Statistical Analysis Plan Version 2 I8F-MC-GPHO

# A Randomized, Phase 3, Open-label Trial Comparing the Effect of Tirzepatide Once Weekly Versus Titrated Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes on Metformin with or without a Sulfonylurea (SURPASS-AP-Combo)

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# 1. Statistical Analysis Plan I8F-MC-GPHO: A Randomized, Phase 3, Open-Label Trial Comparing the Effect of Tirzepatide Once Weekly Versus Titrated Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes on Metformin with or without a Sulfonylurea (SURPASS-AP-Combo)



Tirzepatide for Type 2 Diabetes Mellitus

Phase-3 randomized 4-arm parallel design open label trial comparing 3-doses of TIRZEPATIDE to Insulin Glargine in patients with Type 2 Diabetes


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[Protocol I8F-MC-GPHO]
[Phase 3]

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# 3. Revision History

SAP Version 1 was approved prior to the first patient receiving study drug.

The second version was approved prior to the final database lock. The following represent major changes made for the second version:

1. Corrected the definition of "retrieved dropout." Patients who initiation rescue medication and had their HbA1c value measured at the 40-week visit can't be used as "retrieved dropout." Added cutoff value for multiple imputation to avoid unrealistic imputed values.
2. Update the language to handle lack of convergence in longitudinal logistic regression analysis due to low number of events for hemoglobin A1c (HbA1c) and weight loss target analyses.
3. Update the language in section on adverse events of special interest and renamed section to "Special Safety Topics" to be consistent with the program SAP CCI [redacted]
4. Add section to assess SARS-CoV-2 (COVID-19) impact CCI [redacted]
5. Add subgroup analysis of hypoglycemic events to check the incidence and rate of any hypoglycemic events in different concomitant oral antidiabetic use (See Section 6.18.4)
6. Add a new exploratory objective: proportion of patients achieving an HbA1c target <7.0%, weight loss >=5%, and without clinically significant documented symptomatic hypoglycemia or severe hypoglycemia (See Table GPHO.6.2)
7. In the exploratory objective to compare tirzepatide 5 mg, 10 mg, and 15 mg with insulin glargine for change in lipids was modified to add "non-HDL cholesterol" due to emerging science indicates assessing non-HDL cholesterol should provide more valuable data on CVD risk.

# 4. Study Objectives

## 4.1. Primary Objective

The primary objective of the study is to demonstrate that once-weekly(QW) tirzepatide 10 mg and/or 15 mg are noninferior to insulin glargine for change from baseline in HbA1c at 40 weeks.

## 4.2. Key Secondary Objectives Subject to Strong Type 1 Error Rate Control

Together with the primary objective, the following secondary objectives are subjected to strong control of the type 1 error rate (see Section 6.12.3).

- To demonstrate that QW tirzepatide 5 mg is noninferior to insulin glargine for change from baseline in HbA1c at 40 weeks.
- To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg are superior to insulin glargine for change from baseline in weight at 40 weeks.
- To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg are superior to insulin glargine for change from baseline in HbA1c at 40 weeks.
- To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg are superior to insulin glargine for the proportion of patients with HbA1c target values of <7.0% (53 mmol/mol) at 40 weeks.

## 4.3. Other Secondary and Exploratory Objectives Not Subject to Strong Type 1 Error Rate Control

The following secondary and exploratory objectives are not subjected to strong control of the type 1 error rate.

Secondary Objectives:

- to demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg are superior to insulin glargine at 40 weeks for:
    - mean change in fasting serum glucose (central lab) from baseline
    - proportion of patients achieving an HbA1c target values of ≤6.5% (48 mmol/mol) and <5.7% (39 mmol/mol)
    - mean change in 7-point self-monitored blood glucose (SMBG) profiles from baseline
    - proportion of patients who achieved weight loss ≥5%, ≥10%, and ≥15% from baseline
- to compare tirzepatide 5 mg, 10 mg, and 15mg to insulin glargine at 40 weeks for:
    - patient-reported outcomes:

- Diabetes Treatment Satisfaction Questionnaire status/Diabetes Treatment Satisfaction Questionnaire change

Exploratory objectives:

- to compare tirzepatide 5 mg, 10 mg, and 15 mg with insulin glargine for the following:
  - change in lipids (total cholesterol, high-density lipoprotein [HDL], very low-density lipoprotein [VLDL], non-high-density lipoprotein [non-HDL], and triglycerides [TG])
  - mean change in waist circumference
  - change from baseline in mean body mass index (BMI)
  - European Quality of Life dimension (5-level EuroQol-5D [EQ-5D-5L]) scores
  - Impact of Weight on Self-Perception (IW-SP)
  - Ability to Perform Physical Activities of Daily Living (APPADL)

## 4.4. Safety Objectives

To compare the safety of tirzepatide 5 mg, 10 mg, and 15 mg to insulin glargine for:

- treatment-emergent adverse events (TEAEs)
- early discontinuation of study drug due to adverse events (AEs)
- adjudicated pancreatic AEs
- serum calcitonin
- incidence of allergic and hypersensitivity reactions
- incidence of treatment-emergent anti-drug antibodies to tirzepatide
- mean change in systolic and diastolic blood pressure and heart rate from baseline
- occurrence of hypoglycemic episodes
- incidence of initiation of rescue therapy for severe, persistent hyperglycemia

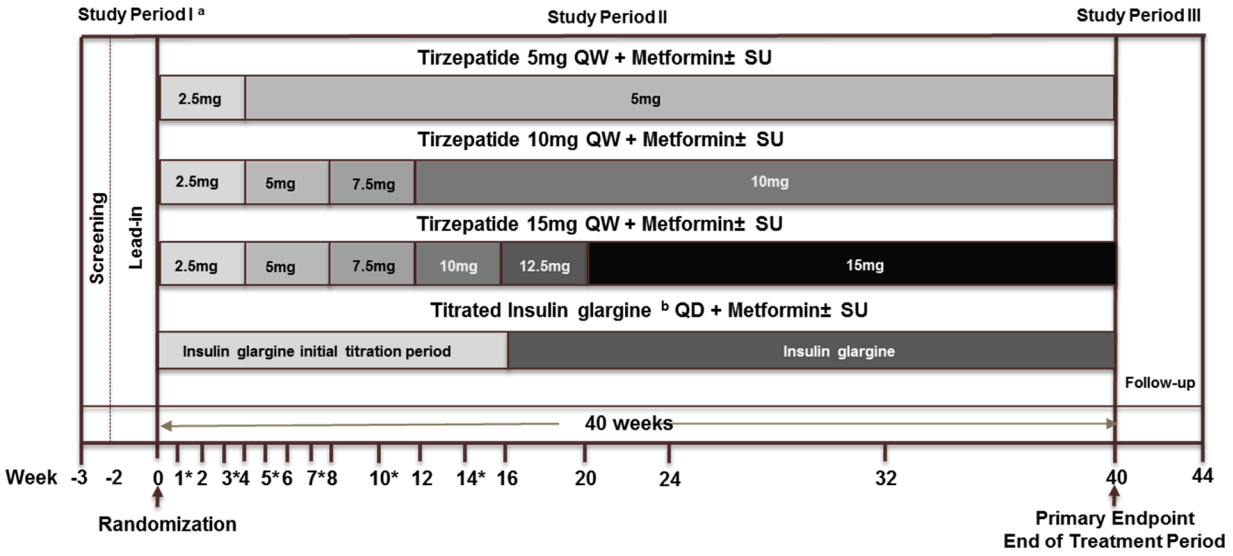
# 5. Study Design

## 5.1. Summary of Study Design

Study GPHO is a Phase 3, multicenter, randomized, open-label, parallel-group study that will investigate the effects of treatment with tirzepatide 5 mg, 10 mg, and 15 mg QW compared with titrated insulin glargine in patients with T2DM who have inadequate glycemic control on stable doses of metformin with or without a sulfonylurea. The primary endpoint will be the mean change in HbA1c from baseline to 40 weeks.

Figure GPHO.5.1 illustrates the study design.

**Figure GPHO.5.1. Illustration of study design for Clinical Protocol I8F-MC-GPHO.**




Abbreviations: FBG = fasting blood glucose; QW = once weekly; QD = once daily; SU = sulfonylurea

a Stable doses of metformin (metformin ≥1000 mg/day and no more than the maximum approved dose per country-specific label) and/or a sulfonylurea for 2 months prior to Visit 1, and during the screening/lead-in Period.

b The initial dose of insulin glargine will be 6 IU/day for patients who have an average FBG concentration of ≥7.8 mmol/L (140 mg/dL). The initial dose of insulin glargine for patients with an average FBG concentration of <7.8 mmol/L (<140 mg/dL) may be reduced by 1-2 IU/day at the investigator's discretion.

*Telephone visits

Note: Patients will titrate insulin glargine dose in a weekly manner and will make the dose decision with the investigator for the first 8 weeks (phone or clinic visit). From Week 8 to Week 16 patients will continue the titration by a phone consultation or clinic visit every other week. It is expected that the insulin dose will stay relatively stable from Week 16 onwards.

### Study Period I (Screening and Lead-in)

Screening (Visit 1)

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2. Patients who

meet all applicable inclusion criteria and none of the applicable exclusion criteria at Visit 1 will continue on their prestudy therapy between Visits 1 and 2.

Lead-in (Visit 2 to Visit 3)

At Visit 2, the screening laboratory results will be reviewed and patient eligibility will be established with the exception of retinopathy status. A dilated fundoscopic exam will be performed between Visit 2 and Visit 3 as results are required to confirm eligibility.

**Study Period II (40-week treatment period)**

Randomization (Visit 3)

At Visit 3, eligible patients will perform all required baseline study procedures (including the collection of all baseline laboratory measures) prior to randomization and prior to taking the first dose of study drug.

Post-randomization period (end of Visit 3 to Visit 19):

The starting dose of tirzepatide will be 2.5 mg once-weekly for 4 weeks, followed by an increase to 5 mg once-weekly, for the duration of the study in the 5 mg group. For the 10-mg group, the starting dose of tirzepatide will be 2.5 mg once-weekly for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg group, the starting dose of tirzepatide will be 2.5 mg once-weekly for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5-15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

The initial dose of insulin glargine should be determined by the patient's average plasmaequivalent FBG concentration from the previous 2-4 days before Visit 3. The initial dose of insulin glargine will be 6 IU/day for patients who have an average FBG concentration of ≥7.8 mmol/L (≥140 mg/dL). The initial dose of insulin glargine for patients with an average FBG concentration of <7.8 mmol/L (<140mg/dL) may be reduced by 1-2 IU/day at the investigator's discretion. All subsequent glargine dose adjustments should be determined based on the algorithm (Kawamori et al. 2008)

**Study Period III (Safety Follow-up Period)**

Safety follow-up (Visit 801) visits:

All patients who complete the treatment period are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after their last visit. Patients discontinuing the study early and performing an early termination (ET) visit will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit. During the safety follow-up period, patients will not receive study drug. Patients will be treated with another glucose lowering intervention decided upon by the investigator. Initiation of new antihyperglycemic therapy for the safety follow-up period will not be classified as "rescue therapy."

## 5.2. Determination of Sample Size

Although the primary objective of the trial is to demonstrate that once-weekly tirzepatide 10 mg and/or 15mg doses are non-inferior to titrated insulin glargine relative to mean change in HbA1c from baseline, the trial is powered to assess superiority of tirzepatide 10 mg and 15mg, each tested in parallel against titrated insulin glargine at two-sided significance level of 0.025, relative to the primary endpoint (mean change in HbA1c from baseline at 40 weeks), under the following assumptions: use of 2-sample t-test utilizing HbA1c data collected before initiation of any rescue medication or premature treatment discontinuation with no more than 25% subjects initiating any rescue medication or premature treatment discontinuation in each treatment group; 0.45% greater mean reduction in HbA1c from baseline for 10mg and 15mg tirzepatide compared to insulin glargine; 1:1:1:1 randomization; and a common standard deviation (SD) of 1.2%. On the basis of these assumptions, approximately 956 patients (80% from China, 20% from other countries/regions) with type 2 diabetes will be enrolled into this study to ensure at least 90% power to demonstrate that tirzepatide 10mg and/or 15mg are superior to insulin glargine relative to the primary endpoint. Using the same assumptions would provide >99% power for the non-inferiority comparison. China patients would provide 82% power to demonstrate the superiority.

## 5.3. Method of Assignment to Treatment

Approximately 956 Patients who meet all criteria for enrollment will be randomized to one 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). Patients will be randomized in a 1:1:1:1 ratio to receive 5 mg tirzepatide, 10 mg tirzepatide, 15 mg tirzepatide, or insulin glargine. The randomization will be stratified by country, baseline HbA1c concentration (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and use of concomitant oral antidiabetic treatments (Metformin alone, metformin plus sulfonylurea).

# 6. A Priori Statistical Methods

## 6.1. Populations for Analyses

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

**Table GPHO.6.1. Analysis Populations/Datasets**

| Population/Dataset | Description |
|---|---|
| Screened population | All participants who sign informed consent |
| Randomized population | All patients who are randomly assigned a treatment arm |
| Modified intent-to-treat (mITT) population | All randomly assigned participants who are exposed to at least 1 dose of study drug. In the event of a treatment error, participants will be analyzed according to the treatment they were randomized. |
| Efficacy analysis set (EAS) | Data obtained during Study Period II from the mITT population, excluding data after initiating rescue antihyperglycemic medication or discontinuing study drug (last dose date +7 days). |
| Full analysis set (FAS) | Data obtained during Study Period II from mITT, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication. |
| Safety analysis set (SAS) | Data obtained during Study Periods II or III from mITT, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication. |
| Per Protocol (PP) | Patients included in the randomized population who have completed Week 40 of study treatment without permanent discontinuation of study drug and without significant protocol deviations through Week 40 that would significantly impact the primary objective, excluding data after initiating rescue antihyperglycemic medication. Treatment group will be defined on the basis of the treatment the patients actually receive. Randomized maintenance dose will be used if patients with de-escalation. |

## 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). Listings 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 primary or final database locks (DBL).

Patients inadvertently receiving incorrect study treatment are expected to switch to their randomized treatment arm as soon as possible. Patients assigned to tirzepatide may not be able to tolerate the maximum dose of the randomized treatment arm and may continue study participation on a reduced maintenance dose. Continuing on a reduced maintenance dose will neither be considered as discontinuation of randomized treatment nor will be considered as non-

compliant to randomized treatment. Additionally, to avoid potential selection biases, unless stated otherwise, statistical summaries and analyses will be conducted based on randomized maintenance dose regardless of the actual treatment received by the patient.

Last available measurement during Visit 1 to Visit 3 (including unscheduled visits) prior to or on the first dose day will serve as baseline. Immunogenicity, urinary albumin to creatinine ratio, lipid values, and health outcome measures obtained at Visit 3, regardless of the timing relative to first dose, will be used as baseline.

Efficacy and safety will be assessed using the modified intent-to-treat (mITT) population, which consists of all randomly assigned participants who are exposed to at least one dose of study drug. The primary and multiplicity adjusted objectives, will be performed on EAS and FAS. When change from baseline is included as a response variable of analysis models, the patient will be included in the analysis only if he/she has a baseline and a postbaseline measurement.

Selected efficacy analyses will also be conducted using the Per-Protocol (PP). PP population will include all patients in the randomized population who completed week 40 of study treatment without permanent discontinuation of study drug and without significant protocol deviations through Week 40 that would significantly impact the primary objective, excluding data after initiating rescue antihyperglycemic medication. Patients in the PP population will be analyzed according to the treatment the patients actually received. Randomized maintenance dose will be used if patients with de-escalation. Those patients who have their dose de-escalated, will not be escalated again. The dose can be de-escalated only once.

Safety assessment will be based on all available data, irrespective of whether they were obtained while the participants had discontinued the study drug or whether the participant had been given rescue medication. Selected safety analysis (e.g., hypoglycemia) will be conducted after excluding data on rescue therapy.

End of study participation for a patient will be the earliest of date of death, date of withdrawal from further participation in the study, or date of safety follow-up visit (Visit 801). For patients considered to be lost-to-follow-up, end of study participation will be the date of lost-to-follow-up reported by the investigator. Patient data included in the database after the last date of study participation (date of early termination or date of safety follow-up) will be excluded from statistical analysis.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The summary statistics will be presented by nominal visit.

Statistical treatment comparisons will only be performed between tirzepatide doses and insulin glargine. Since the trial is not adequately powered to detect differences among tirzepatide doses, comparisons among tirzepatide arms will not be performed unless otherwise specified.

Statistical summaries and results of statistical analyses will be displayed in the following treatment order: 5 mg tirzepatide, 10 mg tirzepatide, 15 mg tirzepatide, insulin glargine.

## 6.3. Adjustments for Covariates

The study is stratified by country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and use of concomitant oral antidiabetic medications (metformin alone, metformin plus SU). For HbA1c related analyses, country and concomitant oral antidiabetic use will be used as stratification factors and baseline HbA1c as a covariate. For other efficacy analyses, country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and use of concomitant oral antidiabetic medications (metformin alone, metformin plus SU) will be used as stratification factors and respective baseline value as a covariate.

## 6.4. Handling of Dropouts or Missing Data

For analyses using in EAS, missing data will be addressed by using a mixed-effect model repeated measures (MMRM) analysis for continuous longitudinal variables. The MMRM model provides consistent estimator when data is missing at random. The model implicitly adjusts for missing data through a variance-covariance structure. For health outcomes data, LOCF will be used for Analysis of Covariance (ANCOVA) analysis and item-level missingness is dealt with as per instrument developers' instruction.

For analyses using FAS, data for patients with missing values at the 40-week visit will be imputed based on the method described in Section6.12.1.3. Unless specified otherwise, imputation of missing data will be limited to primary and key secondary efficacy endpoint analyses.

Missing other secondary or exploratory efficacy parameter values and missing safety laboratory values will not be explicitly imputed.

## 6.5. Multicenter Studies

GPHO is a multi-country, multi-site study. Site will not be analyzed as a fixed effect in any of the models so pooling strategies will not be required.

## 6.6. Multiple Comparisons/Multiplicity

Type 1 Error rate control strategy for primary and key secondary efficacy objectives is illustrated in Section 6.12.3. No multiplicity adjustments will be made for evaluating other secondary and exploratory efficacy objectives and safety assessments.

## 6.7. Patient Disposition

A listing of final study disposition and a listing of randomized treatment assignment (planned treatment) for all randomized patients will be provided. Final study disposition and study drug disposition for all randomized patients will be summarized by planned study treatment.

## 6.8. Patient Characteristics

A listing of patient demographics will be provided. All demographic and baseline clinical characteristics will be summarized by study treatment for the patients in all randomized population and mITT population. Baseline demographic and clinical characteristics of special

interest including but not limited to: age, gender, race, BMI, weight, country of enrollment, HbA1c, fasting serum glucose, duration of T2DM, baseline antihyperglycemic medication, renal function, history of retinopathy, results of the fundoscopic exam, and history of gallbladder disease.

## 6.9. Concomitant Therapy

Prespecified concomitant medications of interest will be summarized by treatment at randomization. Additionally, medications of interest initiated after randomization will be summarized. 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 for reporting purposes.

The concomitant medications of interest include the following groups of medication:

- baseline Antihyperglycemic therapy
    - Prior glucagon-like peptide-1 receptor agonist (GLP-1 RA) use by type
    - Metformin
    - Sulfonylureas, by type
- baseline antihypertensive therapy, by type
- baseline lipid lowering therapy, by type
- changes to baseline medication in Study Period II:
    - Antihypertensive therapy
    - Lipid lowering therapy
- changes to baseline medication in Study Periods II and III:
    - antihyperglycemic therapy
- rescue therapy due to severe persistent hyperglycemia
- utilization of:
    - antidiarrheal medication
    - antiemetic medication

## 6.10. Treatment Exposure and Compliance

A 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, and 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 of follow-up (defined as time in days from date of randomization to date of safety follow-up visit) 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 therapy.

### *6.10.1. Exposure and Compliance to Tirzepatide*

The number of patients prematurely discontinuing study treatment prior to the 40-week visit will be provided by study treatment. Reasons for prematurely discontinuing study treatment prior to the 40-week visit will also be provided by study treatment. A time-to-event analysis of premature study treatment discontinuation will be conducted.

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

A listing and summary of patients continuing on a reduced maintenance dose of tirzepatide compared to the randomized dose will be provided.

Compliance will be defined as taking at least 75% of the scheduled tirzepatide doses. Compliance will be calculated by taking the number of doses administered (regardless of the actual dose administered) divided by the total number of doses expected to be administered ×100. Treatment compliance will be summarized descriptively over the entire study period by treatment using the mITT population.

### *6.10.2. Exposure and Compliance to Insulin Glargine Treat-to-Target Algorithm*

Summary information on total daily dose of insulin glargine will be reported by visit. Information related to compliance to treat-to-target therapy including reasons for non-compliance will be summarized.

Compliance will be defined as taking at least 75% of the scheduled insulin doses. The number of insulin doses administered was calculated by subtracting the number of doses missed as entered in the compliance CRF from the number of doses expected to be administered. Compliance will be calculated by taking the number of doses administered (regardless of the actual dose administered) divided by the total number of doses expected to be administered × 100. Treatment compliance will be summarized descriptively over the entire study period by treatment using the mITT population

Additionally, summaries will be produced for the percent of patients to reach fasting serum glucose goals of <100 mg/dL (5.6 mmol/L) and <126 mg/dL (7 mmol/L) over time at weeks 16, 24, and 40.

## 6.11. Important Protocol Deviations

Important protocol deviations are identified in the Trial Issues Management Plan (TIMP). A listing and a summary of important protocol deviations by treatment will be provided.

## 6.12. Efficacy Analyses

### *6.12.1. Primary Efficacy Analysis*

The primary efficacy measure will be change in HbA1c from baseline (postbaseline – baseline). Both HbA1c values as well as change from baseline in HbA1c will be summarized by treatment and nominal visit (week). If scheduled HbA1c data at the primary endpoint visit are not available, unscheduled HbA1c data collected for the primary endpoint visit will be included in the analysis.

#### 6.12.1.1. Primary Analysis Model

The analysis will be conducted utilizing HbA1c data in EAS from baseline through the 40-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, treatment by visit interaction, country, and baseline concomitant oral antihyperglycemic medication use (metformin alone versus metformin plus SU) 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. The resulting least squares mean (LSM) estimates of mean change from baseline in HbA1c will be plotted by visit and by study treatment.

With the aid of the MMRM analysis, 2-sided 97.5% confidence interval (CI) for mean change in HbA1c from baseline to 40-week visit for (10 mg tirzepatide - insulin glargine) as well as for (15 mg tirzepatide - insulin glargine) will be derived. If the upper limit of the CI is <= 0.4%, then the respective dose of tirzepatide (10 mg and/or 15 mg) will be declared noninferior to insulin glargine relative to change in HbA1c from baseline.

#### 6.12.1.2. Sensitivity analyses for Missing Data

The primary objective will also be repeated utilizing HbA1c data in FAS at baseline and at the 40-week visit with the aid of an ANCOVA. The response variable will be the primary measure and model terms will include treatment, country, baseline concomitant oral antihyperglycemic medication use (metformin alone versus metformin plus SU) as fixed effects, and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted with multiple imputation of missing primary measure (see Section 6.12.1.3 for details) and statistical inference over multiple imputation of missing data guided by Rubin (1987).

With the aid of the ANCOVA analysis 2-sided 97.5% CI for mean change in HbA1c from baseline to 40-week visit for (10 mg tirzepatide - insulin glargine) as well as for (15 mg tirzepatide - insulin glargine) will be derived. If the upper limit of the CI is <= 0.4%, then the respective dose of tirzepatide (10 mg and/or 15 mg) will be declared noninferior to insulin glargine relative to change in HbA1c from baseline.

#### 6.12.1.3. Methods for Multiple Imputations

For ANCOVA sensitivity analyses, missing HbA1c data at the 40-week visit will be imputed based on "retrieved dropouts," defined as patients who had their HbA1c value measured at the 40-week visit in the same treatment arm who prematurely discontinued study drug. If value of the imputed HbA1c change from baseline is <-6.0% or >6.0%, that value will be set to -6.0% or 6.0%, respectively, to avoid unrealistic imputed values.

#### 6.12.1.4. Additional Analyses of the Primary Outcome

The primary MMRM analysis model will be repeated using the PP population as a sensitivity analysis. If the conclusion differs from that of EAS, the data and analyses will be further investigated.

Upon successfully establishing noninferiority of tirzepatide compared to insulin glargine, superiority of tirzepatide compared to insulin glargine relative to change in HbA1c from baseline will be evaluated (see Section 6.12.3).

### *6.12.2. Secondary Efficacy Analyses Subject to Type 1 Error Rate Control*

#### 6.12.2.1. Mean Change in HbA1c from Baseline at the 40 Week Visit

Noninferiority of 5 mg tirzepatide to insulin glargine will be conducted in a manner similar to Section 6.12.1.1. Assessment of Superiority of tirzepatide doses compared to insulin glargine will be conducted using the same statistical models as those used for evaluating the primary objective in Section 6.12.1.1. Decisions will be guided by the two-sided p-values for mean comparisons between tirzepatide doses and insulin glargine (see details in Section 6.12.3).

#### 6.12.2.2. Mean Change in Body Weight from Baseline at the 40 week visit

The analysis for change in body weight from baseline (postbaseline – baseline) will be conducted in a manner similar to the primary analysis in Section 6.12.1.1. Baseline HbA1c concentration (≤8.5%, >8.5% [≤69, >69 mmol/mol]) will be used as a fixed factor in place of baseline HbA1c

as a covariate and baseline body weight will be used as an additional covariate in the statistical model. Least squares mean estimates of mean change in body weight from baseline will be plotted by nominal visit and by study treatment. For multiple imputation of missing values, if the imputed value of weight change from baseline is <-50 kg or >50 kg, then that value will be set to -50 kg or 50 kg, respectively, to avoid unrealistic imputed values.

#### 6.12.2.3. Proportion of Patients Achieving HbA1c<7% at the 40 week Visit

The analysis will be conducted utilizing data using the EAS with missing values imputed from an MMRM model and then dichotomized. The MMRM model includes treatment, country, baseline concomitant oral antihyperglycemic medication use, visit, and treatment-by-visit interaction as fixed effects, and baseline HbA1c as a covariate. After dichotomizing continuous HbA1c, the data are analyzed using a logistic regression model with treatment, country, and baseline concomitant oral antihyperglycemic medication use as fixed effects, and baseline HbA1c as a covariate. In addition, longitudinal logistic regression with repeated measurements with country, baseline concomitant oral antihyperglycemic medication use, treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline HbA1c as a covariate will also be provided using data in EAS. If the longitudinal logistic model does not converge due to a small number of events, logistic regression will be utilized to analyze the proportion of patients achieving HbA1c <7% at nominal visits.

Analyses also will be conducted utilizing HbA1c data in the FAS at baseline and at the 40-week visit with the aid of a logistic regression with multiple imputation of missing HbA1c data at the 40-week visit (see Section 6.12.1.3 for details). Model terms will include treatment, country, and baseline concomitant oral antihyperglycemic medication use as fixed effects, and baseline HbA1c as a covariate. Statistical inference over multiple imputations will be guided by Rubin (1987).

### *6.12.3. Type 1 Error Rate Control Strategy for Primary and Key Secondary Efficacy Analysis.*

Type 1 error rate control strategy for evaluation of primary and key secondary objectives is illustrated in

Figure GPHO.6.1.

1. $H_{15,1}$, $H_{15,2,}$ and $H_{15,3}$ are evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective. In parallel,

2. $H_{10,1}$, $H_{10,2,}$ and $H_{10,3}$ are evaluated hierarchically each at two-sided 0.025 significance level conditioned on successfully achieving the preceding objective.

3.

a) If all objectives in #1 and #2 above are successfully established, $H_{5,1}$, $H_{5,2,}$ and $H_{5,3}$ are evaluated hierarchically, each at a 2-sided 0.05 significance level.

b) If all objectives in only #1 or only #2 above are successfully established, $H_{5,1}$, $H_{5,2,}$ and $H_{5,3}$ are evaluated hierarchically, each at a 2-sided 0.025 significance level.

4. If all objectives: $H_{5,1}$, $H_{5,2,}$ and $H_{5,3}$ are successfully established and

a) if all objectives in #1 and #2 above are successfully established, then $H_{10,4}$, $H_{15,4}$ and $H_{5,4,}$ will be evaluated hierarchically each at two-sided 0.05 significance level conditioned on the successfully achieving the preceding objective.

b) If all objectives in only #1 or only #2 above are successfully established, then $H_{10,4}$, $H_{15,4}$, and $H_{5,4}$ will be evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective.

5. If all objectives in #3 and #4 above are successfully established, and at least 1 objective from #1 or #2 above is not successfully established, recycle 100% of the unused alpha back to #1 or #2 above.

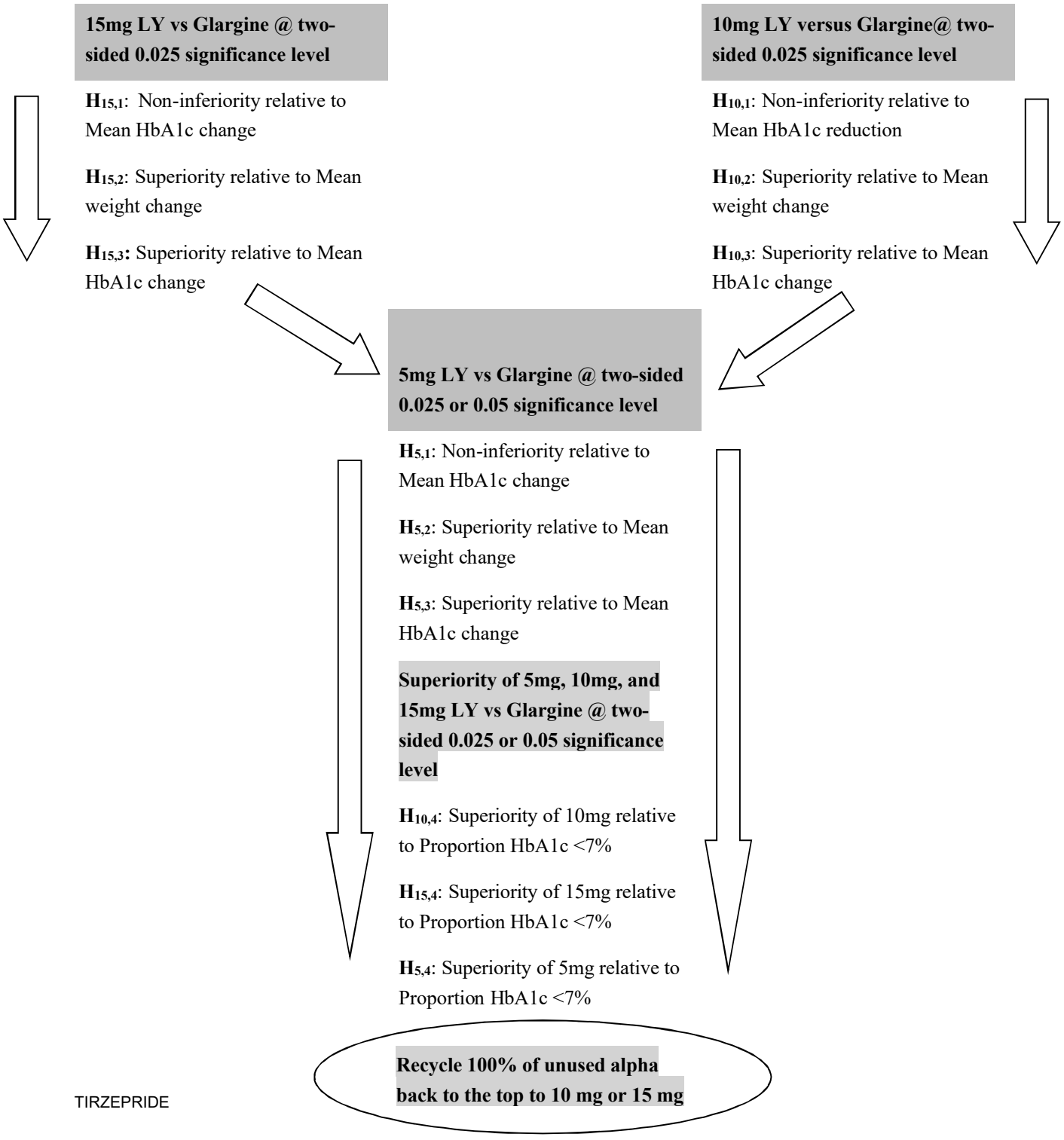

15mg LY vs Glargine @ two-sided 0.025 significance level
H15,1: Non-inferiority relative to Mean HbA1c change
H15,2: Superiority relative to Mean weight change
H15,3: Superiority relative to Mean HbA1c change
10mg LY versus Glargine@ two-sided 0.025 significance level
H10,1: Non-inferiority relative to Mean HbA1c reduction
H10,2: Superiority relative to Mean weight change
H10,3: Superiority relative to Mean HbA1c change
5mg LY vs Glargine @ two-sided 0.025 or 0.05 significance level
H5,1: Non-inferiority relative to Mean HbA1c change
H5,2: Superiority relative to Mean weight change
H5,3: Superiority relative to Mean HbA1c change
Superiority of 5mg, 10mg, and 15mg LY vs Glargine @ two-sided 0.025 or 0.05 significance level
H10,4: Superiority of 10mg relative to Proportion HbA1c <7%
H15,4: Superiority of 15mg relative to Proportion HbA1c <7%
H5,4: Superiority of 5mg relative to Proportion HbA1c <7%
Recycle 100% of unused alpha back to the top to 10 mg or 15 mg

**Figure GPHO.6.1. Type 1 Error control strategy for primary and key secondary efficacy endpoints.**

### *6.12.4. Other Secondary and Exploratory Efficacy Analyses*

Other secondary and exploratory efficacy measures will be summarized by treatment and nominal visit. Statistical analyses will be conducted in a manner similar to Sections 6.12.1 and 6.12.2.

**Table GPHO.6.2. Secondary and Exploratory Efficacy Measures Not Controlled for Type 1 Error**

| Objective | Relative to the efficacy measure: | Analysis Conducted in a manner similar to: | Additional Information |
|---|---|---|---|
| **Secondary Analyses** | | | |
| once-weekly tirzepatide 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine at 40 weeks | Change from baseline in fasting serum glucose (central laboratory) | 6.12.1.1 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use baseline FSG as a covariate. LSM estimates will be plotted by treatment and visit. |
| | Proportion of patients achieving an HbA1c target value of ≤6.5% (48 mmol/mol), | 6.12.2.3 | None |
| | Proportion of patients achieving an HbA1c target value of <5.7% (39 mmol/mol). | 6.12.2.3 | None |
| | Change from baseline in 7-point self-monitored blood glucose (SMBG) profiles | 6.12.1.1 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use baseline SMBG as a covariate. LSM estimates at 40-weeks will be plotted by treatment and 7-points. In addition to the analyses on each of the 7-points, similar analyses will be done for the 2-hour morning, midday, and evening meal excursions, the mean of all meals 2-hour excursion, the mean of all 7-point measurements, the mean of all pre-meal measurements, and the mean of all 2-hour postprandial measurements. |
| | Proportion of patients achieving weight loss of ≥5%, from baseline | 6.12.2.3 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate and baseline weight as a covariate |

| | | | |
|---|---|---|---|
| | Proportion of patients achieving weight loss of ≥10% from baseline | 6.12.2.3 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate and baseline weight as a covariate |
| | Proportion of patients achieving weight loss of ≥15% from baseline | 6.12.2.3 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate and baseline weight as a covariate |
| To compare tirzepatide 5 mg, 10 mg, and 15 mg to insulin glargine at 40 weeks | The various Diabetes Treatment Satisfaction Questionnaire change (DTSQc) scores (see Section 6.17.4 for more details). | 6.12.1.2 CCI [redacted] | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use baseline DTSQs score as a covariate. |
| **Exploratory Analyses** | | | |
| To compare tirzepatide 5 mg, 10 mg, and 15 mg with insulin glargine for the following: | Change from baseline in lipid parameters (total cholesterol, HDL, non-HDL, VLDL, TG). | 6.12.1.1 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use corresponding baseline lipid parameter as a covariate. |
| | Change from baseline in BMI. | 6.12.1.1 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use corresponding baseline BMI as a covariate. |
| | Change from baseline in waist circumference. | 6.12.1.1 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use corresponding baseline waist circumference as a covariate. |
| | Changes from baseline in the European Quality of Life – 5 dimensions (EQ-5D-5L) index and visual analog scale (VAS) scores. | 6.12.1.2 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use baseline EQ-5D-5L score as a covariate. |
| | Changes from baseline in the Impact of Weight on Self-Perceptions Questionnaire (IW-SP) scores. | 6.12.1.2 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use baseline IW-SP score as a covariate. |
| | Changes from baseline in the Ability to Perform Physical Activities of Daily Living (APPADL) scores. | 6.12.1.2 | Use baseline HbA1c strata as a fixed effect in place of baseline HbA1c as a covariate. Use baseline APPADL score as a covariate. |

| | | | |
|---|---|---|---|
| To compare tirzepatide 5 mg, 10 mg, and 15 mg with insulin glargine for the following: | Proportion of patients achieving an HbA1c target ≤6.5%, without weight gain (<0.1 kg), and without documented symptomatic hypoglycemia or severe hypoglycemia | 6.12.2.3 | Include baseline body weight as additional covariate |
| | Proportion of patients achieving an HbA1c target <7.0%, without weight gain (<0.1 kg), and without documented symptomatic hypoglycemia or severe hypoglycemia | 6.12.2.3 | Include baseline body weight as additional covariate |
| | Proportion of patients achieving an HbA1c target <=6.5%, without weight gain (<0.1 kg), and without clinically significant documented symptomatic hypoglycemia or severe hypoglycemia | 6.12.2.3 | Include baseline body weight as additional covariate |
| | Proportion of patients achieving an HbA1c target <7.0%, without weight gain (<0.1 kg), and without clinically significant documented symptomatic hypoglycemia or severe hypoglycemia | 6.12.2.3 | Include baseline body weight as additional covariate |
| | Proportion of patients achieving an HbA1c target <7.0%, weight loss >=5%, and without clinically significant documented symptomatic hypoglycemia or severe hypoglycemia | 6.12.2.3 | Include baseline body weight as additional covariate |

Abbreviations: HbA1c = hemoglobin A1c; QW = once-weekly.

## 6.13. Safety Analysis

Unless specified otherwise, safety assessments will be based on the SS ( Table GPHO.6.1). All events that occur between the date of first dose of study drug to the date of patient's safety follow-up visit or patient's end of study participation will be included, regardless of the adherence to study drug or initiation of rescue therapy. The events occurring on the day of the first dose of study medication will be counted as post-treatment. For assessing benefit and risk profile through 40-weeks, selected safety analyses will be conducted by utilizing safety data from first dose through the date of 40-week visit. Some safety analyses may be conducted after excluding data after the initiation of new antihyperglycemic therapy. Unless specified otherwise, statistical assessment of homogeneity of the distribution of categorical safety responses among treatment arms will be conducted using Fisher's exact test.

The mean change from baseline difference among treatment at all scheduled visits will be assessed via a MMRM using REML. The model will include country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), baseline concomitant oral antihyperglycemic medication, treatment group, visit, and treatment-by-visit interaction as fixed effects, and baseline value of the safety parameter as a covariate. To model the covariance structure within patients, the unstructured covariance matrix will be used. If this model fails to converge, the covariance structures will be tested in order specified in Section 6.12.1.1.

For selected safety parameters, time-to-first-event analysis via the cox-proportional hazards model may be conducted. Patients without the event will be censored at the end of study participation. For patients experiencing the event, the "time-to-first-event" will be the time (in days) from first dose to first occurrence of the event.

Where necessary, the rate of events will be analyzed using a generalized linear mixed-effects model assuming the number of events follow a negative binomial distribution, and with treatment as a fixed effect. The logarithm of days during the active treatment period will be adjusted as an offset to account for possible unequal treatment duration of follow-up between patients.

### *6.13.1. Adverse Events*

A TEAE is defined as an event that first occurred or worsened in severity after baseline. 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. Statistical comparisons will be applied at both the SOC and PT levels. Events will be ordered by decreasing frequency within SOC. For events that are sex-specific, the denominator and computation of the percentage will include only patients from the given sex.

An overview of the number and percentage of patients who experienced a TEAE, serious adverse event (SAE), died due to an AE, discontinued from study treatment, or study due to an AE, relationship to study drug, and outcome of AE, will be summarized by treatment.

The percentages of patients with TEAEs, overall and common (common TEAEs occurred in >=5% of patients before rounding), will be summarized by treatment using MedDRA PT. Events will be ordered by 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.

Patient narratives will be provided for all patients who experience any of the following "notable" events:

- Death
- SAE
- Permanent discontinuations of study or study treatment due to AE
- Pregnancy
- Adjudication Confirmed Major Adverse Cardiovascular Events
- Adjudication Confirmed Pancreatitis

#### 6.13.1.1. Deaths

A listing of all deaths will be provided. The listing will include patient identification including the treatment, site number, date of death, age at the time of enrollment, sex, 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), investigator reported cause of death, and CEC adjudicated cause of death.

#### 6.13.1.2. 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 follow-up will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

A listing of all SAEs will be provided. The listing will include treatment, patient identification including the site number, date of event, age at the time of enrollment, sex, 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.

#### 6.13.1.3. 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.

#### 6.13.1.4. Discontinuation from Study Drug Due to Adverse Event

The number and percentage of patients who prematurely discontinue 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 as well as on time to study drug discontinuation due to an AE.

### *6.13.2. Special Safety Topics*

#### 6.13.2.1. Hypoglycemic Events

Definitions of different categories of hypoglycemic events are included in Table GPHO.6.3.

**Table GPHO.6.3. Definitions of Hypoglycemic Event Categories**

| | Symptoms and/or Signs of Hypoglycemia | Blood Glucose Level |
|---|---|---|
| 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 documented symptomatic hypoglycemia | Yes | <54 mg/dL (3.0 mmol/L) |
| Clinically significant documented asymptomatic hypoglycemia | No | <54 mg/dL (3.0 mmol/L) |
| Clinically significant documented unspecified hypoglycemia | Unknown | <54 mg/dL (3.0 mmol/L) |

**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 an adverse event of special interest (AESI).

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

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

Statistical summaries and analyses will exclude hypoglycemic events occurring while on rescue therapy. For each of the aforementioned hypoglycemia categories, incidence as well as rate per patient year of exposure will be provided by treatment. A listing of hypoglycemic events occurring while on rescue therapy will also be provided.

For each of the hypoglycemia categories mentioned above, the incidence of any hypoglycemic event with blood glucose ≤70 mg/dL [3.9 mmol/L] or <54 mg/dL [3.0mmol/L]) will be analyzed using logistic regression with treatment, country, and baseline concomitant oral antihyperglycemic medication as fixed effects, and baseline HbA1c and rate of hypoglycemic events at baseline as covariates. The rate of hypoglycemic episodes will 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 country, baseline concomitant oral antihyperglycemic medication use, and treatment as a fixed effects and baseline HbA1c as a covariate. The logarithm of days during the active treatment period will be adjusted as an offset to account for possible unequal treatment duration of follow up between patients.

#### 6.13.2.2. Severe Persistent Hyperglycemia

A summary of initiation of rescue therapy in response to severe, persistent hyperglycemia will be provided by treatment. If there are asufficient number of episodes, time-to-first event analyses for the initiation of rescue therapy will be conducted by treatment using cox proportional regression model. A listing of patients who initiating rescue therapy will be provided.

#### 6.13.2.3. Pancreatitis

Summaries of adjudicated and investigator-reported pancreatic events will be provided by treatment. Determination of investigator-reported events will be through the predefined Standardized MedDRA Queries (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 an AESI.

##### *6.13.2.3.1. 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 pancreatic enzyme values exceeding the following thresholds will be provided by treatment, baseline pancreatic enzyme value (≤Upper Limit of Normal [ULN], >ULN), and nominal visit: (>1 to ≤ 3) × ULN, (>3 to ≤5) × ULN, (>5 to ≤10) × ULN, >10 × ULN.

Additionally, the number and proportion of patients with maximum postbaseline pancreatic enzyme values exceeding the following thresholds will be provided by baseline pancreatic enzyme value (<=ULN, >ULN) and treatment: (>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 (postbaseline measure/baseline measure) response variable and stratification factors, treatment, nominal visit, and treatment-by-nominal visit interaction as fixed effects, baseline value as a covariate

#### 6.13.2.4. Thyroid Safety Monitoring

Treatment-emergent thyroid malignancies and C-cell hyperplasia will be identified using predefined 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. Thyroid malignancies and C-cell hyperplasia will be considered AESIs.

##### *6.13.2.4.1. Calcitonin*

Observed calcitonin data will be summarized by treatment and nominal visit. Additionally, the number and proportion of patients with a calcitonin value exceeding the following thresholds will be provided by treatment, baseline calcitonin value (≤20 ng/L, >20 ng/L), nominal postbaseline visit, and postbaseline calcitonin categories: <=20 ng/L, >20 ng/L to <=35 ng/L, >35 ng/L to <=50 ng/L, >50 ng/L to <=100 ng/L, >100 ng/L.

Additionally, the number and proportion of patients with a maximum postbaseline calcitonin value exceeding the following thresholds will be provided by treatment and baseline calcitonin value (<=20 ng/L, >20 ng/L): <=20 ng/L, >20 ng/L to <=50 ng/L, >50 ng/L to <=100 ng/L, >100 ng/L.

#### 6.13.2.5. Malignancies

The AE database will be searched using predefined 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 an AESI.

#### 6.13.2.6. Major Adverse Cardiovascular Events (MACE)

Major adverse cardiovascular events reported by investigators are adjudicated by an independent clinical endpoint committee (CEC) in a blinded fashion. The major adverse cardiovascular events (MACE) events of special interest are: deaths due to CV 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).

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 adjudication-confirmed MACE will be considered an AESI.

#### 6.13.2.7. Arrhythmias and Cardiac Conduction Disorders

The AE database will be searched using predefined SMQs or MedDRA HLTs to identify events consistent with 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 arrhythmias and cardiac conduction disorders will be considered AESIs.

#### 6.13.2.8. Hypersensitivity Events

Hypersensitivity reactions and related information reported via the "Hypersensitivity and Anaphylactic Reactions" 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 CRF, only date (no time) information is collected. Events occurring 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 with decreasing frequency by treatment. The AE database will be searched using predefined 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 predefined SMQ searches will be considered AESIs.

#### 6.13.2.9. 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 location of the reaction, timing of the reaction relative to study drug administration, and characteristics of the injection site reaction: erythema, induration, pain, pruritus, and edema.

Additionally, injection site reactions will be reported by PT within MedDRA HLTs of injection site reactions and 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 within each HLT category. Only severe/serious injection site reactions will be considered AESIs.

#### 6.13.2.10. 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 TE ADA to tirzepatide 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 reactions by TE ADA status will be tabulated if warranted by the data.

A listing may be provided of all immunogenicity assessments for those patients who at any time had detected Tirzepatide Anti-Drug antibodies. This includes the tirzepatide concentration from a simultaneous PK sample, and the clinical interpretation result.

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 ADAs that are associated with AEs of either severe/serious hypersensitivity or severe/serious injection site reactions will be classified as AESIs.

#### 6.13.2.11. 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 PTs defined in searching criteria in Appendix 1 will be considered AESIs and summarized.

#### 6.13.2.12. Hepatobiliary Safety

##### *6.13.2.12.1. Hepatobiliary 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 AESIs.

##### *6.13.2.12.2. Acute Gallbladder Disease*

The AE database will be searched using predefined SMQs to identify events consistent with acute gallbladder diseases. Detailed searching criteria 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 AESIs.

##### *6.13.2.12.3. Liver Enzymes*

Analyses for laboratory analyte measurements are described in Section 6.16. This section describes additional analyses of liver enzymes. In addition, the following will be provided by treatment group:

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

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

#### 6.13.2.13. Gastrointestinal Safety

The time courses of prevalence and incidence (newly occurring episodes) of nausea, vomiting, diarrhea, and combined will be plotted by treatment and maximum severity.

The maximum severity and duration of treatment-emergent nausea, vomiting, diarrhea, 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. Preferred Terms with severe/serious cases in the gastrointestinal SOC will be considered AESIs.

#### 6.13.2.14. Acute Renal Events

Laboratory measures related to renal safety will be analyzed as specified for laboratory measurements in Section 6.16.

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 unit ml/min/1.73m$^2$, using categories (<30, ≥ 30-to 45, ≥45- to <60, ≥60 to <90, and ≥90 mL/min/1.73m2). 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).

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 AESIs.

#### 6.13.2.15. Dehydration

The AE database will be searched using an 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 AESIs.

#### 6.13.2.16. 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 an AESI.

#### 6.13.2.17. Amputation/Peripheral Revascularization

The AE database will be searched using MedDRA PT to identify events consistent with amputation or peripheral revascularization. The incidence of the resulting TEAEs will be summarized by treatment and PT. Amputation/peripheral revascularization will be considered an AESI.

#### 6.13.2.18. Major Depressive Disorder or Suicidal Ideation or Behavior

The AE database will be searched using MedDRA PT 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 an AESI.

#### 6.13.2.19. Treatment of Overdose

A listing of patients reporting overdosing of tirzepatide will be provided.

## 6.14. 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.

A MMRM using REML will be used to fit the changes from baseline in vital signs at all scheduled postbaseline visits. The model will include country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), baseline concomitant oral antihyperglycemic medication (metformin alone vs metformin plus SU), treatment group, visit, 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. If this model fails to converge, the covariance structures will be tested in order specified in Section 6.12.1.1.

Counts and percentages of patients with 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 GPHO.6.4.

**Table GPHO.6.4. 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 |

## 6.15. Electrocardiograms

Summary statistics by treatment and by nominal visit will be provided for electrocardiogram (ECG) parameters (heart rate, PR, QRS, QT, and QT corrected using Fridericia's correction factor [QTcF]). When the QRS is prolonged (for example, a complete bundle branch block), QT and QTc should not be used to assess ventricular repolarization. Thus, for a particular ECG, the following will be set to missing (for analysis purposes) when QRS is ≥120 msec: QT and QTcF.

The criteria for identifying patients with treatment-emergent quantitative ECG abnormalities is based on Table GPHO.6.5. Selected Categorical Limits for ECG Data

| | Low | | High | |
|---|---|---|---|---|
| **Parameter** | **Males** | **Females** | **Males** | **Females** |
| Heart Rate (bpm) | <50 and decrease ≥15 | <50 and decrease ≥15 | >100 and increase ≥15 | >100 and increase ≥15 |
| PR Interval (msec) | <120 | <120 | ≥220 | ≥220 |
| QRS Interval (msec) | <60 | <60 | ≥120 | ≥120 |
| QTcF (msec) | <330 | <340 | >450 | >470 |

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In addition, the percentage of patients with QT greater than 500 msec will be summarized, and the percentage of patients with QTcF greater than 500 msec will be summarized.

The percentage of patients who experienced a treatment-emergent increase from baseline in QTcF interval of greater than 30 msec, 60 msec, or 75 msec at any time will be summarized. The maximum value during the study follow up will be analyzed. Planned and unplanned measurements will be included.

Treatment-emergent qualitative ECG abnormalities are defined as qualitative abnormalities that first occurred after baseline. A listing of abnormal qualitative ECGs will be created.

**Table GPHO.6.5. Selected Categorical Limits for ECG Data**

| | Low | | High | |
|---|---|---|---|---|
| **Parameter** | **Males** | **Females** | **Males** | **Females** |
| Heart Rate (bpm) | <50 and decrease ≥15 | <50 and decrease ≥15 | >100 and increase ≥15 | >100 and increase ≥15 |
| PR Interval (msec) | <120 | <120 | ≥220 | ≥220 |
| QRS Interval (msec) | <60 | <60 | ≥120 | ≥120 |
| QTcF (msec) | <330 | <340 | >450 | >470 |

## 6.16. Clinical Laboratory Evaluation

All laboratory data will be reported in the International System of Units. Selected laboratory measures will also be reported using 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.

Observed and change from baseline values for each visit will be displayed in box plots for patients who have both a baseline and a postbaseline planned measurement. Unplanned measurements will be excluded from box plots.

A shift table will be provided including 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. The proportion of patients shifted will be compared between treatments using Fisher's exact test.

For qualitative laboratory analytes, the number and percentage of patients with normal and abnormal values will be summarized by treatment.

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

## 6.17. Health Outcomes

The patient-reported outcome questionnaires will be completed by the patients at baseline and at 40 weeks (or early termination visit prior to 40 weeks). These include use of the mITT population on the EAS and use of a 2-sided alpha level of 0.05 and a 2-sided 95% CI for pairwise comparisons.

No multiplicity adjustment will be made in the evaluation of health outcome measures. Item-level missingness is dealt with as per instrument developers' instruction.

### *6.17.1. EQ-5D-5L*

Each item will be summarized descriptively by treatment at each scheduled visit at which the EQ-5D-5L is administered. The changes from baseline to week 40 (last observation carried forward [LOCF]) in the index and Visual Analog Scale (VAS) scores will be analyzed using an ANCOVA model with model terms of treatment, country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and baseline concomitant oral antihyperglycemic medication use (metformin alone vs metformin plus SU) as fixed effects, and baseline EQ-5D-5L score as a covariate.

### *6.17.2. Impact of Weight on Self-Perceptions Questionnaire*

Descriptive summaries by treatment at each scheduled visit at which the IW-SP is administered will be presented for each item. Treatment comparisons of the raw and transformed overall IW-SP score changes from baseline to week 40 (LOCF) will be analyzed using an ANCOVA model with model terms of treatment, country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and baseline concomitant oral antihyperglycemic medication use (metformin alone vs metformin plus SU) as fixed effects, and baseline IW-SP score as a covariate.

### 6.17.3. Ability to Perform Physical Activities of Daily Living

Descriptive summaries by treatment at each scheduled visit at which the APPADL is administered will be presented for each item. Treatment comparisons of the raw and transformed overall APPADL score changes from baseline to week 40 will be analyzed using an ANCOVA model with model terms of treatment, country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and baseline concomitant oral antihyperglycemic medication use (metformin alone vs metformin plus SU), and baseline APPADL score as a covariate.

### 6.17.4. Diabetes Treatment Satisfaction Questionnaire

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) contains 8 items (conceptually the same items in the status [DTSQs] and change [DTSQc] versions). Six items (1, and 4 through 8) are summed to produce a measure of treatment satisfaction and the 2 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 40 or early termination.

Descriptive summaries will be provided at baseline (DTSQs only) and at 40 weeks (DTSQc only) for the perceived hyperglycemia item, perceived hypoglycemia item, and 6-item overall satisfaction score

Treatment comparisons in the DTSQc at week 40 will be analyzed using an ANCOVA model with model terms of treatment, country, baseline HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and baseline concomitant oral antihyperglycemic medication use (metformin alone vs metformin plus SU) as fixed effects and baseline DTSQs score as a covariate. The analyses will be conducted for the perceived hyperglycemia item, perceived hypoglycemia item, and 6-item overall satisfaction score.

## 6.18. Subgroup Analyses

Efficacy subgroup analyses will be conducted on EAS. Safety subgroup analyses will be conducted on SAS.

Subgroup analyses may be done by country to support local regulatory registrations. Subgroups with few subjects may be excluded from subgroup analyses when appropriate.

### 6.18.1. Subgroup Analysis of HbA1c change at 40-week

Subgroup analyses by the following baseline characteristics will be provided: age group (<65, ≥65 years), gender, geographic region (China vs non-China), duration of diabetes (<median, ≥median), baseline HbA1c (≤8.5%, >8.5%), type of antihyperglycemic medication use (metformin alone, metformin plus SU), renal impairment (eGFR<60, >=60), body mass index (BMI) group (<28, >=28),

### 6.18.2. Subgroup Analysis of Weight Change at 40-week

Subgroup analyses by the following baseline characteristics will be provided: age group (<65, ≥65 years), gender, geographic region (China vs non-China), duration of diabetes (<median, ≥median), baseline HbA1c (≤8.5%, >8.5%), type of antihyperglycemic medication use

(metformin alone, metformin plus SU), renal impairment (eGFR<60, >=60), BMI group (<28, >=28).

### 6.18.3. Subgroup Analysis of TEAE Through Safety Follow-up

Subgroup analyses by the following baseline characteristics will be provided: age group (<65, ≥65 years), age group (<75, ≥75 years), gender, renal impairment (eGFR<60, >=60), BMI group (<28, >= 28).

### 6.18.4. Subgroup Analysis of Hypoglycemic events

Subgroup analyses of hypoglycemic events categories defined in Table GPHO.6.3 by baseline OAM use (Metformin, Metformin plus SU) will be provided. Analysis will be conducted in safety analysis set but exclude hypoglycemic events occurring after initiation of a new antihyperglycemic therapy.

Other exploratory subgroup analyses may be performed as deemed appropriate

## 6.19. Interim Analyses and Data Monitoring Committee

No interim analyses and data monitoring committee are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

## 6.20. COVID impact Assessment

This section lists the potential statistical analyses that may be performed to assess the impact of the COVID-19 pandemic when appropriate.

### 6.20.1. Patients Impacted by COVID-19

A listing of patients impacted by COVID-19 will be provided. The listing will include patient identification, treatment, date of impact, and description of impact.

### 6.20.2. Adverse Events

A summary table for patients with AEs related to COVID-19, including death due to COVID-19, COVID-19 SAEs, and COVID-19 AEs, will be provided by study treatment.

### 6.20.3. Patient Disposition

Patient disposition with reasons related to COVID-19 (such as, COVID-19 AE, patient decision, etc.) will be summarized for study and study treatment discontinuation by treatment group.

### 6.20.4. Study Visits

A summary of patients with study visits impacted by COVID-19 will be provided by treatment group. In this table, the number and proportion of patients missing study visits, including the primary endpoint visit, and having virtual visits will be summarized.

### 6.20.5. Mitigation Summary

A summary table for patients having protocol deviations and mitigations due to COVID-19 (such as missing study visit) will be provided by treatment group. An additional summary may be provided by country of enrollment and treatment group.

### 6.20.6. Measures Related to Primary and Key Secondary Objectives

Patients missing measures (HbA1c and body weight) related to primary and key secondary objectives will be summarized by visit and treatment group.

# 7. Unblinding Plan

Not applicable. GPHO is an open label trial. To minimize bias, review of summary data by the Lilly study team (i.e., CRP/CRS overseeing the global conduct of the study, statisticians, and statistical analysts) prior to the final database lock of the study (at the end of 40 weeks of treatment) will remain blinded to treatment assignment.

# 8. References

Protocol I8F-MC-GPHO (a) Efficacy and Safety of tirzepatide Once Weekly versus Titrated insulin glargine in Patients with Type 2 Diabetes on Metformin with or without a Sulfonylurea (SURPASS-AP-COMBO).

Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons Inc.; 1987.

# Appendix 1. Searching Criteria for Adverse Events of Special Interest

The AESI analyses are detailed in Section 6.13.2. The search criteria for each AESI are stored in CLUWE: T:\qa\ly3298176\common\AESI_Lab\AESI_TZP.xlsx.

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