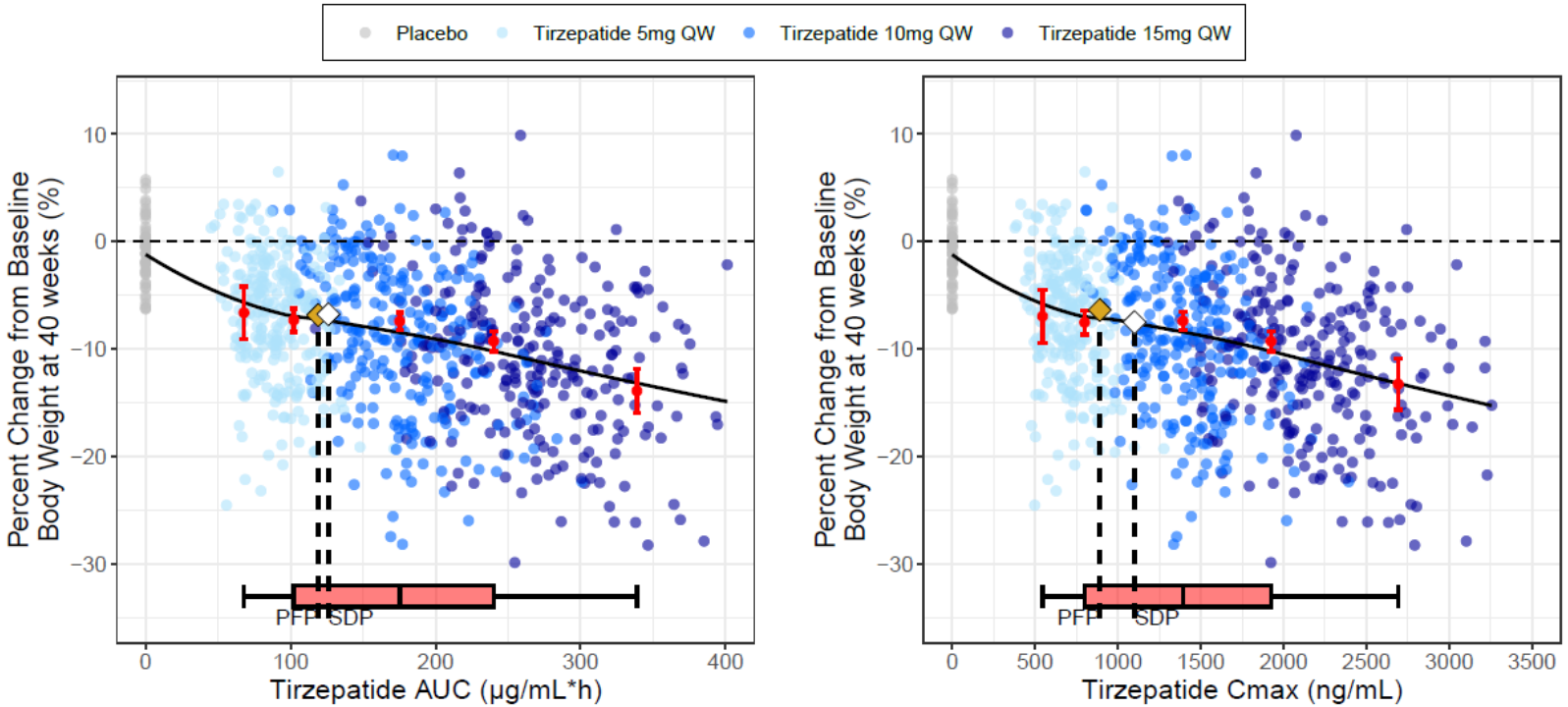
Body weight

Body weight data from multiple Phase 2 and 3 studies were used to build the PK/PD model. Module 5.3 (Section 5.3.3.5) of the initial T2DM application summarizes a comprehensive description of the development of the body weight PK/PD model3.

A sequential PK/PD modeling approach was used to characterize the effect of tirzepatide on body weight reduction. An indirect response model was used to account for a delay in the effect of tirzepatide in reducing body weight. The typical 'half-life' for weight loss was estimated to be about 9 weeks. This means that it would take about 45 weeks of exposure to tirzepatide concentrations to get to a new steady state of body weight. There is a clear exposure-response relationship between tirzepatide dose and body weight reduction. Average steady-state tirzepatide concentrations following maintenance doses of 5, 10, and 15 mg QW ranged from 491 to 1470 ng/mL (approximately equivalent to $AUC_{[0\text{-}tau]}$ of 82500 to 247000 ng/mL·h) and resulted in model-predicted percent change from baseline weight reduction at 40 weeks of -6.9%, -9.9%, and -12.5%, respectively.

The projected steady-state exposures (AUC and C_{max}) from Study GPIP for both PFP and SDP delivery (Table 2.7.2.3) fall within the range of model-predicted exposures after 40 weeks of treatment with 5, 10, and 15 mg QW tirzepatide in Phase 3 Studies GPGI, GPGK, and GPGM and these exposures were associated with clinically relevant observed and model-predicted body weight reduction (Figure 2.7.2.5).

Therefore, considering the totality of evidence, the small differences in C_{max} observed when comparing the PFP with the SDP in the crossover Study GPIP are not clinically relevant for efficacy of QW tirzepatide.



Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; PCFB = percent change from baseline; PFP = prefilled pen; Phase 3 studies = Study I8F-MC-GPGI, Study I8F-MC-GPGK, and Study I8F-MC-GPGM; QW = once weekly; SDP = single-dose prefilled pen.

Note: The circles represent the individual observed PCFB body weight and the corresponding model-predicted AUC or C_{max} after 40 weeks of treatment with placebo or tirzepatide 5, 10, and 15 mg QW in Phase 3 studies. The solid black line represents the loess fit of the observed PCFB body weight in Phase 3 studies. The red circles represent the mean model-predicted PCFB body weight and 95% confidence interval at the 5th, 25th, 50th, 75th, and 95th percentiles of the overall model-predicted AUC or C_{max} in Phase 3 studies. At the bottom of each plot, the middle line in the boxplot represents the median; the left and right margins of the boxplot represent the 25th and 75th percentiles; the whiskers extend to the 5th and 95th percentiles of Phase 3 exposure across dose groups. The horizontal dashed line is a reference line at 0. The vertical dashed lines and the yellow and white diamond symbols represent the projected steady-state exposure based on tirzepatide 5 mg PFP and SDP from Study GPIP, and the expected PCFB body weight associated with the exposure.

Figure 2.7.2.5. Tirzepatide exposure and percent change from baseline body weight after 40 weeks of tirzepatide 5, 10, and 15 mg QW – AUC (left) and C_{max} (right).

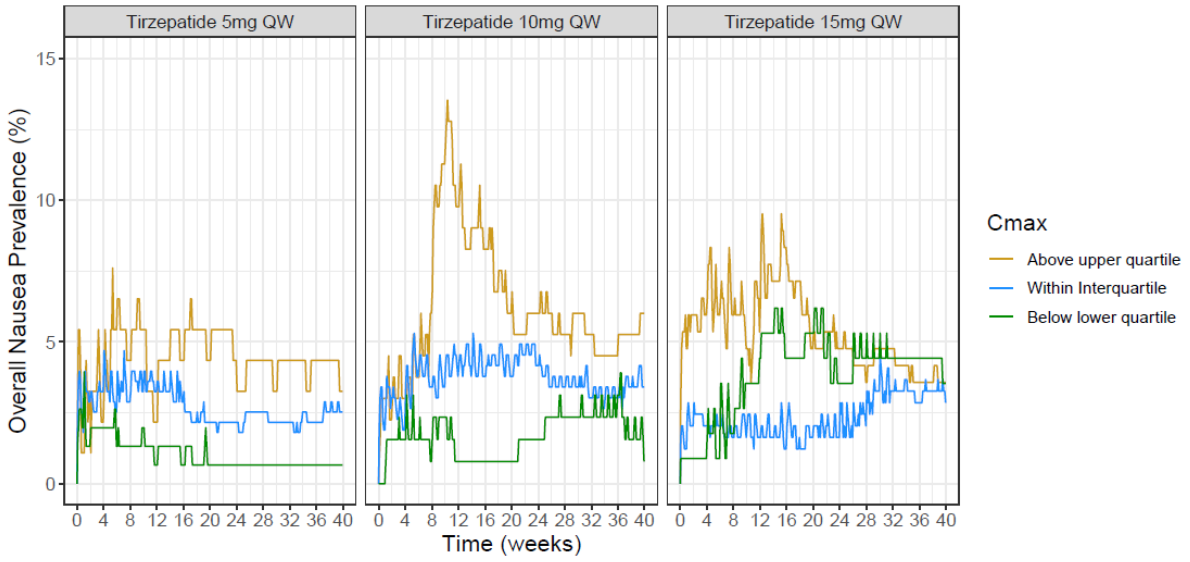
2.7.2.3.2.2. Exposure-Response Relationships for Tolerability

Reports of nausea symptoms collected from multiple Phase 2 and 3 studies were used to build the PK/PD models for GI tolerability. Module 5.3 (Section 5.3.3.5) of the initial T2DM application summarizes a comprehensive description of the development of the GI tolerability PK/PD models.

A sequential modeling approach was taken to fit individual patient's PK time course with the occurrence of nausea. A discrete-time Markov model was used to estimate transition probabilities between adverse event states and assess the impact of tirzepatide exposure and potential covariates on these probabilities.

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, mitigated the incidence of GI adverse events, especially at the 10- and 15-mg doses. A majority of the events of nausea at the 5-, 10-, and 15-mg dose levels were reported during the dose-escalation phase, and these events decreased with time, and the incidence rate was <10% once steady-state concentrations for the maintenance doses were attained, i.e., after 24 weeks.

To illustrate the impact of C_{max} on the prevalence of nausea, the model-predicted exposure from three Phase 3 studies (Studies GPGI, GPGK, and GPGM) was stratified by quartiles, and the observed prevalence of nausea over time for the bottom quartile, interquartile, and top quartile of exposure was plotted (Figure 2.7.2.6). Generally, lower values of C_{max} are associated with better tolerability as indicated by the decreased prevalence of nausea.



Abbreviations: C_{max} = maximum observed drug concentration; Phase 3 studies = Study I8F-MC-GPGI, Study I8F-MC-GPGK, and Study I8F-MC-GPGM; QW = once weekly.

Figure 2.7.2.6. Observed nausea prevalence during 40 weeks of treatment with tirzepatide 5, 10, and 15 mg QW in Phase 3 studies stratified by quartiles of C_{max}.

2.7.2.3.3. Summary of the Comparison and Analyses of Pharmacokinetics and Exposure-Response Relationships across Studies

In summary, Study GPIP results demonstrated that tirzepatide exposure (AUC) when comparing the multi-dose PFP and SDP were well within the prespecified bioequivalence criteria. While the C_{max} geometric mean ratio for PFP versus SDP was 0.809, with a lower 90% CI of 0.780, thereby residing outside the prespecified criteria of 0.80 to 1.25, Lilly does not consider this difference in C_{max} between the test and reference to impact the overall benefit-risk assessment for tirzepatide.

Tirzepatide is a long-acting GIP/GLP-1 RA administered QW therapy and HbA1c and body weight reduction are primarily influenced by the steady-state extent of exposure ($AUC_{[0\text{-tau}]}$). The tirzepatide exposure as defined by $AUC_{(0\text{-tlast})}$ and $AUC_{(0\text{-}\infty)}$ in Study GPIP was well within prespecified criteria and are the critical exposure parameters when considering efficacy.

While tirzepatide peak concentrations may show a more direct correlation with GI tolerability, the differences in tirzepatide C_{max} between PFP and SDP delivery observed in Study GPIP have a low likelihood of resulting in additional tolerability or safety concerns based on the current understanding of exposure-response relationships.

Conclusions:

- Tirzepatide administered using a multi-dose PFP is expected to result in comparable efficacy to SDP (autoinjector) because both AUC parameters met the bioequivalence criteria in Study GPIP and the tirzepatide exposure metrics in Study GPIP were comparable to the exposure data from Phase 1, 2, and 3 studies supporting the initial T2DM application.
- While the lower bound of 90% CI for C_{max} did not meet the prespecified criteria, this excursion (lower C_{max}) is not expected to result in additional concerns over safety and tolerability and continues to maintain a favorable benefit-risk assessment of tirzepatide treatment.