Statistical Analysis Plan I8F-JE-GPGP (V2)

A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus (SURPASS J-combo)

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Approval Date: 17-Feb-2021

1. Statistical Analysis Plan: I8F-JE-GPGP: A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus (SURPASS J-combo)

LY3298176 for Type 2 Diabetes Mellitus

Phase 3, randomized, open-label, long-term safety study of tirzepatide in combination with monotherapy of oral antihyperglycemic medications in patients with Type 2 Diabetes Mellitus.

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[Protocol I8F-JE-GPGP]
[Phase 3]

Statistical Analysis Plan and approved by Lilly on date provided below.

Approval Date: 17-Feb-2021 GMT

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3. Revision History

SAP Version 1 was approved prior to the first visit when a subject receives any protocol intervention.

SAP Version 2 was approved prior to the primary DBL. The following topics were major updates from SAP version 1. Minor updates (e.g., clarification of definitions, addition of listings, examples for clarification, and the same analysis with different population) were not listed in general.

- Section 6.2 (General Considerations): The following sentence is added "For efficacy, health outcome and safety analysis, overall population and each OAM class analysis will be conducted separately, using the same statistical model, unless otherwise specified. When MMRM/ANCOVA is used for each OAM class, OAM class will be excluded from the model covariate."
- Section 6.2: Chi-Squared test is added for categorical analysis.
- Section 6.4 (Patient Disposition): Following analyses are added;
  - Kaplan-Meier analysis of time from randomization to study treatment discontinuation,
  - The listing for subjects who discontinued due to COVID-19 (if such patients exist).
- Section 6.5 (Patient Characteristics): Analysis population for demographic, medical history, and preexisting conditions are clarified.
- Section 6.6 (Concomitant Therapy): ATC code level is specified as Level 4.
- Section 6.6: Clarify that the analysis for concomitant medications is conduced separately for baseline and postbaseline.
- Section 6.7.1 (Exposure and Compliance to LY3298176): Following analyses are added;
  - Summary of number of patients who have missed >=3 consecutive doses (3 doses, 4 doses, >=5 doses),
  - Listing of Patients with Treatment Noncompliance or Missed >=3 Consecutive Doses.
- Section 6.8 (Important Protocol Deviation): The method to identify IPD is clarified. COVID-19 related TFLs are added.
- Section 6.9.1 (Mean change in HbA1c from baseline at the 52-week visit): The following sentence is added "Mean baseline value will be estimated using ANOVA model with treatment as the explanatory variable."
- Section 6.9.1: The following figures are added:
  - Mean HbA1c (baseline, planned postbaseline visit),
  - Estimated HbA1c Change from Baseline (planned postbaseline visit).

- Section 6.9.2 (Other efficacy endpoints): Analysis method (log transformed or not) are specified.
- Section 6.9.2: Analysis units (CN and SI) for FSG and fasting C-peptide are clarified.
- Section 6.9.2: Analysis for HOMA2-%B and HOMA2-%S are clarified (using C-peptide and using insulin).
- Section 6.9.2: Analysis units for weight (kg and %) are specified.
- Section 6.9.2: Analysis of mean change in serum Triglycerides (CN units, SI units) are added.
- Section 6.9.2: Following figures are added:
  - Mean Weight (kg) (baseline, planned postbaseline visit),
  - Mean Waist Circumference (cm) (baseline, planned postbaseline visit),
  - Mean Weight (kg) Change from Baseline (planned postbaseline visit), using the MMRM model,
  - Mean Waist Circumference Change from Baseline (planned postbaseline visit), using the MMRM model.
- Section 6.9.2: Analysis of 7-point SMBG profiles are clarified.
- Section 6.9.2: Categorical Analysis of HbA1c and weight loss are clarified.
- Section 6.9.3 (Supplemental analyses): There will be no supplemental analysis.
- Section 6.10.1 (EQ-5D-5L): Analysis method is clarified.
- Section 6.10.2 (DTDQ): The total score definition is clarified. The analysis method is clarified. Following analysis is added;
  - Frequency of Responses to Individual Items on the DTSQs and DTSQc will be summarized at baseline and at 52 weeks.
- Section 6.11.1 (AEs): Following analysis are added;
  - The percentages of patients with TEAEs related to study drug, summarized by treatment using MedDRA PT nested within SOC,
  - The percentages of patients with TEAEs, summarized by treatment using MedDRA PT (decreasing frequency),
  - The percentages of patients with common TEAEs (≥5%) related to study drug, summarized by treatment using MedDRA PT,
  - The percentages of patients with TEAEs by maximum severity, summarized by treatment using MedDRA PT nested within SOC.
- Section 6.11.1: The analysis of “Overview of AE” is clarified.

- Section 6.11.1: Notable events for patient narratives are updated.
- Section 6.11.1.2 (Other Serious Adverse Events): The following analysis is added;
  - Summary of treatment related SAE will be summarized by treatment by MedDRA PT.
- Section 6.11.1.3 (Discontinuation from Study Due to Adverse Event): The "Time-to-event analyses" is added.
- Section 6.11.2.1 (Hypoglycemic Events): Table GPGP.6.2 is updated.
- Section 6.11.2.1: For [1] including hypoglycemic events occurring after initiation of a new antihyperglycemic therapy, and for [2] excluding them, following analysis are planned;
  - For **severe hypoglycemia** and **level 2 hypoglycemia**, incidence as well as rate per patient per year of exposure will be provided by treatment at specified time intervals,
  - Summary and Analysis of Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL,
  - Summary and Analysis of Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL or Severe Hypoglycemia,
  - Summary and Analysis of **Nocturnal** Hypoglycemia Incidence with blood glucose <54 mg/dL,
  - Summary and Analysis of **Nocturnal** Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL,
  - Summary and Analysis of **Nocturnal** Hypoglycemia Incidence and Rate with Blood Glucose <54 mg/dL (level 2) or Severe Hypoglycemia.
- Section 6.11.2.1: Analysis method is specified.
- Section 6.11.2.2 (Severe Persistent Hyperglycemia): Analysis method is specified. Definition is clarified.
- Section 6.11.2.2: Following analysis are added;
  - Time-to-first-event analyses for the initiation of rescue therapy,
  - Summary of Hyperglycemic Events Leading to Rescue Therapy.
- Section 6.11.2.3 (Pancreatitis): Definition is clarified.
- Section 6.11.2.3.1 (Pancreatic Enzyme Assessment): Analysis is clarified, including using postbaseline or maximum postbaseline, using baseline value or maximum baseline value, and using log transformation or no transformation in MMRM/ANOVA models.
- Section 6.11.2.3.1: Following analysis is added;
  - Plot of time profile for pancreatic enzyme.

- Section 6.11.2.4 (Thyroid Malignancies and C-Cell Hyperplasia): The section name is updated. Definition is updated.
- Section 6.11.2.5 (Malignancy): This section is newly added.
- Section 6.11.2.6 (Calcitonin): The MMRM analysis is clarified. The plot of time profile is added. The eGFR condition is dropped. Nominal visit analysis is deleted. For maximum postbaseline analysis, 35 ng/L cutoff is added.
- Section 6.11.2.8 (Supraventricular Arrhythmias and Cardiac Conduction Disorders): Definition is updated.
- Section 6.11.2.9 (Hypersensitivity Events): Definitions of potential immediate hypersensitivity and hypersensitivity events are clarified.
- Section 6.11.2.10 (Injection Site Reactions): Definition is clarified. A subset analysis is deleted.
- Section 6.11.2.11 (Diabetic Retinopathy Complications): Definition is clarified.
- Section 6.11.2.12.1 (Hepatobility Disorders): This section is newly added.
- Section 6.11.2.12.2 (Acute Gallbladder Disease): Definition is clarified.
- Section 6.11.2.12.3 (Liver Enzymes): For ALT, and AST shift tables, the baseline category (baseline ($\leq 1 \times$ ULN, $> 1 \times$ ULN)) is added.
- Section 6.11.2.13 (Gastrointestinal Safety): Definition is clarified, including constipation and constipation for the combined analysis. Plotting method is clarified.
- Section 6.11.2.14 (Acute Renal Events): Definition is clarified. Analysis are clarified to create following TFL;
  - Summary and Analysis of Percentage Change from Baseline for Urine Albumin/Creatinine Ratio,
  - Summary and Analysis of Percentage Change from Baseline for Estimated Glomerular Filtration Rate.
- Section 6.11.2.15 (Dehydration): This section is newly added.
- Section 6.11.2.16 (Metabolic Acidosis, including Diabetic Ketoacidosis): Definition is clarified.
- Section 6.11.2.17 (Amputation/Peripheral Revascularization): Definition is clarified.
- Section 6.11.2.18 (Major Depressive Disorder/Suicidal Ideation): Definition is clarified.
- Section 6.12 (Vital): Following analysis is added;
  - Plot of Time Profile for Vital Sign Parameters.

- Section 6.13 (Laboratory): Conventional Units (CN) analysis is added. Box plots analysis is clarified.
- Section 6.14 (Immunogenicity): The analysis "Summary of Postbaseline Cross-Reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA" is clarified (with/without inconclusive information).
- Section 6.14: Following figures are added:
  - Summary of First Time to TE ADA+ (figure),
  - Summary of First Time to Reach Maximum Titer (figure).
- Section 6.15 (Subgroup): Analysis method (2 separate MMRM analysis) is specified. TFLs for safety analysis are specified.
- Section 6.15: Definition of "duration of diabetes analysis" is updated.
- Section 6.15: Definition of Renal impairment is added.

4. Study Objectives

4.1. Primary Objective

Primary objectives of the study is to assess safety and tolerability of once-weekly tirzepatide during 52 weeks of treatment as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides or SGLT-2i's in the treatment of T2DM in terms of incidence of TEAEs.

4.2. Secondary Objectives

To assess safety and tolerability of once-weekly tirzepatide during 52 weeks of treatment as an add-on therapy to oral antihyperglycemic medication (OAM) in the treatment of T2DM relative to the following:

- Early discontinuations of investigational product due to AEs
- Adjudicated all deaths and nonfatal major CV events
- Adjudicated pancreatic AEs
- Serum calcitonin
- Incidence of allergic and hypersensitivity reactions
- Incidence of injection site reactions
- Incidence of treatment-emergent ADA to tirzepatide
- The change in systolic and diastolic blood pressure, and heart rate from baseline
- Occurrence of hypoglycemic episodes
- Time to initiation of rescue therapy for severe persistent hyperglycemia

To assess the efficacy of once-weekly tirzepatide as an add-on therapy to oral antihyperglycemic medication (OAM) in the treatment of T2DM at 52 weeks relative to the following:

- Mean change in HbA1c
- Proportion of patients who achieve HbA1c <7%, ≤6.5%, and <5.7%
- Mean change in FSG
- Mean change in daily average 7-point SMBG profiles
- Mean change in body weight
- Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline
- Mean change in fasting insulin
- Mean change in fasting C-peptide
- Mean change in HOMA-2

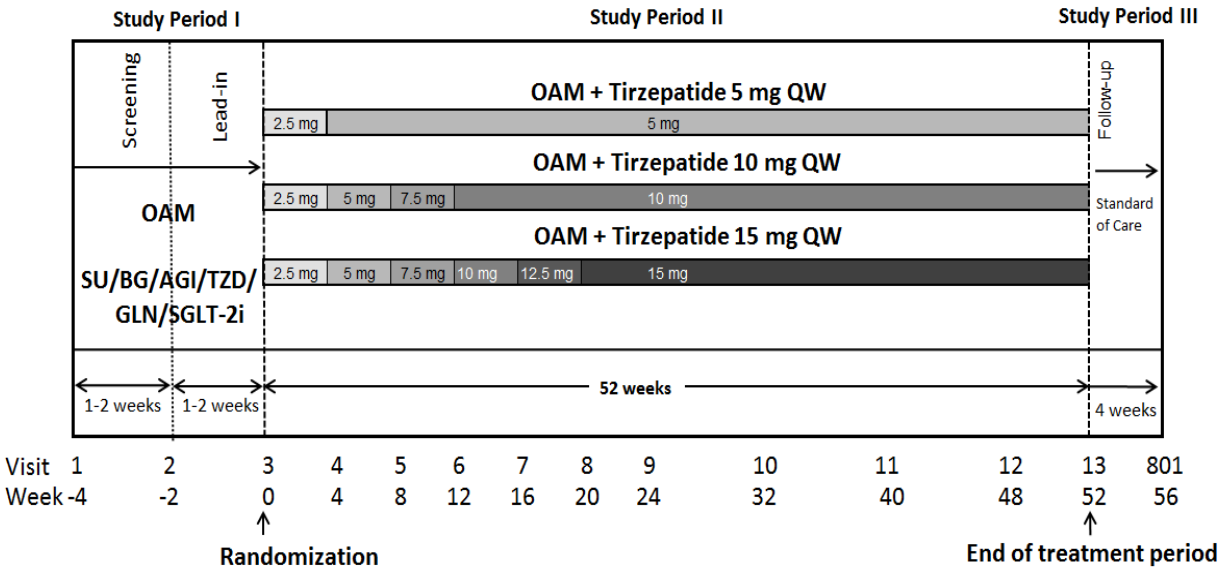
5. Study Design

5.1. Summary of Study Design

Study GPGP is a multicenter, randomized, Phase 3, long-term, add-on treatment study, which will assess the safety and efficacy of tirzepatide (5, 10, or 15 mg) in patients with T2DM taking therapeutic doses of various OAMs; SUs, biguanides, a-GIs, TZD, glinides, or SGLT-2i's. Approximately 441 patients who have been taking SUs (126 patients), or biguanides, TZD, a-GIs, glinides, or SGLT-2i (63 patients each) monotherapy will be randomized.

Study GPGP will consist of 4 periods (see Figure GPGP.5.1):

- 2-week screening period
- 2-week lead-in period
- 52-week treatment period
- 4-week safety follow-up period



- Abbreviations: AGI = alpha-glucosidase inhibitor; BG = biguanide; GLN = glinide; OAM = oral antihyperglycemic medication; QW = once weekly; SGLT-2i = sodium-glucose cotransporter type 2 inhibitor, SU = sulfonylurea, TZD = thiazolidinedione.
- Note: All doses will be administered QW subcutaneously using single-use pens. Patients who have been taking each OAM monotherapy will be randomized to tirzepatide (5-, 10-, or 15-mg arm).

Figure GPGP.5.1. Illustration of study design for Clinical Protocol I8F-JE-GPGP.

5.2. Determination of Sample Size

Because the primary objective is to assess the safety of long-term treatment of tirzepatide and no formal hypothesis testing on the efficacy measures are planned, statistically derived power calculations were not considered for the determination of sample size. The sample size of the study was based on the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2012). The guideline requires long-term safety data of 1 year of treatment with combination therapy using other antihyperglycemic medications. At least 100 patients treated for 1 year in combination with SUs and at least 50 patients in combination with each of the other agents are required. By taking into account the overall drop-out rate of approximately 20%, 126 patients for the combination with SUs and 63 patients for the combination with each of the other agents are planned to be randomized; therefore, a total of 441 patients are planned to be randomized.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to 1 of the study treatment arms at Visit 3. Assignment to treatment arms will be determined by a computer-generated random sequence using an interactive web response system (IWRS), stratified by OAM classes. Patients will be randomized in a 1:1:1 ratio to receive 5 mg tirzepatide, 10 mg tirzepatide, or 15 mg tirzepatide.

6. A Priori Statistical Methods

6.1. Populations for Analyses

For purposes of analysis, Table GPGP.6.1 defines the following analysis sets:

Table GPGP.6.1. Analysis Populations/Data Sets

Population	Description
Enrolled	All participants who sign informed consent
Randomized	All patients who are randomly assigned a treatment arm
Modified intention-to-treat (mITT)	All randomly assigned participants who are exposed to at least 1 dose of investigational product
Efficacy analysis set (EAS)	Data obtained during Study Period II from mITT, excluding data after initiating rescue antihyperglycemic medication or permanently stopping investigational product (last dose date + 7 days). De-escalation will not be considered as stopping investigational product. In the event of a treatment error, participants will be analyzed according to the treatment to which they were randomized.
Safety analysis set (SS)	All available data during Study Period II or III from mITT, regardless of adherence to investigational product or initiation of rescue antihyperglycemic medication.

6.2. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. All statistical analyses will be conducted with SAS Version 9.4 or higher unless otherwise stated. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other changes to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the clinical study report (CSR). Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data (e.g., few events to justify conducting an analysis). Listing of events will be provided in such situations. Additional analyses of the data may be conducted as deemed appropriate without further changes made to the protocol or SAP, even after the database locks (DBL).

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) will be calculated at 95%, 2-sided. In statistical summaries and analyses, patients will be analyzed as randomized.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses, irrespective of adherence to investigational product or initiation of antihyperglycemic rescue medication. Thus, safety analysis will be conducted using safety analysis set (SS). A selected safety analyses (e.g., hypoglycemia) will be conducted after

excluding data while on rescue therapy or data after starting another permitted antihyperglycemic medication following permanent discontinuation of investigational product.

The efficacy measure is mean change in HbA1c from baseline to 52-week visit. The "efficacy" estimand represents efficacy prior to discontinuation of investigational product without confounding effects of rescue therapy for persistent severe hyperglycemia.

The efficacy assessment, guided by the "treatment-regimen" estimand might be conducted as supplemental analyses. The "treatment-regimen" estimand represents the efficacy irrespective of adherence to investigational product or initiation of rescue antihyperglycemic medications, which will be conducted using mITT. Because no formal hypothesis testing on the efficacy measures is planned, no multiplicity adjustments will be made for conducting 2 efficacy assessments.

Unless specified otherwise, summary statistics will be presented by treatment groups (3 different tirzepatide doses) and overall within each of the combination therapies. Since the trial is not adequately powered to detect differences among tirzepatide doses, comparisons among tirzepatide arms will not be performed.

Summary statistics for continuous measures will include sample size, mean, standard deviation [SD], median, minimum, and maximum. Dose-response relationship will be assessed, if appropriate.

The Kaplan-Meier method will be used for estimation of cumulative event-free survival rates over time for each treatment.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Fisher's exact test or Chi-Squared test will be used to examine the treatment difference in categorical outcomes. Summary statistics for discrete count measures will include sample size, mean, SD, median, minimum, and maximum. Dose response relationship will be assessed if appropriate.

For efficacy, health outcome and safety analysis, overall population and each OAM class analysis will be conducted separately, using the same statistical model, unless otherwise specified. When MMRM/ANCOVA/negative binomial regression is used for each OAM class, OAM class will be excluded from the model covariate.

6.3. Multiple Comparisons/Multiplicity

Because no formal hypothesis testing on the efficacy measures is planned, no multiplicity adjustments will be made.

6.4. Patient Disposition

Frequency counts all patients screened will be provided. Frequency counts and percentages of all patients randomized, and receiving at least 1 dose of investigational product will be presented by treatment groups. A listing of randomized patients not receiving investigational product will be provided. Summary of study disposition and study drug disposition for all randomized

patients will be provided by planned study treatment. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study and from study treatment by treatment group will be provided.

The listing for subjects who discontinued due to COVID-19 will be created if such patients exist.

6.5. Patient Characteristics

Listing of patient demographics will be provided for all randomized patient.

Demographic (mITT and all randomized population), medical history, and preexisting conditions (all randomized population) will be descriptively summarized by treatment groups.

6.6. Concomitant Therapy

The prespecified concomitant medications of interest will be summarized by treatment at randomization using the mITT set. Additionally medications of interest initiated after randomization and change to medications of interest used at randomization will be summarized. The concomitant therapies will be mapped using the World Health Organization (WHO) DRUG dictionary in the clinical trial database and will be further classified using Anatomic-Therapeutic-Chemical (ATC) codes (Level 4) for reporting purposes.

The concomitant medications of interest include the following groups of medication (show them separately for baseline and postbaseline):

- Antihyperglycemic therapy by drug
- Use of
    - Antihypertensive therapy by type
    - Lipid lowering therapy by type
- Rescue therapy due to severe persistent hyperglycemia
- Initiation of antiemetic and antidiarrheal medication

The frequencies and percentages of patients taking concomitant medications before and after allocation (Visit 3) will be summarized. Patient listings for the use of concomitant medications will be provided, if necessary.

6.7. Treatment Exposure and Compliance

Listing of patients randomized but not receiving study treatment will be provided, if applicable. The listing will include patient identification, randomized treatment arm, and the reason for not receiving study treatment.

A listing of randomized patients who had inadvertently received incorrect study treatment anytime during the study will be provided, if applicable. The listing will include patient identification, randomized treatment arm, information related to the treatment incorrectly

received: incorrectly received study treatment, start and stop dates during which the incorrect treatment was received.

Summary of duration on Study(defined as time in days from date of randomization to date of safety follow-up or date of early study discontinuation) and duration on study treatment (defined as time in days from date of first dose of study treatment to date of last dose of study treatment plus 7 days) will be provided by study treatment.

6.7.1. Exposure and Compliance to LY3298176

Number of patients prematurely discontinuing study treatment prior to the 52-week visit as well as before the end of efficacy follow-up will be provided by study treatment. Reasons for prematurely discontinuing study treatment prior to the 52-week visit as well as before the end of efficacy follow-up will be provided by study treatment.

Proportion of patients with missing dosing information, receiving no LY dose, receiving 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg or 15mg will be presented by randomized treatment and week from first dose.

Listing and summary of patients continuing on a reduced maintenance dose of LY3298176 compared to the randomized dose will be provided.

Treatment compliance, overall, is defined as taking at least 75% of the total required injections of investigational product. Compliance will be calculated by taking the number of doses administered (regardless the actual dose administered) divided by the total number of doses expected to be administered ×100. Frequency counts and percentages of patients compliant to investigational product will be summarized by treatment groups and visits using the mITT population. In addition, number of patients who have missed >=3 consecutive doses (3 doses, 4 doses, >=5 doses) will be summarized.

Listing of patients with treatment noncompliance or missed >=3 consecutive doses will be created.

6.8. Important Protocol Deviations

Important protocol deviations (IPD) are identified in Trial Issues Management Plan (TIMP). TIMP specifies the method to capture IPD, either by programming or by non-programming. Programming method will find potential IPD. Those potential IPD will be reviewed to identify IPD. Non-programming method is based on information from Simplicity Clinical Trial Management System (sCTMS).
A listing and a summary of **important protocol deviations** by treatment will be provided.

In addition, a listing and a summary of COVID-19 related **protocol deviations (PD)** by treatment will be provided.

6.9. Efficacy Analyses

The efficacy assessment, guided by the "efficacy" estimand, will use Efficacy Analysis Set (EAS) which consists of data obtained before the initiation of any rescue therapy and before premature treatment discontinuation.

6.9.1. Mean change in HbA1c from baseline at the 52-week visit

Both HbA1c values as well as change from baseline in HbA1c will be summarized by treatment and nominal visit (week). The analysis will be conducted utilizing HbA1c data in EAS from baseline through the 52-week visit with the aid of a mixed model for repeated measures (MMRM). Restricted maximum likelihood (REML) will be used to obtain model parameter estimates and Kenward-Roger option will be used to estimate denominator degrees of freedom. The response variable of the MMRM model will be the primary measure and model terms will include treatment, visit, OAM class, and treatment by visit interaction as fixed effects, and baseline HbA1c as a covariate. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the following covariance structures will be tested in order:

- Heterogeneous Toeplitz;
- Heterogeneous First Order Autoregressive;
- Heterogeneous Compound Symmetry;
- Toeplitz;
- First Order Autoregressive;
- Compound Symmetry.

The first covariance structure that converges will be used. Resulting Least Squares Mean (LSM) estimate of mean change from baseline in HbA1c along with standard error will be tabulated and plotted by visit and by study treatment.

Mean baseline value will be estimated using ANOVA model with treatment as the explanatory variable.

Following figures will be created:

- Mean HbA1c (baseline, planned postbaseline visit)
  - The baseline value will be estimated using ANOVA model with treatment as the explanatory variable.
  - Postbaseline values will be estimated using the MMRM model specified above with actual visit wise values as the response variable.
- Estimated HbA1c Change from Baseline (planned postbaseline visit)
  - The MMRM model specified above will be used.

6.9.2. Other efficacy endpoints

The following efficacy measures will be summarized by treatment and nominal visit (week). The analyses for following efficacy measures will be conducted similar manner as HbA1c except for baseline measurements as covariate. (e.g., For mean change in FSG analysis, baseline FSG will be used as a covariate instead of baseline HbA1c.)

- Mean change in FSG (CN units, SI units)
- Mean change in body weight (kg)
- Mean change in body weight (%)
- Mean change in waist circumference

The following change from baseline analysis will be based on the MMRM model specified above, except [1] the response value replaced by log transformed actual value, (not change from baseline), and [2] "baseline" model term replaced by log transformed baseline.

- Mean change in fasting insulin
- Mean change in fasting C-peptide (CN units, SI units)
- Mean change in HOMA2-%B (beta-cell function) and HOMA2-%S (insulin sensitivity), using C-peptide
- Mean change in HOMA2-%B (beta-cell function) and HOMA2-%S (insulin sensitivity), using insulin
- Mean change in serum Triglycerides (CN units, SI units)

Following figures will be created:

- Mean Weight (kg) (baseline, planned postbaseline visit)
- Mean Waist Circumference (cm) (baseline, planned postbaseline visit)
  - The baseline value will be estimated using ANOVA model with treatment as the explanatory variable.
  - Postbaseline values will be estimated using the MMRM model specified above with actual visit wise values as the response variable.
- Mean Weight (kg) Change from Baseline (planned postbaseline visit), using the MMRM model
- Mean Waist Circumference Change from Baseline (planned postbaseline visit), using the MMRM model

Mean change in daily average 7-point SMBG profiles will be summarized by treatment (SI units, CN units). Baseline values will be estimated by ANOVA model (treatment as the model term). Postbaseline changes will be estimated using ANCOVA model (model terms of treatment and OAM classes as fixed effects, and baseline score as a covariate.)

The associated figures will be created.

Following other parameters derived from 7-point SMBG profile will be summarized by treatment using the same ANCOVA/ANOVA models specified above

- the average of all pre-meal measurements,
- the average of all post-meal measurements,
- the average of all 7-point measurements (daily mean),
- morning premeal to 2-hour postmeal excursion,
- midday premeal to 2-hour postmeal excursion,
- evening premeal to 2-hour postmeal excursion,
- premeal to 2-hour postmeal excursion daily mean.
- within-day CV
- within-day SD

The following categorical efficacy measures will be summarized by treatment and nominal visit (week). These will be estimated using two methods

[1] Descriptive statistics at each visit

[2] Descriptive statistics with missing value imputed by MMRM at week 52

- Proportion of patients who achieve HbA1c <7%, ≤6.5%, and <5.7%
- Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline

6.9.3. Supplemental analyses

None.

6.10. Health Outcomes/Quality-of-Life Analyses

The patient-reported outcome questionnaires will be completed by the patients at baseline and at 52 weeks (or early termination visit prior to 52 weeks). These include use of the mITT population (all randomized patients who have taken at least 1 dose of study medication). No multiplicity adjustment will be made in the evaluation of health outcome measures. Item-level missingness is dealt with as per instrument developers' instruction.

6.10.1. European Quality of Life – 5 Dimension – 5 Level (EQ-5D-5L)

Each item will be summarized descriptively by treatment at each scheduled visit at which the 5 level European Quality of Life – 5 dimensions (EQ-5D-5L) is administered. The changes from baseline to week 52 (LOCF) in the index and visual analog scale (VAS) scores will be analyzed using an ANCOVA model with model terms of treatment and OAM classes as fixed effects, and baseline EQ-5D-5L score as a covariate. The baseline value will be estimated by ANOVA model (treatment as the model term)

6.10.2. Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) contains 8 items (conceptually the same items in the status [DTSQs] and change [DTSQc] versions). The total score which is based on six items (1, and 4 through 8) which is a measure of treatment satisfaction and the two remaining items (2 and 3) are treated individually to assess, respectively, the perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is used to assess treatment satisfaction at baseline and the DTSQc is used to assess relative change in satisfaction from baseline at week 52 or early termination. In addition, a 5-item (1, 4, 5, 7, 8) treatment-specific satisfaction score, and its two sub-measures: a measure of convenience/flexibility (items 4, 5) and a measure of general satisfaction (items 1, 7, 8) will be derived by summation.

Frequency of Responses to Individual Items on the DTSQs and DTSQc will be summarized at baseline and at 52 weeks.

Descriptive summaries will be provided at baseline (DTSQs only) and at 52 weeks (DTSQc only) for the perceived hyperglycemia item, perceived hypoglycemia item, the six-item overall satisfaction score (total score), the 5-item treatment-specific satisfaction score, the 2-item measure of convenience/flexibility and the 3-item measure of general satisfaction.

The DTSQc at baseline will be analyzed using an ANOVA model with model term of treatment. The DTSQc at week 52 will be analyzed using an ANCOVA model with model terms of treatment and OAM classes as fixed effects and baseline DTSQs score as a covariate. The analyses will be conducted for the perceived hyperglycemia item, perceived hypoglycemia item, the 6-item overall satisfaction score, the 5-item treatment-specific satisfaction score, the 2-item measure of convenience/flexibility and the 3-item measure of general satisfaction.

6.11. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses, irrespective of adherence to investigational product or initiation of rescue therapy. Thus, safety analysis will be conducted using the SAS (See Table GPGP.6.1). A selected safety analyses (e.g., hypoglycemia) will be conducted after excluding data while on rescue therapy or data after starting another permitted antihyperglycemic medication following permanent discontinuation of investigational product.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or standardized MedDRA queries. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, investigational product discontinuation due to AEs, deaths, and other CV endpoints. Counts and proportions of subjects experiencing AEs will be reported for each treatment group.

6.11.1. Adverse Events

A listing of AEs will be provided. Listing will include patient identification including the treatment, site number, event information: AE group ID, event start date, MedDRA System Organ Class (SOC), and Preferred Term (PT), seriousness, severity, outcome, relationship to study drug, time from first dose of study drug to the event, time from last dose of study drug to event, and time from end of study participation to the event.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after the first dose. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent derivation. The maximum severity for each LLT during the baseline period including ongoing medical history will be used as baseline severity. For events with a missing severity during the baseline period, it will be treated as 'mild' in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as 'severe' and treatment-emergence will be determined by comparing to baseline severity.

The percentages of patients with TEAEs will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC, with the SOC in alphabetical order. For events that are sex-specific, the denominator and computation of the percentage will include only patients from the given sex.

Similarly, the percentages of patients with TEAEs related to study drug will be summarized by treatment using MedDRA PT nested within SOC.

The percentages of patients with TEAEs will be summarized by treatment using MedDRA PT (decreasing frequency)

Overview of the number and percentage of patient who experienced a TEAE, serious adverse event (SAE), death, discontinued from study treatment due to an AE, discontinued from study due to an AE, as well as relationship to study drug will be summarized by treatment.

Similarly, the overview restricting to drug related adverse events will be created.

The percentages of patients with common TEAEs (TEAEs occurred in ≥5% of patients before rounding for all treatment arm combined), will be summarized by treatment using MedDRA PT (decreasing frequency).

The percentages of patients with common TEAEs related to study drug (TEAEs related to study drug occurred in ≥5% of patients before rounding in any OAD class (3 doses combined)), will be summarized by treatment using MedDRA PT nested within SOC (SOC in alphabetical order and PT in decreasing frequency).

The percentages of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT. For each patient and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. The maximum severity will be determined based on the non-missing severities. If all

severities are missing for the defined postbaseline period of interest, it will show as missing in the table. Only counts and percentages will be included for the TEAEs by maximum severity.

Similarly, the percentages of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT nested within SOC (SOC in alphabetical order and PT in decreasing frequency).

Patient narratives will be defined in a patient narrative tool.

For example, the listing will include all patients who experience any of the following "notable" events:

- deaths
- serious adverse events
- pregnancy
- permanent discontinuations of study treatment due to AEs
- severe adverse events of special interest

6.11.1.1. Deaths

A listing of all deaths will be provided. Listing will include patient identification including the treatment, site number, date of death, age at the time of enrollment, gender, MedDRA PT of associated AE, time from first dose of study drug to death, time from last dose of study drug to death (if patient had discontinued study drug), cause of death as reported by investigator, caused of death as adjudicated by Clinical Endpoint Committee (CEC).

6.11.1.2. Other Serious Adverse Events

The number and percentage of patients who experienced an SAE (including deaths and SAEs temporally associated or preceding deaths) during the study will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

Summary of treatment related SAE will be summarized by treatment by MedDRA PT.

A listing of all SAEs will be provided. Listing will include and not limit to treatment, patient identification including the site number, treatment group, date of event, age at the time of enrollment, sex, AE group ID, MedDRA SOC and PT, severity, action taken, outcome, relationship to study drug, time from first dose of study drug to the event, and event duration.

6.11.1.3. Discontinuation from Study Due to Adverse Event

The number and percentage of patients who prematurely discontinue the study due to an AE will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. Time-to-event analyses will be conducted by treatment on time to study discontinuation.

6.11.1.4. Discontinuation from Study Drug Due to Adverse Event

The number and percentage of patients who prematurely discontinue the study drug due to an AE will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered

by decreasing frequency within SOC. Time-to-event analyses will be conducted by treatment on time to study drug discontinuation.

6.11.1.5. Treatment of Overdose

A listing of patients reporting over-dosing of tirzepatide will be provided as a protocol deviation. Note that overdosing of tirzepatide will be provided as a protocol deviation.

6.11.2. Adverse Events of Special Interest

6.11.2.1. Hypoglycemic Events

Definitions of different categories of hypoglycemic events are included in Table GPGP.6.2.

Table GPGP.6.2. Definitions of Hypoglycemic Event Categories

	Symptoms and/or Signs of Hypoglycemia	Blood Glucose Level
Glucose Alert Value:		
Documented symptomatic hypoglycemia	Yes	≤70 mg/dL (3.9 mmol/L)
Documented asymptomatic hypoglycemia	No	≤70 mg/dL (3.9 mmol/L)
Documented unspecified hypoglycemia	Unknown	≤70 mg/dL (3.9 mmol/L)
Clinically Significant Hypoglycemia (Level 2):		
Documented symptomatic hypoglycemia	Yes	<54 mg/dL (3.0 mmol/L)
Documented asymptomatic hypoglycemia	No	<54 mg/dL (3.0 mmol/L)
Documented unspecified hypoglycemia	Unknown	<54 mg/dL (3.0 mmol/L)
Severe Hypoglycemia (Level 3)		

Severe hypoglycemia: Defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia will be reported as an SAE. Severe hypoglycemia will be considered as AESI.

Nocturnal hypoglycemia: Defined as any hypoglycemic event that occurs between bedtime and waking.

To avoid duplicate reporting, all consecutive blood glucose (BG) values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event.

Following statistical summaries will be created:

- For **severe hypoglycemia** and **level 2 hypoglycemia**, incidence as well as rate per patient per year of exposure will be provided by treatment at specified time intervals.

  Note: If a patient discontinues the study treatment and a hypoglycemia occurs after that, then the duration after the study treatment discontinuation will be also counted as the exposure period.

- Summary and Analysis of Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL

- Summary and Analysis of Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL or Severe Hypoglycemia
- Summary and Analysis of **Nocturnal** Hypoglycemia Incidence with blood glucose <54 mg/dL
- Summary and Analysis of **Nocturnal** Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL
- Summary and Analysis of **Nocturnal** Hypoglycemia Incidence and Rate with Blood Glucose <54 mg/dL (level 2) or Severe Hypoglycemia

Following statistical summaries and analyses will exclude hypoglycemic events occurring after initiation of a new antihyperglycemic therapy.

- For **severe hypoglycemia** and **level 2 hypoglycemia**, incidence as well as rate per patient per year of exposure will be provided by treatment at specified time intervals.
- Summary and Analysis of Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL
- Summary and Analysis of Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL or Severe Hypoglycemia
- Summary and Analysis of **Nocturnal** Hypoglycemia Incidence with blood glucose <54 mg/dL
- Summary and Analysis of **Nocturnal** Hypoglycemia Incidence and Rate with Blood Glucose <=70 mg/dL
- Summary and Analysis of **Nocturnal** Hypoglycemia Incidence and Rate with Blood Glucose <54 mg/dL (level 2) or Severe Hypoglycemia

A listing of hypoglycemic events will also be provided.

The incidence of hypoglycemic event will be analyzed using logistic regression with treatment as fixed effects. The rate of hypoglycemic episodes per patient year may be analyzed using a generalized linear mixed-effects model assuming the number of hypoglycemic episodes follows a negative binomial distribution with the mean modeled using treatment and OAM classes as fixed effects. When the number of hypoglycemic events is less 10, a listing of hypoglycemic events will be provided instead.

6.11.2.2. Severe Persistent Hyperglycemia

A summary of initiation of rescue therapy in response to severe, persistent hyperglycemia will be provided by treatment. If there are sufficient number of patients (≥10) who experience events, time-to-first-event analyses for the initiation of rescue therapy will be conducted by treatment using a cox proportional regression model. For patients without event "time-to-event", event time will be censored at end of treatment period. A listing of patients who initiated rescue therapy will be provided.

Summary of Hyperglycemic Events Leading to Rescue Therapy will be created.

6.11.2.3. Pancreatitis

If data warrants, summaries of adjudicated and investigator-reported pancreatic events will be provided by treatment. Associated listings will be created. Determination of investigator-reported events will be through the pre-defined SMQ search for acute pancreatitis and MedDRA PT of pancreatitis chronic. Detailed searching criteria can be found in Appendix 1. Treatment-emergent adjudication-confirmed pancreatitis will be considered as AESI.

6.11.2.3.1. Pancreatic Enzyme Assessment

Observed pancreatic enzyme data (p-amylase and lipase) will be summarized by treatment and nominal visit.

The number and proportion of patients with **maximum postbaseline** pancreatic enzyme values exceeding the following thresholds will be provided by treatment, maximum baseline pancreatic enzyme value (≤ 1×upper limit of normal [ULN], >1×ULN), and treatment: ≤1×ULN, (>1 to ≤3) × ULN, (>3 to ≤5) × ULN, (>5 to ≤10) × ULN, >10 × ULN.

An MMRM analysis will be used to analyze each pancreatic enzyme with a log transformed (post-baseline measure) response variable and treatment, nominal visit, OAM class and treatment-by-nominal visit interaction as fixed effects, and log transformed baseline value as a covariate. Log transformed baseline value will be estimated by ANOVA with treatment as a model term.

Plot of time profile for pancreatic enzyme from the MMRM results will be created.

6.11.2.4. Thyroid Malignancies and C-Cell Hyperplasia

Treatment-emergent thyroid malignancies and C-cell hyperplasia, and neoplasms will be identified using pre-defined MedDRA High Level Terms (HLTs) of thyroid neoplasms malignant, and PT of thyroid C-cell hyperplasia. Detailed searching criteria can be found in Appendix 1. A summary by treatment and PT/PT within SMQ and HLT will be provided. Its listing will be created. Thyroid malignancies and C-cell hyperplasia will be considered as AESI.

6.11.2.5. Malignancy

The AE database will be searched using pre-defined SMQs to identify events consistent with malignancy. Detailed searching criteria can be found in Appendix 1. A summary by treatment and PT within SMQ and a listing of TEAEs will be provided. Malignancy will be considered as AESI.

6.11.2.6. Calcitonin

Observed calcitonin data will be summarized by treatment and by nominal visit. An MMRM analysis (log transformed) will be used similar to Section 6.11.2.3.1. Plot of time profile will be used.

The number and proportion of patients with **maximum postbaseline calcitonin value** exceeding the following thresholds will be provided by treatment and maximum baseline calcitonin value

(≤20ng/L, >20ng/L to ≤35ng/L, >35ng/L): ≤20 ng/L, >20 ng/L to ≤35 ng/L >35 ng/L to ≤50 ng/L, >50 ng/L to ≤100 ng/L, >100ng/L

6.11.2.7. Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE) reported by investigators are adjudicated by an independent CEC in a blinded fashion. The MACE events of special interest include: deaths due to cardiovascular cause, myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, coronary interventions (such as coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack (TIA).

Summary of Composite MACE, its Component, and All Cause Death will be created.

A listing of patients reporting MACE events, either reported by investigator or identified by the CEC, will be provided. The listing will include treatment, patient identification including the site number, date of event, type of event as reported by the investigator, type of event as adjudicated by the CEC, time from first dose of study drug to the event, and time from last dose to the event (if patient has discontinued study drug prior to the event). Only positively adjudicated MACE will be considered as AESI.

Listing of Components of Adjudicated Major Adverse Cardiovascular Events reported as Adverse Event will be created.

6.11.2.8. Supraventricular Arrhythmias and Cardiac Conduction Disorders

The AE database will be searched using pre-defined SMQ or MeDRA HLT to identify events consistent with supraventricular arrhythmias and cardiac conduction disorders. Detailed searching criteria can be found in Appendix 1. Incidence of the resulting TEAEs will be summarized by treatment and PT within SMQ and HLT. Treatment-emergent severe/serious supraventricular arrhythmias and cardiac conduction disorders will be considered as AESI.

The listing will be created.

6.11.2.9. Hypersensitivity Events

Hypersensitivity reactions and related information reported via the "Hypersensitivity and Anaphylactic Reactions" electronic case report form (eCRF) will be summarized by treatment. Two main analyses are performed:

- **Potential Immediate Hypersensitivity**: Analysis of TEAEs occurring from the start of study drug administration up to 24 hours after the end of study drug administration. For events without the hypersensitivity eCRF, only date (no time) information is collected, the events occurred on the same date as the study drug injection date will be included.
- **Potential Non-Immediate Hypersensitivity:**
  Analysis of TEAEs occurring more than 24 hours after the end of study drug administration, but prior to subsequent study drug administration.

Summaries of all potential hypersensitivity reactions will be generated by PT (alphabetical order) by treatment. The AE database will be searched using pre-defined SMQs to identify events consistent with hypersensitivity events. Detailed searching criteria for hypersensitivity events can be found in Appendix 1. Severe/serious hypersensitivity events identified by pre-defined SMQ search will be considered as AESIs and will be summarized.

The listing will be created.

6.11.2.10. Injection Site Reactions

Injection site reactions, incidence, and related information reported via the "Injection Site Reactions" eCRF will be summarized by treatment. Information to be summarized includes the timing of the reaction relative to study drug administration, and characteristics of the injection site reaction: erythema, induration, pain, pruritus, and edema.

Additionally, potential injection site reactions will be searched by pre-defined MedDRA HLTs of injection site reactions, administration site reactions, and infusion related reactions. Detailed searching criteria for injection site reaction events can be found in Appendix 1. The PT will be used for summary by treatment within each HLT category.

Only the severe/serious injection site reactions will be considered as AESI.

The listing will be created.

6.11.2.11. Diabetic Retinopathy Complications

Results of the baseline dilated fundoscopic exam will be summarized by treatment. Any TEAE suspected of worsening retinopathy triggers a follow-up dilated fundoscopic exam. A summary of TEAEs suspected of worsening retinopathy and a summary of the results of the follow-up dilated fundoscopic exam will be summarized by treatment and PT.

The cases with repeated fundoscopy during the course of the trial, based on clinical suspicion of worsening retinopathy that have either findings of de novo retinopathy or progression of retinopathy, and severe/serious adverse events from the PTs defined in searching criteria in Appendix 1 will be considered as AESI and summarized.

Listing of treatment emergent worsening of fundoscopy exam results will be created.

6.11.2.12. Hepatobiliary Safety

6.11.2.12.1. Hepatobility Disorders

The AE database will be searched using SMQs to identify events consistent with hepatobiliary disorders. Detailed searching criteria can be found in Appendix 1. A summary by treatment and PT within SMQ will be provided. Severe/serious hepatobiliary disorders will be considered as AESI.

6.11.2.12.2. Acute Gallbladder Disease

The AE database will be searched using pre-defined SMQs to identify events consistent with acute gallbladder diseases. Detailed searching criteria for these AEs can be found in Appendix 1. A summary by treatment and PT within SMQ will be provided. Severe/serious acute gallbladder diseases will be considered as AESI

The listing will be created.

6.11.2.12.3. Liver Enzymes

Analyses for laboratory analyte measurements are described in Section 6.13. This section describes additional analyses of liver enzymes. Following summaries will be created using the statistical models in Section 6.11.2.3.1:

- Summary and Analysis of Hepatic Enzymes Using (CN units, SI units)

In addition, the following will be provided by treatment group:

- Shift table of maximum to maximum alanine aminotransferase (ALT) measurement from baseline (≤1 × ULN, > 1 × ULN) to postbaseline with the following categories: ≤1 × ULN, >1 to <3 × ULN, ≥3 to <5 × ULN, ≥5 to <10 × ULN, ≥10 × ULN.

- Shift table of maximum to maximum aspartate transaminase (AST) measurement from baseline (≤1 × ULN, > 1 × ULN) to postbaseline with the following categories: ≤1 × ULN, >1 to <3 × ULN, ≥3 to <5 × ULN, ≥5 to <10 × ULN, ≥10 × ULN.

- Shift tables of maximum to maximum total bilirubin and direct bilirubin from baseline to postbaseline with the following categories: ≤1 × ULN, > 1 to <2 × ULN, ≥2 × ULN.

- Shift tables of serum alkaline phosphatase (ALP) from baseline to postbaseline with the following categories: ≤1 × ULN, > 1 to <2 × ULN, ≥2 × ULN.

Maximum baseline will be the maximum non-missing observation in the baseline period. The maximum postbaseline value will be the maximum non-missing value from the postbaseline period. Planned and unplanned measurements will be included.

6.11.2.13. Gastrointestinal Safety

The time courses of prevalence and incidence (newly-occurring episodes) of nausea, vomiting, diarrhea, and constipation will be plotted by treatment (Kaplan-Meier plot).

The maximum severity and duration of treatment-emergent nausea, vomiting, diarrhea, constipation and combined through the end of the study will be summarized by treatment.

The PTs in the gastrointestinal SOC will be used to identify gastrointestinal AEs. The incidence of the resulting TEAEs will be summarized by treatment and PT. PTs with severe/serious cases in the gastrointestinal SOC will be considered as AESIs.

The listing will be created.

6.11.2.14. Acute Renal Events

Laboratory measures related to renal safety will be analyzed as specified for laboratory measurements in Section 6.13.

Additionally, two shift tables examining renal function will be created. A min-to-min shift table of estimated glomerular filtration rate (eGFR) estimated by the Chronic Kidney Disease

Epidemiology Collaboration (CKD-EPI) equation with units ml/min/1.73 m^2, using categories (<30, ≥30 to <45, ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2). A max-to-max shift table of urine albumin-to-creatinine ratio (UACR), using the categories UACR<30 mg/g, 30 mg/g ≤UACR≤300 mg/g, UACR>300 mg/g (respectively, these represent normal, microalbuminuria, and macroalbuminuria).

Following summaries will be created:

- Summary and Analysis of Percentage Change from Baseline for Urine Albumin/Creatinine Ratio
  - Log transformed model specified in Section 6.11.2.3.1 will be used.
- Summary and Analysis of Percentage Change from Baseline for Estimated Glomerular Filtration Rate
  - MMRM model for the primary efficacy analysis will be used

The AE database will be searched using SMQs of acute renal failure and chronic kidney disease to identify events consistent with acute renal events. The incidence of the resulting TEAEs will be summarized by treatment and PT. Detailed searching criteria can be found in Appendix 1. Severe/serious acute renal events will be considered as AESI.

The listing will be created.

6.11.2.15. Dehydration

The AE database will be searched using SMQ of dehydration to identify events consistent with dehydration. Detailed searching criteria can be found in Appendix 1. Severe/serious dehydration events will be considered as AESIs.

6.11.2.16. Metabolic Acidosis, including Diabetic Ketoacidosis

The AE database will be searched using MedDRA PT to identify events consistent with metabolic acidosis, including diabetic ketoacidosis. Detailed searching criteria can be found in Appendix 1. The incidence of the resulting TEAEs will be summarized by treatment and PT. Severe/serious metabolic acidosis, including diabetic ketoacidosis will be considered as AESIs.

The listing will be created.

6.11.2.17. Amputation/Peripheral Revascularization

The AE database will be searched using MedDRA PT to identify events for amputation or peripheral revascularization. The incidence of the resulting TEAEs will be summarized by treatment and PT. Amputation/Peripheral Revascularization will be considered as AESIs.

The listing will be created.

6.11.2.18. Major Depressive Disorder/Suicidal Ideation

The AE database will be searched using SMQs to identify events consistent with major depressive disorder or suicidal ideation. Detailed searching criteria can be found in Appendix 1.

The incidence of the resulting TEAEs will be summarized by treatment and PT. Severe/serious major depressive disorder/suicidal ideation or behavior will be considered as AESIs.

The listing will be created.

6.12. Vital Signs

Descriptive summaries by treatment and by nominal visit will be provided for baseline and postbaseline values as well as change from baseline values. If 2 records are taken at the same visit, they will be averaged prior to being used for data summaries and analyses.

An MMRM using REML will be used to fit the changes from baseline in vital signs at all scheduled postbaseline visits. The model will include treatment group, visit, OAM class, and treatment-by-visit interaction as fixed effects, and baseline value of the dependent variable as a covariate. To model the covariance structure within patients, the unstructured covariance matrix will be used.

Plot of Time Profile for Vital Sign Parameters from MMRM Results will be created.

Counts and percentages of patients with treatment-emergent abnormal sitting systolic blood pressure (BP), sitting diastolic BP, and pulse will be presented by treatment. The criteria for identifying patients with treatment-emergent vital sign abnormalities are stated in Table GPGP.6.3.

Table GPGP.6.3. Categorical Criteria for Abnormal Blood Pressure and Pulse Measurements

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15

Abbreviation: BP = blood pressure.

6.13. Clinical Laboratory Evaluation

All laboratory data will be reported in the International System of Units and Conventional Units. Values that are outside of reference ranges will be flagged as high (H) or low (L) in the listings. Descriptive summaries by treatment and by nominal visit will be provided for the baseline and postbaseline values as well as the change from baseline values for selected measurements.

For Pancreas (p-amylase, lipase), observed values for each visit will be displayed graphically for patients who have both a baseline and a postbaseline planned measurement. Unplanned measurements will be excluded from graphs. These are based on both SI and CN units.

Shift tables will be produced for selected measurements. A shift table will include unplanned measurements. The shift table will include the number and percentage of patients within each baseline category (low, normal, high, or missing) versus each postbaseline category (low, normal, high, or missing) by treatment. These are based on CN units.

A listing of abnormal findings will be created for laboratory analyte measurements. The listing will include patient ID, treatment group, laboratory collection date, study day, analyte name, and analyte finding.

6.14. Immunogenicity

Treatment-emergent anti-drug antibodies (TE ADA) are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment boosted ADA). A patient is evaluable for TE ADA if the patient has a non-missing baseline ADA result, and at least 1 non-missing postbaseline ADA result.

The frequency and percentage of patients with preexisting ADA, with TE ADA, and with cross-reactive antibodies and with neutralizing antibodies will be tabulated by dose, where proportions are relative to the number of patients who are TE ADA evaluable. The frequency and percentage of patients with hypersensitivity and injection site reaction TEAEs by TE ADA status will be tabulated if data warrant.

A listing will be provided of all immunogenicity assessments for those patients who at any time had ADA present. This includes the LY3298176 concentration from a simultaneous PK sample, and the clinical interpretation result.

A listing of patients who are not TE ADA evaluable will be created

A listing will be provided for all participant who had ADA present at any time (including baseline) or had any hypersensitivity or injection site reaction TEAE.

Depending on the number of patients with TE ADA, selected efficacy and safety subgroup analyses by TE ADA categories may be performed, if deemed necessary.

Treatment-emergent ADA that are associated with AEs of either severe/serious hypersensitivity or severe/serious injection site reaction will be classified as AESIs.

Following Summary and figures (Kaplan-Meier analysis) will be created for [1] during planned treatment period, and [2] during the entire postbaseline period including safety follow-up;

- Summary of TE Tirzepatide Anti-Drug Antibodies Status
- Summary of Postbaseline Cross-Reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA (**with** inconclusive information)

Note: Inconclusive information consists of followings;

- Neutralizing TZP for GIPR Inconclusive

- Neutralizing TZP for GLP-1R Inconclusive
- In Silico Neutralizing to Native GIP Inconclusive
- In Silico Neutralizing to Native GLP-1 Inconclusive

Abbreviation: GIP = glucose-dependent insulinotropic polypeptide; GIPR = GIP receptor; GLP-1 = glucagon-like peptide-1; GLP-1R = GLP-1 receptor; TZP = Tirzepatide.

- Summary of Postbaseline Cross-Reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA (**without** inconclusive information)
- Summary of First Time to TE ADA+ (figure)
- Summary of First Time to Reach Maximum Titer (figure)

6.15. Subgroup Analyses

Efficacy subgroup analyses will be guided by the efficacy estimand. Subgroup analyses of mean change in HbA1c and mean change in body weight at 52-weeks, AE (TEAE by PT, cutoff=5%) and hypoglycemic events through safety follow-up (Summary and Analysis of Hypoglycemia Incidence and Rate with Blood Glucose <54 mg/dL (level 2) or Severe Hypoglycemia, exclude hypoglycemic events occurring after initiation of a new antihyperglycemic therapy) will be provided. Subgroup analyses will be conducted for each of the combination therapies by the following baseline characteristics:

- Age group (<65 years, ≥65) and (<75 years, ≥75)
- Gender
- BMI group (<25 or ≥25 kg/m^2)
- Duration of diabetes (≤10 or >10 years)
- Baseline HbA1c (≤8.5%, >8.5%)
- Renal impairment (eGFR <60, ≥60 mL/min/1.73m^2)

For efficacy analysis, two statistical models will be used:

[1] For each subgroup, estimation is based on the MMRM model with treatment, visit, OAM class, and treatment by visit interaction as fixed effects, and baseline value as a covariate.

[2] For interaction term test, it is based on the MMRM model with the terms specified above, as well as subgroup, subgroup by treatment, subgroup by visit, and subgroup by treatment by time interactions.

Other exploratory subgroup analyses may be performed as deemed appropriate.

6.16. Interim Analyses

No interim analyses are planned for this study.

7. Unblinding Plan

Not applicable. GPGP is an open label trial.

8. References

Protocol I8F-JE-GPGP (a) A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus (SURPASS J-combo).

9. Appendices

Appendix 1. Searching Criteria for Adverse Events of Special Interest (AESI)

The AESI analyses are detailed in Section 6.11.2. The search criteria for each AESI are defined in AdaM ADAE specification.

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