2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods

Tirzepatide (LY3298176)

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Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.7.1.1. Background and Overview

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor 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 once weekly through subcutaneous (SC) injection.

The initial presentation approved for commercial use was a single integral product with 0.5-mL non-preserved drug product contained in a 1-mL glass syringe with a plunger, assembled into single-dose prefilled pen (SDP), also referred to as an autoinjector. The single 0.5-mL dose is automatically administered through a needle operated by a spring-driven mechanism contained within the device, which is activated by the user depressing a button. The 6 available dose strengths are 2.5, 5, 7.5, 10, 12.5, and 15 mg/0.5 mL. Additionally, a vial presentation containing a single dose of the same non-preserved formulation of each strength has been submitted and approved in various markets.

Tirzepatide indication

Tirzepatide is approved as an adjunct to diet and exercise to treat adults with insufficiently controlled type 2 diabetes mellitus 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.

Proposed clinical use of tirzepatide preserved formulation for administration via fixed, multi-dose, single-patient use prefilled pen

The proposed multi-dose, single-patient use prefilled pen, hereafter termed multi-dose PFP, is a KwikPen, which is a well-established delivery device platform for insulins with necessary modifications to allow use with the fixed-dose weekly tirzepatide.

The present application comprises one Phase 1 Study I8F-MC-GPIP (GPIP) investigating the pharmacokinetics (PK) using prespecified bioequivalence criteria between the tirzepatide preserved formulation administered via multi-dose PFP, and the non-preserved formulation administered via a single dose pen (SDP).

The tirzepatide non-preserved formulation delivered via SDP and the proposed preserved formulation delivered via multi-dose PFP have the same quantity of active ingredient, tirzepatide, per dose. (See initial application Summary of Biopharmaceutics and Associated Analytical Methods Section 2.7.1.1.1.)

2.7.1.1.1. Formulation Development Process Overview

Table 2.7.1.1 summarizes the formulations, container closure systems, and devices used in Study GPIP. Table 2.7.1.2 compares the composition Tirzepatide Drug Product Formulations Used in Study GPIP.

Table 2.7.1.1. Summary of Drug Product Formulations and Presentations Used in Clinical Study GPIP

Drug Product	Tirzepatide 5 mg via SDP (Reference)	Tirzepatide 5 mg via Multi-dose PFP (Test)
Dosage levels	5 mg tirzepatide/0.5 mL	5 mg tirzepatide/0.6 mL
Route of administration	SC injection	SC injection
Delivery method	SDP (also referred to as an Autoinjector)	Manually operated fixed multi-dose PFP
Pharmaceutical form	Solution for injection in disposable prefilled pen	Solution for injection in a cartridge in disposable pen
Active substance	Tirzepatide	Tirzepatide
Excipients	Dibasic sodium phosphate heptahydrate, sodium chloride, hydrochloric acid, sodium hydroxide, water for injection	Dibasic sodium phosphate heptahydrate, sodium chloride, hydrochloric acid, sodium hydroxide, phenol, benzyl alcohol, glycerin, water for injection

Abbreviations: GPIP = Study I8F-MC-GPIP; PFP = prefilled pen; SC = subcutaneous; SDP = single-dose prefilled pen.

Table 2.7.1.2. Comparison of the Composition of Tirzepatide Drug Product Formulations Used in Study GPIP

Attribute	Formulation	
	Single-Dose Prefilled Pen (SDP)	Multi-dose PFP
Dose strength	5 mg/0.5 mL	5 mg/0.6 mL
Injection volume (mL)	0.5	0.6
[redacted]		
Container closure system	1-mL semi-finished syringe (SFS)	3-mL cartridge

Redacted under Section 41 and Section 43 of the FOI Act.

Abbreviations: GPIP = Study I8F-MC-GPIP; PFP = prefilled pen.

2.7.1.1.1.1. Device Development Process Overview

Six presentations are proposed containing different drug substance concentrations in a 0.6-mL preserved formulation. The multi-dose PFP is configured to deliver 4 once-weekly, 0.6-mL doses of a single strength. The multi-dose PFP contains a 3-mL cartridge that is preassembled into a disposable pen. Six doses are proposed: 2.5, 5, 7.5, 10, 12.5, and 15 mg/0.6 mL.

2.7.1.1.2. Approach and Rationale for Biopharmaceutical Strategy

To evaluate bioequivalence between the proposed new product presentation (preserved formulation administered via multi-dose PFP) and the initial product presentation (non-preserved formulation administered via SDP), Study GPIP, a multicenter, Phase 1, open-label, randomized, 2-period, 2-sequence, crossover study of tirzepatide was conducted in healthy participants.

Tirzepatide dose of 5 mg was selected for investigation in this study since this is the highest dose that can be administered as a single dose, without the need for stepwise dose escalation, as determined in a Phase 1 single- and multiple-dose safety, PK, and pharmacodynamic Study I8F-MC-GPGA. The PK of tirzepatide has been shown to be linear and dose proportional across the entire dose range of 2.5 to 15 mg. Based on this information a dose of 5 mg administered twice, due to the crossover design in Study GPIP, was reasonably anticipated to be tolerable in healthy participants and sufficient to provide PK data to evaluate the bioequivalence of tirzepatide preserved formulation administered via multi-dose PFP versus the non-preserved formulation administered via SDP across the 2.5- to 15-mg dose range.

Study GPIP was conducted in healthy participants to mitigate the potential confounding effects of any disease state and concomitant medications in patients. A population of healthy

participants is frequently used in the assessment of the bioequivalence of both small and large molecules. Using this bridging approach, tirzepatide clinical safety and efficacy data from the SDP can be leveraged without the need for additional studies in patients with the multi-dose PFP. Exposure-efficacy and tolerability analysis further supported the bioequivalence evaluation as part of the strategy. Further details are summarized in Module 2.7.2 Summary of Clinical Pharmacology Studies.

2.7.1.1.3. Overview of Analytical Methodology

The PK samples collected during Study GPIP were analyzed to measure concentrations of tirzepatide. Samples were analyzed for tirzepatide utilizing the same method that was used over the course of clinical development. The method was a validated liquid chromatography with mass spectrometry (LC/MS) assay, which detected tirzepatide intact mass, comprising the full-length peptide plus the linker and acyl side chain. The LC/MS method was developed and validated by Q2 Solutions in Ithaca, New York, USA.

Section 2.7.1.4.2 of the appendix to this summary includes details of the method and history of the assay performance for assessing tirzepatide concentrations in Study GPIP. Table APP.2.7.1.3 in the appendix lists the method used to quantify tirzepatide concentrations in Study GPIP and contains an overview of the method used, including procedures, assay range, interassay precision, interassay accuracy, and stability assessment. Detailed reports, including the method and validations, are available in Section 5.3.1.4 (Reports of Bioanalytical and Analytical Methods for Human Use).

Tirzepatide method at Q2 Solutions

A fully validated LC/MS assay was used to measure tirzepatide concentrations in human plasma samples from Study GPIP (see Appendix Section 2.7.1.4.2). First, 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 Q Exactive or Q Exactive Plus quadrupole-orbitrap mass spectrometer equipped with Heated Electrospray Ionization™ and high mass resolution, accurate mass monitoring detection over a standard curve range of 2.00 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 $1/x^2$ weighting. The interassay accuracy (% relative error) during validation ranged from -2.1% to 2.8%. The interassay precision (% coefficient of variation) during validation was 8.1% to 12.0%. The interassay 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 10-fold. Incurred sample reanalysis (ISR) was conducted for Study GPIP, and the results indicated that the assay method performed according to established ISR acceptance criteria with ≥2/3 of ISR results within 30% difference.

2.7.1.2. Summary of Results of Individual Studies

2.7.1.2.1. Study I8F-MC-GPIP

Study GPIP was a multicenter, open-label, randomized, 2-period, 2-sequence, crossover study conducted in healthy participants. The study included 2 treatment arms. The treatment sequences were:

- a single dose of 5 mg tirzepatide administered SC via multi-dose PFP followed by SDP or
- a single dose of 5 mg tirzepatide administered SC via SDP followed by multi-dose PFP.

This study was conducted to evaluate

- the PK, safety, and tolerability of a 5-mg SC dose of tirzepatide preserved formulation administered via multi-dose PFP (test) versus the non-preserved SDP (reference).

Results and conclusions

The PK of tirzepatide was considered comparable following administration of 5 mg tirzepatide via the SDP or the multi-dose PFP, with the 90% confidence intervals for the ratios of geometric least square means of area under the concentration versus time curve from time zero to infinity ($AUC_{[0-\infty]}$), area under the concentration versus time curve from time zero to time t ($AUC_{[0-t]}$) contained within the prespecified criteria of 0.8 to 1.25. For maximum observed drug concentration (C_{max}) following a 5-mg dose of tirzepatide using the preserved formulation administered through the multi-dose PFP compared to the non-preserved formulation administered through an SDP, the ratio of corrected geometric LS means was 0.809 with the 90% CI upper bound within (0.8, 1.25) and the lower bound was just outside of the 0.80 limit (0.780).

The median terminal elimination half-life ($t_{1/2}$) and geometric mean apparent clearance (CL/F) were similar following administration of tirzepatide via the SDP or the multi-dose PFP (CL/F: 0.0397 L/h vs 0.0419 L/h; and $t_{1/2}$: 122 hours vs. 126 hours for the SDP vs PFP).

Complete PK results from Study GPIP are provided in the Clinical Study Report (CSR).

Overall, the extent of absorption of tirzepatide 5 mg was equivalent between the multi-dose PFP (test) compared to SDP (reference) with the rate of absorption being slightly slower with the former, as observed with a numerically lower C_{max} and extended t_{max} for the test formulation. The clinical effects of tirzepatide are driven by the AUC and thus a slightly lower C_{max} is considered not clinically significant. Further details are summarized in Module 2.7.2 Summary of Clinical Pharmacology Studies. Data on safety and tolerability from Study GPIP are summarized in Module 2.5 Clinical Overview and detailed in the GPIP CSR.