2.7.6. Synopses of Individual Studies

Tirzepatide (LY3298176)

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Synopses of Individual Studies

Table 2.7.6.1 summarizes the clinical study that contributed data for this submission.

Table 2.7.6.1. Listing of the Clinical Study for the Bioequivalence Submission

Study Identifier; Type of study; Location of Study Report; Status; Participating Country	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Healthy Participants	Duration of Treatment
I8F-MC-GPIP; Bioequivalence, 5.3.1.2; Complete; the United States	To evaluate the bioequivalence between the multi-dose prefilled pen (test) and the single-dose pen (reference), as assessed using tirzepatide pharmacokinetics in healthy participants	Multicenter, open-label, randomized, 2-period, 2-sequence, crossover study	• Tirzepatide preserved formulation administered via multi-dose prefilled pen; 5 mg; subcutaneous • Tirzepatide non-preserved formulation administered via single-dose pen; 5 mg; subcutaneous	Enrolled: 65 Completed: 62	Single-dose crossover with a washout of at least 35 days between tirzepatide doses

Appendix 1. Study I8F-MC-GPIP

I8F-MC-GPIP Synopsis

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Synopsis

Study Title:
A Bioequivalence Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by a Fixed-Dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

Study Number: I8F-MC-GPIP

Study Phase: 1

Compound: Tirzepatide (LY3298176)

Name of Sponsor/Company: Eli Lilly and Company

Number of Study Center(s), Participants, and Countries:
This study was conducted at 3 centers that enrolled participants in the US.

Study Period:
Study Initiation Date: 03 April 2023 (first participant first visit)

Study Completion Date: 17 July 2023 (last participant visit)

Objectives, Endpoints, and Statistical Methods:

Objectives	Endpoints	Statistical Analyses
Primary		
• To evaluate the bioequivalence between the multi-dose prefilled pen (PFP; test) and the single-dose prefilled pen (SDP; reference), as assessed using tirzepatide PK in healthy participants	• C_{max}, AUC(0-t), and AUC(0-∞)	Log-transformed data were analyzed using a linear mixed-effects model to derive the ratios of geometric means and the 90% CIs
Secondary		
• To evaluate the additional PK parameter	• t_{max}	Nonparametric method with Wilcoxon's rank sum test comparing median of t_{max}
• To evaluate the safety and tolerability of a single subcutaneous dose of tirzepatide administered through a multi-dose PFP (test) versus SDP (reference)	• Incidence of AEs	Frequency and percentage for AEs

Abbreviations: AE = adverse event; AUC(0-∞) = area under the concentration versus time curve from zero to infinity; AUC(0-t) = area under the concentration versus time curve from time zero to time t; CI = confidence interval; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; t_{max} = time of maximum observed drug concentration.

Methodology:
Study I8F-MC-GPIP (GPIP) was a multicenter, open-label, randomized, 2-period, 2-sequence, crossover study conducted in healthy participants.

Participants were randomly assigned 1:1 to the 2 treatment sequences:

- a single dose of 5 mg tirzepatide administered subcutaneously via a fixed, multiple-dose, single-patient use prefilled pen (PFP; hereafter termed multi-dose PFP [test]; also referred to as fixed-dose multi-use PFP in the protocol), followed by a single-dose prefilled pen (SDP [reference]), or
- a single dose of 5 mg tirzepatide administered subcutaneously via an SDP followed by a multi-dose PFP.

The study had 2 treatment periods of 36 days duration each, including single dosing with tirzepatide on Day 1 of each period, with a washout period of at least 35 days between tirzepatide dose administrations.

Number of Participants (planned and analyzed):
Number planned: approximately 65 participants

Number randomly assigned: 65 participants

Number treated: 65 participants

Number completed: 62 participants

Number included in the primary PK analysis population (as per the statistical analysis plan definition): 65 participants.

Diagnosis and Main Criteria for Inclusion and Exclusion:
Participants were required to be males or females who were overtly healthy, aged 18 to 70 years, and had a body mass index of 18.5 to 30.0 kg/m^2, inclusive

Study Interventions, Dose, and Mode of Administration:
The study intervention was 5 mg of tirzepatide administered subcutaneously using a multi-dose PFP and an SDP.

Duration of Study Intervention:
The study duration for each participant was up to 14 weeks. Participants were screened within 28 days prior to enrollment. The study had 2 treatment periods of 36 days duration each, including single dosing with tirzepatide on Day 1 of each period, with a washout period of at least 35 days between tirzepatide dose administrations.

Demographic and Other Baseline Characteristics:
A total of 65 healthy participants (30 males and 35 females) between the ages of 22 and 70 years, inclusive, participated in this study. Body mass index ranged from 19 to 30 kg/m^2.

Exposure:
Sixty-five participants were enrolled in the study and randomly assigned to receive 2 doses of tirzepatide 5 mg: 1 dose via a multi-dose PFP and the other via an SDP. A total of 62 participants subsequently completed the study treatments. Two participants discontinued from the study due to treatment-emergent adverse events (TEAEs) and 1 participant was withdrawn by a physician. All 3 participants who discontinued from the study received tirzepatide via the SDP and did not receive tirzepatide via the multi-dose PFP.

Safety Results:
No deaths or serious adverse events were reported during this study. Two participants discontinued from the study due to AEs. These AEs were not considered related to the study drug. Overall, the incidence of TEAEs was similar after both modes of administration of tirzepatide, that is, via the multi-dose PFP and SDP. The most common TEAEs were gastrointestinal disorders and metabolism or nutrition disorders, with the most frequently reported TEAEs being nausea and decreased appetite. The majority of TEAEs were of mild severity.

Pharmacokinetic Results:
The 90% confidence interval (CI) ratios of multi-dose PFP:SDP for area under the concentration versus time curve (AUC) from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-tlast]), AUC from time zero to infinity (AUC[0-∞]), and maximum observed drug concentration (C_{max}) were 0.943 (0.931, 0.965), 0.948 (0.927, 0.960), and 0.809 (0.780, 0.838), respectively. The 90% CIs for the ratios of geometric means for AUC(0-tlast) and AUC(0-∞) were contained within the prespecified limits (0.80, 1.25). The geometric mean for C_{max} was 0.809 with the 90% CI upper bound within (0.8, 1.25) and lower bound just outside of the 0.80 limit (0.780).

Conclusions:
- Overall exposures as measured by PK parameters AUC(0-tlast) and AUC(0-∞) 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 geometric least square (LS) means ratio and associated 90% CIs of the geometric LS means ratios were contained within the prespecified limits of 0.80 and 1.25.
- Peak exposure as measured by 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 geometric LS means 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 of the prespecified criteria.
- Median time to maximum observed drug concentration was attained about 12 hours later when tirzepatide was administered by a multi-dose PFP versus when administered by an SDP.

- Administration of 5-mg doses of tirzepatide solution 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, with similar incidence of TEAEs. The most common TEAEs were gastrointestinal disorders, consistent with the safety profile of the glucagon-like peptide 1 receptor agonist class and the established safety profile of tirzepatide.