Statistical Analysis Plan Version 3 J2A-MC-GZGE

A Phase 2 Study of Once-Daily LY3502970 Compared with Placebo and Once-Weekly Dulaglutide in Participants with Type 2 Diabetes Mellitus

NCT05048719

Approval Date: 24-Oct-2022

Statistical Analysis Plan (J2A-MC-GZGE): A Phase 2 Study of Once-Daily LY3502970 Compared with Placebo and Once-Weekly Dulaglutide in Participants with Type 2 Diabetes Mellitus

Protocol Title: A Phase 2 Study of Once-Daily LY3502970 Compared with Placebo and Once-Weekly Dulaglutide in Participants with Type 2 Diabetes Mellitus

Protocol Number: J2A-MC-GZGE

Amendment Number: a

Compound: LY3502970

Brief Title: Effect of LY3502970 Versus Placebo and Dulaglutide in Participants with Type 2 Diabetes Mellitus

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 142842

EudraCT: 2021-002806-29

Document ID: VV-CLIN-074813

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Version History

Statistical Analysis Plan (SAP) Version 1 for Study J2A-MC-GZGE (GZGE) was approved on 10 January 2022 and is based on the protocol amendment (b) dated 27 October 2021.

SAP Version 2 was approved prior to the interim analysis after all participants complete Visit 12 (Week 16) of the treatment period dated 04 August 2022. The main changes are summarized below:

- Changed wording in the post-baseline observation for the logistic regression "efficacy estimand" to clarify that only Visit 15 will be modelled
- Further clarified the hybrid estimand description and method
- Updated the "Treatment Discontinuation Reasons" table to match that of current CRF
- Clarified analyses for the pancreatic enzymes
- Updated shift table categories for hepatic biomarkers ALT.
- Removed "Period A" and "Period B" analyses related to hypersensitivity events since we did not collect when the event occurs relative to dose
- Removed two listings related to COVID 19 pandemic
- Updated variables used in the demographics table
- Included "Percentage of participants with HbA1c ≤5.7% at Week 26" and "Percentage of participants with ≥15% body weight loss from baseline at Week 26" in the Exploratory Analyses
- Clarified that mechanistic biomarkers analyses will be conducted through MMRM for hepatic biomarkers (Cytokeratin 18 and Pro-C3).
- Added "constipation medication" to the concomitant medication list

SAP Version 3 was approved prior to the final analysis after all participants completed Visit 15 (Week 26) of the treatment period and safety follow-up. The main changes are summarized below:

- Added Chi-Square tests when Fisher's exact fails and Updated "Changes to Protocol" section to "None", per this change
- Added additional exploratory analyses:
    - Kaplan-Meier plot of time to initially achieve body weight loss of ≥5% and ≥10%
    - Change from baseline in fasting lipids at Week 26
- Added ECG MMRM analyses for heart rate and PR interval.
- Updated liver enzyme categories based on the most recent standard
- Added Abuse Liability section and analyses
- Clarified the limitations in the planned Bayesian model for long-term prediction due to the study design. Added that additional modelling will be explored for better long-term prediction.

1. Introduction

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that at least one dose level of QD oral doses of LY3502970 is superior in change from baseline for HbA1c relative to placebo at Week 26, in participants with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.	• Difference between LY3502970 and placebo in change from baseline in HbA1c at Week 26
Secondary	
To compare the effect of QD LY3502970 versus placebo and versus dulaglutide on glucose control at Week 26	• Difference between LY3502970 and dulaglutide in change from baseline in HbA1c at Week 26 • Percentage of participants with HbA1c ≤6.5% and of <7.0% at Week 26 • Change from baseline in fasting blood glucose at 26 weeks
To compare the effect of QD LY3502970 versus placebo and versus dulaglutide on body weight at Week 26	• Change from baseline in body weight at Week 26 • Percent change in body weight from baseline at Week 26 • Percentage of participants with ≥5%, ≥10% body weight loss from baseline at Week 26
To assess safety and tolerability of LY3502970	• Adverse events overall • Adverse events of special interest • Laboratory parameters • Electrocardiogram • Vital signs
To assess the PK of LY3502970 and potential participant factors that may influence its PK	• Population PK Parameters
Exploratory	
To assess the relationship between QD LY3502970 dose and/or exposure and key efficacy and safety measures and potential participant factors that may influence these relationships	• Dose-response and concentration-response analyses for key efficacy and safety parameters
To evaluate the effect of QD LY3502970 versus placebo and versus dulaglutide on body weight as measured by BMI and waist circumference at Week 26	• Change from baseline in BMI at 26 weeks • Change from baseline in waist circumference at 26 weeks
To evaluate the effects of QD LY3502970 versus placebo and versus dulaglutide on 7-point SMBG profile	• Change from baseline in 7-point SMBG values at Week 26

Objectives	Endpoints
Exploratory	
To evaluate the effects of QD LY3502970 versus placebo and versus dulaglutide on biomarkers	• Change from baseline in mechanistic biomarkers at Week 26
To evaluate the effects of QD LY3502970 versus placebo and versus dulaglutide on patient-reported outcomes • Health-related quality of life • Diabetes treatment satisfaction • Participant experience	• Change from baseline in SF-36v2 acute form domains and summary scores at Week 26 • Change from baseline in DTSQs at Week 26 • Actual responses to DTSQc at Week 26 • Summary statistics of actual responses to Participant survey at Week 26

Abbreviations: BMI = body mass index; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change Version; DTSQs = Diabetes Treatment Satisfaction Questionnaire-Status Version; HbA1c = hemoglobin A1c; PK = pharmacokinetics; QD = once daily; SF-36v2 = Short Form 36 version 2 health survey acute form; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus.

Primary Estimand

The primary clinical question of interest is: What is the treatment difference in hemoglobin A1c (HbA1c) change from baseline after 26 weeks of treatment in participants who meet the inclusion criteria and would have completed the treatment period without additional anti-hyperglycemic rescue medication?

The "efficacy estimand" is described by the following attributes:

- Population: participants who meet the inclusion criteria. Further details can be found in Section 5 and Section 9 of the Study Protocol J2A-MC-GZGE (a).
- Endpoint: change from baseline in HbA1c at Week 26.
- Treatment condition: the randomized treatment with allowance for down-titration based on gastrointestinal (GI) tolerability.

The two intercurrent events "permanent discontinuation of study drug" and "initiation of rescue medication" are handled by the hypothetical strategy and the potential outcome of interest is the response in the efficacy measurement if participants had adhered to the randomized treatment without using additional anti-hyperglycemic rescue medication. There are no other defined intercurrent events. Down-titration will not be considered as intercurrent events for the definition of estimand in this study.

Population-level summary: difference in mean changes in HbA1c at Week 26 between once daily (QD) LY3502970 and placebo.

Rationale for "efficacy estimand": This Phase 2 study aims to study the efficacy of LY3502970 under the ideal condition that all participants adhere to the randomized treatment without using additional anti-hyperglycemic rescue medication.

Estimand(s) for Secondary Objectives

The same estimand for the primary objective will be used for the following efficacy endpoints for the secondary objectives:

- Change from baseline in HbA1c at Week 26 (LY3502970 vs dulaglutide)
- Percentage of participants with HbA1c ≤6.5% and of <7.0% at Week 26
- Change from baseline in fasting blood (serum) glucose (FSG) at 26 weeks
- Change from baseline in body weight at Week 26
- Percent change in body weight from baseline at Week 26
- Percentage of participants with ≥5%, ≥10% body weight loss from baseline at Week 26

Unless specified otherwise, safety and tolerability assessments will be guided by an estimand comparing safety of LY3502970 doses with placebo and dulaglutide for the entire study period (the treatment period plus safety follow-up period) irrespective of adherence to study intervention for all study population (including inadvertently enrollment).

Supplemental Estimand(s) for Primary Efficacy Endpoint

An alternative estimand, called "hybrid estimand", is the mean treatment difference in HbA1c from baseline at 26 weeks between LY3502970 and placebo in participants who meet the inclusion criteria with intercurrent events handled differently according to the reasons for the events:

- Category 1: The intercurrent events of permanent discontinuation of study drug due to reasons unlikely related to the efficacy/safety outcomes will be handled by the hypothetical strategy.
- Category 2: The intercurrent events of permanent discontinuation of study drug due to lack of efficacy or use of rescue medication before study treatment discontinuation will be handled by the hypothetical strategy.
- Category 3: All other intercurrent events will be handled by the treatment policy strategy.

Population-level summary: difference in mean changes in HbA1c at Week 26 between QD LY3502970 and placebo.

Rationale for "hybrid estimand": Following the International Conference on Harmonization (ICH) E9 (R1) guidance on estimands, this Phase 2 study will collect informative treatment disposition reasons and intercurrent events will be handled differently according to the reasons of intercurrent events for this supplemental estimand.

Further details can be found in Section 4.3.3.

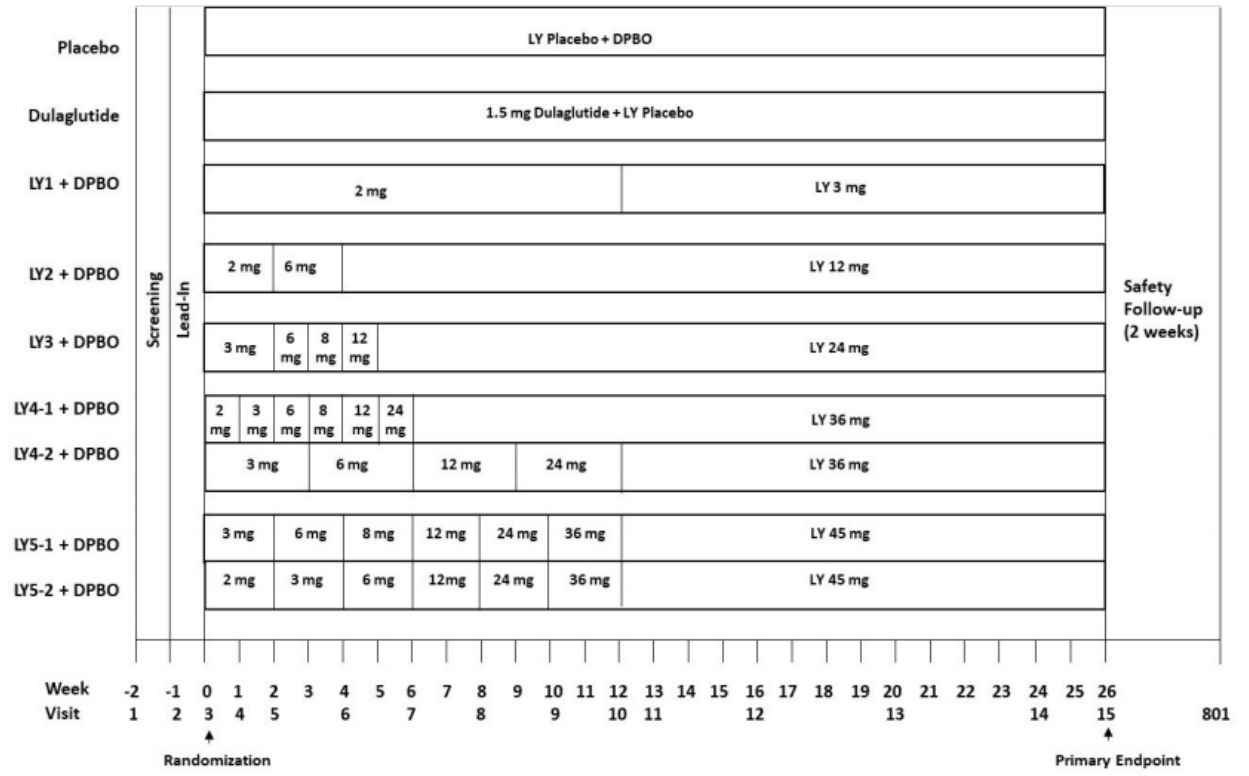
1.2. Study Design

Study GZGE is a Phase 2, multicenter, randomized, double-blinded, parallel, placebo- and active comparator (1.5 mg dulaglutide once weekly) -controlled 26-week study, to investigate the safety and efficacy of LY3502970 in participants with type 2 diabetes mellitus (T2DM) who failed to achieve adequate glycemic control on diet and exercise alone or on a stable dose of metformin for at least 3 months prior to Visit 1. The duration of study participation for each participant will be approximately 30 weeks. The study will consist of an approximately 2-week screening/lead in

period followed by a 26-week treatment period. There will also be a 2-week off-drug safety follow-up period.

Participants will be randomly assigned to study intervention in a randomization ratio of 5:5:5:5:5:3:3:3:3, including 50 participants per treatment group to placebo, dulaglutide, LY1, LY2 and LY3 treatment groups, and 30 participants per treatment group to the LY4-1, LY4-2, LY5-1, and LY5-2 treatment groups. This is a double-blind study. All participants will take daily oral blinded study drug and weekly subcutaneously injected blinded study drug. Participants will not know if they are receiving active or matching placebo oral study drug or active or matching placebo injectable study drug. Stratification will be by country and HbA1c stratum (≤8.0%, >8.0%) at Visit 1.

Figure 1.1 illustrates the study design.



Abbreviations: DPBO = dulaglutide placebo; LY = LY3502970; LY1 = LY 3 mg; LY2 = LY 12 mg; LY3 = LY 24 mg; LY4 = LY 36 mg; LY5 = LY45 mg.

Figure 1.1 Illustration of study design for clinical protocol GZGE.

Dose Modification

Participants who do not tolerate the first capsule dose escalation, in other words from 2 mg or 3 mg to 6 mg (or placebo equivalent), will need to discontinue from study treatment. If a participant does not tolerate a dose level higher than 6 mg for 1 week (for example, moderate-to-severe nausea, vomiting, or diarrhea) and the investigator does not believe that the participant will tolerate the dose with further exposure, then the investigator may reduce the dose to the next lower target dose (for example, 3 mg, 12 mg, 24 mg, or 36 mg). If this dose is tolerated after 2 weeks, the dose should be increased per original protocol dose escalation until the target dose is achieved. If this dose escalation is not tolerated, the dose should be reduced to the next lower target dose that was tolerated (for example, 3 mg, 12 mg, 24 mg, or 36 mg). The participant will remain at that dose level for the duration of the study. Maintenance doses of 2 mg, 6 mg, or 8 mg will not be allowed. The injectable study treatment should be maintained during dose modification of the capsule treatment. Participants who do not tolerate the injectable study treatment, such as participants who have moderate to severe nausea and/or vomiting following 2 injections (2 weeks of treatment) and the investigator believes the participant will not tolerate the injectable treatment with further dosing will need to discontinue the injectable study treatment. The participant should continue taking the capsule study treatment. To maintain blinding to study drug, the site should contact the Interactive Web Response System (IWRS) help desk for next steps.

Temporary Discontinuation

After randomization, the investigator may interrupt study drug, for example, due to an adverse event (AE) (for example, nausea of moderate severity or vomiting), or a clinically significant laboratory value. If study drug interruption is due to an AE, the event is to be followed and documented. Every effort should be made by the investigator to maintain participants in the study and to restart study drug promptly after any interruption, as soon as it is safe to do so (see following paragraph for restarting study drug). The dates of study drug interruption and restart must be documented. The data related to interruption of study treatment will be documented in source documents and entered on the electronic case report form (eCRF).

Restarting Study Drug after Interruption

If the number of consecutive missed capsule doses is ≤7, the treatment can be restarted at the same dose. Participants who have missed >7 days of capsule study drug will need to restart the study drug at the 8-mg dose (LY3502970 treatment groups 2, 3, 4-1, 4-2, 5-1, and 5-2) and dose escalate according to the protocol. LY3502970 treatment group 1 (2/3 mg group) will restart study drug at 3 mg and remain at that level for the duration of the study. To maintain blinding of the investigator and participant, the investigator should call the IWRS to explain that the participant needs the dose reduced or is restarting study drug and IWRS will provide dispensing information. Dose reductions may occur at unscheduled visits.

Participants who have missed any amount of injectable study drug may restart the injectable study drug at any time. There is no dose escalation procedure associated with the injectable study drug.

The investigator will use the IWRS to receive the appropriate study drug dispensing information to preserve blinding of the study drug.

2. Statistical Hypotheses

The study hypothesis for the primary objective is that at least one dose level of QD oral doses of LY3502970 is superior in change from baseline for HbA1c relative to placebo at Week 26 in participants with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin. Thus, the null hypothesis corresponding to the primary estimand is as follows:

- Null hypothesis: No dose level of QD oral doses of LY3502970 is different from placebo in change from baseline for HbA1c at Week 26, in participants with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.

2.1. Multiplicity Adjustment

Treatment comparisons will be performed for the primary objective at the full significance level of 0.05. No multiplicity adjustments will be made for the analyses of secondary and exploratory objectives.

Approved on 24 Oct 2022 GMT

3. Analysis Sets

For the purposes of analysis, the following analysis population and datasets are defi*ned:*

Participant Analysis Population/Datasets	**Description**
Entered Participants	All participants who sign informed consent.
Randomized	All participants who are randomly assigned a study drug.
Efficacy Analysis Set (EAS)	Data obtained during the treatment period from all randomized participants who are exposed to at least 1 dose of study drug. Excludes data after permanent discontinuation of study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomly assigned.
Full Analysis Set (FAS)	Data obtained during the treatment period from all randomized participants who are exposed to at least 1 dose of study drug, regardless of adherence to study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomly assigned.
Safety Analysis Set (SS)	Data obtained during the treatment period plus safety follow-up from all randomized participants who are exposed to at least 1 dose of study drug, regardless of adherence to study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomly assigned.

Note: Inadvertently enrolled participants who are discontinued from the study due to deviation from inclusion/exclusion criteria will not be included for efficacy analyses but will be included for all other analyses.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data (for example, too few events to justify conducting an analysis). Additional analyses of the data may be conducted as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

Unless stated otherwise, statistical summaries and analyses will be conducted based on planned randomized treatment group (placebo, dulaglutide, LY1, LY2, LY3, LY4-1, LY4-2, LY5-1, or LY5-2), regardless of the actual treatment(s) received by the participant due to any dose modification. The evaluation of the efficacy and safety endpoints for LY4 (36 mg) and LY5 (45 mg) compared with placebo or dulaglutide will be made by pooling two dose escalation regimens, that is, combine LY4-1 and LY4-2 for LY4, and combine LY5-1 and LY5-2 for LY5. Therefore, the statistical comparisons between treatment groups covers the following:

1) between each of LY3502970 treatment groups (LY1, LY2, LY3, LY4, or LY5) and placebo,
2) between each of LY3502970 treatment groups (LY1, LY2, LY3, LY4, or LY5) and the dulaglutide treatment group,
3) between the dulaglutide treatment group and placebo.

In addition, to better understand the tolerability of LY3502970, statistical summary will be provided between the 2 dose escalation regimens with a maintenance dose of 36 mg or 45 mg on endpoints regarding GI reactions.

The primary estimand (a precise definition of the treatment effect to be estimated) of interest in comparing efficacy of LY3502970 doses with placebo is the “efficacy estimand” (Section 1.1). The primary efficacy assessment, guided by the “efficacy estimand” will be conducted using the Efficacy Analysis Set (EAS) (Section 3). A restricted maximum likelihood-based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment group (placebo, dulaglutide, LY1, LY2, LY3, LY4-1, LY4-2, LY5-1, LY5-2), strata (country, baseline HbA1c stratum [≤8%, >8%]), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on least squares (LS) means and Type III tests. If this analysis fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Compound symmetry with heterogeneous variances
- Toeplitz

- Autoregressive
- Compound symmetry without heterogeneous variances

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3502970 doses with placebo and dulaglutide irrespective of adherence to study drug. Thus, safety analyses will be conducted using the Safety Analysis Set (SS).

For continuous measures, summary statistics will include sample size, mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. LS means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons. All baseline measures will be analyzed using an analysis of variance model that has treatment group as the model term.

For categorical measures, summary statistics will include sample size, frequency, and percentages. A logistic regression model will be used to examine the treatment difference in binary efficacy outcomes. Fisher's exact test (or Chi-square test where Fisher's exact test fails) will be used for treatment comparisons in other categorical outcomes.

For laboratory values, both conventional (CN) and Systeme International (SI) units will be presented. Therefore, both % and mmol/mol will be presented for HbA1c and both mg/dL and mmol/L will be presented for glucose measurements. For body weight, kilogram (kg) will be presented.

Details about the analyses regarding demographic and baseline characteristics, historical illnesses and pre-existing conditions, treatment compliance, concomitant medications and important protocol deviations can be found in Appendices 1-5 (Section 7.1 through Section 7.6), respectively.

Baseline is defined as the last non-missing measurement (including both scheduled and unscheduled visits) at or before randomization visit (prior to first dosing of study drug) unless otherwise specified. For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early termination visit that do not correspond to the planned collection schedule will be excluded from the MMRM, ANCOVA or logistic regression analysis.

Table 4.1 summarizes the rules for determining the estimand, analysis set, baseline and postbaseline observations by study period and type of analysis.

Table 4.1. Baseline, Postbaseline Definitions, Analysis Set and Estimand by Study Period and Type of Analysis

Study Period/Analysis Type (Estimand)	Analysis Set	Baseline Observations	Postbaseline Observations
26-Week Treatment Period			
HbA1c MMRM ("efficacy estimand")	EAS	Last of Visits 1 to 3	Visits 6, 8, 10, 12, 13, and 15 prior to any ICEs
HbA1c ANCOVA ("hybrid estimand")	FAS	Last of Visits 1 to 3	Visit 15, with missing values or observed values at the visit that are collected after ICEs handled as described in Section 4.3.3
HbA1c categorical analyses logistic regression ("efficacy estimand")	EAS	Last of Visits 1 to 3	Visit 15, with missing values imputed using non-missing data from Visits 6, 8, 10, 12, 13, and 15 prior to any ICEs
HbA1c categorical analyses logistic regression ("hybrid estimand")	FAS	Last of Visits 1 to 3	Visit 15, with missing values or observed values at the visit that are collected after ICEs handled as described in Section 4.3.3 and Section 4.4.1.1
Fasting blood (serum) glucose MMRM ("efficacy estimand")	EAS	Last of Visits 1 to 3	Visits 6, 8, 10, 12, 13 and 15 prior to any ICEs
Fasting blood (serum) glucose ANCOVA ("hybrid estimand")	FAS	Last of Visits 1 to 3	Visit 15, with missing values or observed values at the visit that are collected after ICEs handled as described in Section 4.3.3
Body Weight and BMI MMRM ("efficacy estimand")	EAS	Last of Visits 1 to 3	Visits 4-15 prior to any ICEs
Body Weight and BMI ANCOVA ("hybrid estimand")	FAS	Last of Visits 1 to 3	Visit 15, with missing values or observed values at the visit that are collected after ICEs handled as described in Section 4.3.3
Body Weight categorical analyses logistic regression ("efficacy estimand")	EAS	Last of Visits 1 to 3	Visit 15, with missing values imputed using non-missing data from Visits 4-15 prior to any ICEs
Body Weight categorical analyses logistic regression ("hybrid estimand")	FAS	Last of Visits 1 to 3	Visit 15, with missing values or observed values at the visit that are collected after ICEs handled as described in Section 4.3.3 and Section 4.4.1.1
26-Week Treatment Period			
Waist Circumference MMRM ("efficacy estimand")	EAS	Last of Visits 1 to 3	Visits 6, 8, 10, 13 and 15 prior to any ICEs
Seven-point SMBG MMRM ("efficacy estimand")	EAS	Visit 3 prior to first dose of randomized study drug	Visits 6, 10, 13 and 15 prior to any ICEs

Study Period/Analysis Type (Estimand)	Analysis Set	Baseline Observations	Postbaseline Observations
Population PK parameters (N/A)	FAS	N/A	Predose at Visits 8, 10, and 15 Postdose at Visits 6, 8, 12, 13 and ET.
Patient-reported outcomes: SF-36v2 and DTSQs MMRM ("efficacy estimand")	EAS	Visit 3	Visits 12 and 14 prior to any ICEs
Patient-reported outcomes: DTSQc MMRM ("efficacy estimand")	EAS	N/A	Visits 12 and 14 prior to any ICEs
Patient-reported outcomes: Participant Survey Statistical Summary ("efficacy estimand")	EAS	N/A	Visit 14 prior to any ICEs
Hypoglycemia events ("efficacy estimand")	EAS	Visit 3	All Visits 4-15 prior to any ICEs
26-Week Treatment Period (including Safety Follow-Up Visit)			
1.1) Treatment-Emergent Adverse Events	SS	The baseline period is defined as the start of screening and ends prior to the first dose of study drug (or prior to Visit 3 date if first dose date is missing).	Starts after the first dose of study drug and ends at the end of the study period (including off-drug follow up visit).
1.2) Treatment-Emergent Abnormal Labs, Vital Signs, and ECGs	SS	Baseline will be all scheduled and unscheduled measurements recorded during the baseline period as defined above (1.1).	Postbaseline will be defined as above (1.1). All scheduled and unscheduled measurements will be included.
1.3) Change from Last Baseline to Week *xx* and to Last Postbaseline for Labs, Vital Signs, and ECGs	SS	The last scheduled non-missing assessment recorded prior to the date of first dose of study treatment during the baseline period defined above (1.1).	Postbaseline will be defined as above (1.1). Only scheduled visits will be included. The ET visits are considered scheduled visits.

Abbreviations: ANCOVA = analysis of covariance ; BMI = body mass index; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change Version; DTSQs = Diabetes Treatment Satisfaction Questionnaire-Status Version; EAS = Efficacy Analysis Set; ECG = electrocardiogram; ET = early termination; FAS = Full Analysis Set; HbA1c = hemoglobin A1c; ICEs = intercurrent events; MMRM = mixed-effect model repeated measures; N/A = Not Applicable; PK = pharmacokinetic; SF-36 v2 acute form = Short Form 36 version 2 health survey acute form; SMBG = self-monitoring of blood glucose; SS = Safety Analysis Set; TEAE = treatment-emergent adverse event.

Notes: If a participant ED from the study drug, no further PK samples will be collected following ED PK sample. Therefore, FAS for PK parameters only includes data that are collected while participant is on study drug, but regardless of rescue therapy.

4.2. Participant Dispositions

A listing of study disposition for all randomized participants will be provided. Summaries of study disposition and study drug disposition for all randomized participants will be provided by treatment groups.

Kaplan-Meier plots of time from randomization to premature study drug discontinuation, premature study drug discontinuation due to AE and initiation of rescue medication, will be provided based on all randomized population. Time-to-event analyses of premature study treatment discontinuation, study drug discontinuation due to AE and study discontinuation may be conducted.

4.3. Primary Estimand Analysis

The primary efficacy assessment, guided by the "efficacy estimand", will be conducted using the EAS for the primary endpoint (change from baseline in HbA1c at Week 26).

For the "efficacy estimand", the hypothetical strategy is used to handle the intercurrent events (permanent discontinuation of study drug or initiation of rescue medication), so only data collected before the occurrence of any intercurrent events will be used in the MMRM analysis (Section 4.1). Through the MMRM, the potential efficacy measures (after the intercurrent events) had participants not had intercurrent events will be implicitly imputed.

To confirm efficacy of LY3502970 with adequate statistical power, the evaluation of the primary efficacy endpoint for LY4 (36 mg) and LY5 (45 mg) compared to placebo will be made by pooling two dose escalation regimens, that is, combine LY4-1 and LY4-2 for LY4, and combine LY5-1 and LY5-2 for LY5.

The primary efficacy comparison will be based on the contrast between each treatment group of LY3502970 and placebo at Week 26 (Visit 15) from the MMRM analysis of change from baseline in HbA1c using the EAS (Section 4.1). The analysis model and selection of covariance structure is described in Section 4.1.

Treatment comparisons will be performed for the primary objective at the full significance level of 0.05.

4.3.1. Definition of Endpoint(s)

The primary efficacy measure will be change from baseline in HbA1c at Week 26. The change from baseline in HbA1c for each participant at each nominal visit is defined as: postbaseline HbA1c – baseline.

4.3.2. Main Analytical Approach

Change from baseline in HbA1c will be analyzed using the MMRM model for the "efficacy estimand" as described in Section 4.1.

4.3.3. Analyses for a Supplemental Estimand

ICH E9 (R1) Addendum provides a general framework for defining estimands for clinical trials. The Addendum recommends handling intercurrent events according to the study objectives and the causes of the intercurrent events. Naturally, it requires mixed strategies to handle various

types of intercurrent events due to different reasons in the same study. This approach has been advocated in the CHMP draft guidance for the development of treatment for diabetes mellitus (CPMP/EWP/1080/00 Rev.2) and several recent publications (Darken et al. 2020, Qu et al 2021, Qu and Lipkovich 2021). In addition, the imputation of missing values should be consistent with the potential outcome of interest and the assumption for the missingness should be based on the causes of the intercurrent events and missingness (ICH E9 (R1), Qu and Lipkovich 2021).

Therefore, an analysis related to a supplemental estimand, "hybrid estimand" (Section 1.1), will be conducted following the potential outcomes framework introduced by Lipkovich et al (2020).

The hybrid estimand is defined as the treatment difference in the mean change in HbA1c from baseline at Week 26 between LY3502970 and placebo for the study target population with intercurrent events (ICEs) handled differently according to the reasons of the events as follows:

- Category 1- The ICEs of permanent discontinuation of study drug due to reasons unlikely related to the efficacy/safety outcomes will be handled by the hypothetical strategy. Generally, these ICEs will also cause participants to discontinue from the study. The potential outcome of interest is the response in the efficacy measurement if participants had continued the study drug. This is of best clinical interest as in real life — either these ICEs do not prevent participants from taking the medication or these ICEs (pandemic or geographic conflicts) do not represent the situation at normal time.
- Category 2-The ICEs of permanent discontinuation of study drug due to lack of efficacy or use of rescue medication before study treatment discontinuation will be handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants had continued the study drug without rescue medication.
- Category 3- All other ICEs will be handled by the treatment policy strategy. The potential outcome of interest is the response after stopping the study drug from the time of treatment discontinuation events.

In this study, following ICH E9 (R1) guidance, a plan was made to collect informative treatment discontinuation reasons, through eCRF, for why data intended for collection are missing and classify them into category 1-3 as shown in Table 4.2 (EMA 2020).

Table 4.2. Treatment Discontinuation Reasons

Disposition Reason	Associated Sub-Categories	Category
Adverse Event		3
Death		3
Protocol Deviation	Due to Epidemic/Pandemic	1
	Other (option to include a specify field)	3
Pregnancy		3
Lack of Efficacy		2
Withdrawal by Subject	Concern about study procedures/perceived risks	3
	Scheduling conflicts	1
	Subject is moving or has moved	1
	Personal issue unrelated to trial	1
	Due to Epidemic/Pandemic	1
	Other (option to include a specify field)	3
Physician Decision	Concern about study procedures/perceived risks	3
	Scheduling conflicts	1
	Subject is moving or has moved	1
	Due to epidemic/pandemic	1
	Other (option to include a specify field)	3
Study Terminated by Sponsor		1
Site Terminated by Sponsor		1
Study Terminated by IRB/ERB		1
Lost to Follow-up	Due to Epidemic/Pandemic	1
	Other	3
Other		3

Abbreviations: ERB = ethical review board; IRB = institutional review board.

To estimate the "hybrid estimand", multiple imputation will be used to impute the corresponding missing potential outcome according to the missingness patterns (Table 4.3) with ICEs handled differently according to the reasons of the events. Note that if a participant had both early treatment discontinuation and rescue therapy during the study, then missingness will be handled according to the first ICE.

When participants have missing values without ICEs, the missing values will be imputed using data from participants from the same treatment group who do not have ICE or missing values based on the MAR assumption.

Change from baseline in HbA1c will then be analyzed using an analysis of covariance (ANCOVA) with terms for treatment group (placebo, dulaglutide, LY1, LY2, LY3-1, LY3-2, LY4-1, LY4-2) and strata, and the baseline value as a covariate.

Table 4.3. Strategy to Handle ICE and Missingness for Hybrid Estimand

ICE	Strategy to Handle ICE	Potential Outcome	Assumptions for Missingness	Methods to Handle Missing Values at Endpoint
Category 1: Treatment discontinuation due to reasons unlikely related to efficacy/safety outcome	Hypothetical	The response if participants had continued the study drug without using rescue medication	MAR (since missing data unlikely depend on the efficacy outcomes)	Data collected after the ICE will be discarded. Missing values will be imputed using all non-missing data (excluding data collected after ICEs) from the same treatment group based on the MAR assumption.
Category 2: Treatment discontinuation due to lack of efficacy or initiation of rescue therapy	Hypothetical	The response if participants had continued the study drug without using rescue medication	MAR (since such an intercurrent event can likely be modeled by the observed efficacy data)	Data collected after the ICE will be discarded. Missing values will be imputed using all non-missing data (excluding data collected after ICEs) from the same treatment group based on the MAR assumption.
Category 3: All other treatment discontinuations	Treatment policy	The response without taking study drug from the time of treatment discontinuation events	MNAR Consider that these participants could not adhere to their assigned treatment and may not benefit from the assigned treatment.	Missing values will be imputed using participants in the same treatment group with similar intercurrent events but non-missing values (retrieved dropout imputation), including the data collected after the ICE. In cases where there are not enough retrieved dropouts (<10 pts) to provide a reliable imputation model, will impute the missing data using the jump-to-reference (placebo) imputation approach.

Abbreviations: ICE = intercurrent events; MAR = Missing at Random; MNAR = Missing Not at Random.

4.4. Secondary Endpoint(s)/Estimand(s) Analysis

4.4.1. Secondary Endpoint(s)

The following secondary study objectives will be analyzed with the "efficacy estimand" using the data in the EAS:

- Change from baseline in HbA1c at Week 26 (LY3502970 vs dulaglutide)
- Percentage of participants with HbA1c ≤6.5% and of <7.0% at Week 26

- Change from baseline in fasting blood (serum) glucose at Week 26
- Change from baseline in body weight at Week 26
- Percent change in body weight from baseline at Week 26
- Percentage of participants with ≥5%, ≥10% body weight loss from baseline at Week 26

4.4.1.1. Main Analytical Approach

Actual and change from baseline in HbA1c, FSG, and body weight, and percent change in body weight will be analyzed using the MMRM model for the "efficacy estimand" as described in Section 4.1.

For the change in HbA1c from baseline at 26 weeks, noninferiority of LY3502970 to dulaglutide will be concluded if the upper limit for the 95% CI for the difference between LY3502970 and dulaglutide is less than 0.4% (non-inferiority margin) for at least 1 LY3502970 group.

Missing values for binary endpoints will be imputed by categorizing (Yes, No) the imputed values for the corresponding continuous endpoints through multiple imputation using data from participants from the same treatment group who do not have missing values as described in Section 4.3.3 and then analyzed using a logistic regression model with treatment and strata as fixed effects and the continuous baseline value as a covariate.

4.4.2. Analyses for a Supplemental Estimand

The secondary endpoints listed in Section 4.4.1 will also be analyzed for the "hybrid estimand" using the data in the FAS.

Continuous endpoints with missing values imputed and then will be analyzed by an ANCOVA model as described in Section 4.3.3.

Binary endpoints will be analyzed by a logistic regression as described in Section 4.4.1.1.

4.5. Exploratory Endpoints Analysis

4.5.1. Exploratory Efficacy Analysis

The following exploratory study objectives will be analyzed using the MMRM model for the "efficacy estimand" as described in Section 4.1.

- Change from baseline in body mass index (BMI) at Week 26
- Change from baseline in waist circumference at Week 26
- Change from baseline in 7-point self-monitoring of blood glucose (SMBG) values (before meal, 2 hours after each meal, and bedtime) at Week 26
- Percentage of participants with HbA1c ≤5.7% at Week 26
- Percentage of participants with ≥15% body weight loss from baseline at Week 26
- Kaplan-Meier plot of time to initially achieve body weight loss of ≥5% and ≥10%
- Change from baseline in fasting lipids at Week 26

4.5.2. Biomarker Analysis

- Change from baseline in mechanistic biomarkers at Week 26

Hepatic biomarkers (Cytokeratin 18 and Pro-C3) will be analyzed using the MMRM model for the "efficacy estimand" as described in Section 4.1.

4.5.3. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK), pharmacodynamic (PD), and PK/PD analysis are the responsibility of Lilly's PK/PD group.

A summary of LY3502970 concentration-time data will be reported in the clinical study report. Exposure-response analysis between LY3502970 concentration and safety, pharmacology, and efficacy may be performed using population PK and population PK/PD nonlinear mixed-effects modeling techniques implemented on Nonlinear Mixed Effects Modeling (NONMEM) software. Additionally, the impact of intrinsic and extrinsic factors (such as age, weight, sex, renal and hepatic functions) on PK and/or PD parameters may be evaluated.

4.5.4. Patient-Reported Outcomes

The following patient-reported outcomes will be analyzed for the EAS using the MMRM model as specified in Section 4.1, except that baseline will not be used for Diabetes Treatment Satisfaction Questionnaire-Change Version (DTSQc) as a covariate.

- Change from baseline in Short Form 36 version 2 health survey acute form (SF-36v2) acute form domains and summary scores at Week 24,
- Change from baseline in Diabetes Treatment Satisfaction Questionnaire-Status Version (DTSQs) at Week 24
- Actual responses to DTSQc at Week 24

In addition, actual responses to participant survey at Week 24 and ET will be summarized by treatment group.

Both DTSQs and DTSQc contain 8 items:

- For DTSQs, 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.
- For DTSQc, each item is scored on a scale of -3 to +3. For all items except items 2 (perceived frequency of hyperglycemia) and item 3 (perceived frequency of hypoglycemia):
    - the higher the score, the greater the improvement in treatment satisfaction
    - the lower the score, the greater the deterioration in treatment satisfaction, and
    - a score of 0 represents no change.
    - For items 2 and 3: the lower the score, the better the perception.

The analyses for both DTSQs and DTSQc will be conducted for the perceived hyperglycemia item, perceived hypoglycemia item, and 6-item overall satisfaction score.

Per copyright owner, the PRO CoRE 2.0 Smart Measurement® System will be used to derive the following domain and component scores:

- Mental Component Score (MCS)
- Physical Component Score (PCS)
- Physical Functioning domain (PF)

- Role-Physical domain (RP)
- Bodily Pain domain (BP)
- General Health domain (GH)
- Vitality domain (VT)
- Social Functioning domain (SF)
- Role-Emotional domain (RE), and
- Mental Health domain (MH).

The Physical Functioning domain assesses limitations due to health "now" while the remaining domains assess functioning "in the past week." Each domain is scored individually and information from these 8 domains are further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales). Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

4.5.5. Bayesian Analyses for Dose-Response

The longitudinal dose-response model proposed in Qu et al. (2019) will be applied. This approach models the impact of dose titration on the response longitudinally and can flexibly account for deviations from the pre-planned dose titration schedule that is likely to occur within the titration period of the clinical trial.

Let $\theta = (\theta_1, \theta_2, \ldots, \theta_m)$ be the m doses a participant has planned to take and $t_c = (t_{c1}, t_{c2}, \ldots, t_{cm})$ be the corresponding time points when the dose changes where t_{ci} indicates the time for dose to change from θ_i to θ_{i+1}. Therefore, the mean function of the parameter of interest at time t is modelled by:

$$f_{\theta,t_c}(t) = f(t;\theta_1) + \sum_{i=1}^{m-1} [f(t - t_{ci};\theta_{i+1}) - f(t - t_{ci};\theta_i)]I(t > t_{ci}),$$

where I(X) is the indicator function that takes value 1 when the condition X holds. The function, $f(t;\theta)$, is defined such that

$$f(t;\theta) = \frac{\lambda(\theta)(1 - e^{-k(\theta)t})}{1 - e^{-k(\theta)d}},$$

where d is the maximum duration of the treatment period in weeks (Week 26), $\lambda(\theta)$ is the dose-response function for the maximum response at dose θ and $k(\theta)$ is dose θ's rate parameter. This formulation of the mean function $f(t;\theta)$ was introduced by Fu and Manner (2010) to characterize the change from baseline over time in a continuous outcome that could be approximated with a pattern of exponential decay. It assumes a monotone time profile with the maximum effect reached at time d. Historical data demonstrated reasonable model fit for the change from baseline in HbA1c. The longitudinal data $Y_{\theta,t_c,jt}$ for participant j at time t with titration scheme (θ, t_c) will be fitted by adding the error terms to the mean function $f_{\theta,t_c}(t)$ where

$$Y_{\theta,t_c,jt} = f_{\theta,t_c}(t) + \frac{s_j(1-e^{-k(\theta_1)t})}{1-e^{-k(\theta_1)d}} + \epsilon_{jt},$$

$s_j \sim N(0, \sigma_s^2)$ and $\epsilon_{jt} \sim N(0, \sigma^2)$ are independent, denoting between-subject variation and within-subject variation respectively. Given s_j, $Y_{\theta,t_c,jt} \sim N(f_{\theta,t_c}(t) + \frac{s_j(1-e^{-k(\theta_1)t})}{(1-e^{-k(\theta_1)d})}, \sigma^2)$.

The longitudinal dose-response analysis specified above applies to HbA1c. A slight modification to the model for the mean function for body weight, which has demonstrated reasonable model fit for historical data, is outlined below:

$$f_{\theta,t_c}(t) = f(t;\theta_1) + \sum_{i=1}^{m-1} h(t-t_{ci})[f(t-t_{ci};\theta_{i+1}) - f(t-t_{ci};\theta_i)]I(t > t_{ci}),$$

where $h(t-t_{ci}) = \frac{(1-e^{-k'(t-t_{ci})})}{1-e^{-k'd}}$. The parameter k'controls the rate at which the response (body weight) changes when titrating from one dose to the next dose.

The dose-maximum response function $\lambda(\theta)$ is provided below

- HbA1c

An Emax model is assumed where

$$\lambda(\theta) = \alpha_0 + \frac{\alpha_1\theta}{\alpha_2 + \theta},$$

and parameters $\alpha_0, \alpha_1,$ and α_2 represent, respectively, the basal effect when the dose level is zero (placebo), the maximum effect that can be achieved by any dose level on top of placebo, and the dose level that produces half of the maximum improvement (ED_{50}). For Dulaglutide 1.5 mg, $\lambda(\theta)$ will be modelled separately as a distinct dose.

- Body Weight

A power model is assumed where

$$\lambda(\theta) = a + b * \theta^{\gamma}$$

γ is a sigmoidicity parameter indicating shape or steepness of dose response.

Other dose-response models for $\lambda(\theta)$ may be explored if the aforementioned dose-response models do not fit the data well, for example, Simple Normal Dynamic Linear Modeling (NDLM). Additionally, the different formulation of $f_{\theta,t_c}(t)$ may also be considered if the current specification does not provide an adequate fit to the data.

The estimation of those parameters will be carried out in a Bayesian framework assuming non-informative priors for the hyperparameters in the model as follows:

$$\begin{cases} k(\theta), \tau \sim \text{Uniform}(0,1), \\ \alpha_0, \alpha_1, \alpha_2, a, b \sim N(0, 100^2), \\ \frac{1}{\sigma^2}, \frac{1}{\sigma_s^2} \sim \text{Gamma}(0.01, 0.01), \\ \gamma \sim N(1,5). \end{cases}$$

Posterior inference will be drawn for the dose-response at time t of clinical interest and the 95% credible intervals will also be plotted.

Additional modelling may be explored for better long-term efficacy prediction if the model does not fit the data well, due to the follow study features: (1) fast titration (weekly), (2) lack of long-term follow-up for lower doses, and (3) HbA1c/weight is not always measured at the week of titration.

4.6. Safety Analyses

Unless specified otherwise, safety will be assessed by comparing safety of LY3502970 doses with placebo irrespective of adherence to study drug. Thus, safety analyses will be conducted using the safety analysis set (SS, Table 4.1) except hypoglycemia events which will be conducted using the EAS. For selected lab values that are only scheduled to be measured for the treatment period, the MMRM model or ANCOVA (if MMRM model is not applicable) using the SS will only show nominal visits during the treatment period.

4.6.1. Extent of Exposure

Summary of duration of follow-up (defined as time in days from date of randomization to the date of the last study visit) and/or duration of exposure to study drug (defined as time in days from date of first dose of study drug to date of last dose of study drug plus 1 day) will be provided by treatment group using data from SS. The following descriptive statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (that is, total participant-years of exposure).

4.6.2. Treatment Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline (Table 4.1). The Medical Dictionary for Regulatory Activities (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.

For events occurring on the day of first taking study medication, the CRF-collected information (for example, treatment emergent flag, start time of study treatment and event) will be used to determine whether the event was pre- versus post-treatment if available. If the relevant information is not available, then the events will be counted as post-treatment.

The counts and percentages of participants with TEAEs will be summarized by treatment group using MedDRA Preferred Term (PT) nested within System Organ Class (SOC). Statistical comparisons will be applied at both the SOC and PT levels. Events will be ordered by decreasing frequency within SOC. The SOC will be in alphabetical order. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex.

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

The counts and percentages of participants with TEAEs by maximum severity will be summarized by treatment using MedDRA PT. For each participant 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.

4.6.2.1. Common Adverse Events

The counts and percentages of participants with TEAEs, overall and common (common TEAEs occurred in ≥5% of participants before rounding), will be summarized by treatment using MedDRA PT. Events will be ordered by decreasing frequency. 6.14.1.3.

4.6.2.2. Deaths

A listing of all deaths during the study will be provided. The listing will include participant identification including the treatment, site number, date of death, age at the time of enrollment, sex, cause of death as reported by investigator, cause of death as adjudicated by CEC, etc.

4.6.2.3. Other Serious Adverse Events

The counts and percentages of participants who experienced a SAE (including deaths and SAEs temporally associated or preceding deaths) during the postbaseline period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. The SOC will be in alphabetical order.

A listing of all SAEs will be provided. The listing will include treatment, participant identification including the site number, date of event, age at the time of enrollment, sex, MedDRA SOC and PT, reported term, severity, outcome, relationship to study drug, time from first dose of study drug to the event, AE start date, AE end date, seriousness, and action taken related to study treatment.

4.6.3. Patient Narratives

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

- Death
- Serious adverse event, or
- Permanent discontinuation of study treatment due to AEs.

Patient narratives (patient level data and summary paragraph) will be provided for participants in all randomized population with at least 1 notable event.

4.6.4. Vital Signs

In the case where multiple records of an individual vital sign are collected at the same visit, they will be averaged prior to being used for data summaries and analyses.

Descriptive summaries by treatment and by nominal visit will be provided for baseline and postbaseline values as well as change from baseline values.

Treatment differences in mean change will be analyzed using the MMRM model as described in Section 4.1.

Counts and percentages of participants with treatment-emergent abnormal sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP), and pulse will be presented by treatment for participants who have both baseline and at least 1 postbaseline result. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria during the postbaseline period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time that meets the specified change criteria during the postbaseline period. To assess decreases, change from the minimum value during the baseline period to the minimum value during the postbaseline period will be used. To assess increases, changes from the maximum value during the baseline period to the maximum value during the postbaseline period will be used. Both planned and unplanned measurements will be included in the analysis. The criteria for identifying participants with treatment-emergent vital sign abnormalities are stated in Table 4.4.

Table 4.4. Categorical Criteria for Abnormal Treatment-Emergent 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	≥129 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

Abbreviations: BP = blood pressure; bpm = beats per minute.

4.6.5. Electrocardiograms

Summary statistics by treatment group and by nominal visit will be provided for electrocardiogram (ECG) parameters (heart rate, pulse rate (PR), QRS, QT, and QT corrected using Fredericia's correction factor [QTcF = QT / RR^0.333]). When the QRS is prolonged (for example, a complete bundle branch block), QT and QTc should 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.

Change from baseline to postbaseline values for ECG parameters will be summarized for participants who have both a baseline and at least 1 postbaseline result. Only planned measurements will be included in the mean change analyses.

The criteria for identifying participants with treatment-emergent quantitative ECG abnormalities is based on Table 4.5.

The counts and percentages of participants who meet following criteria at any time during the entire study period (including the off-drug follow-up period) will be summarized by treatment group:

- treatment-emergent ECG abnormalities as listed in Table 4.5
- QT greater than 500 msec
- QTcF greater than 500 msec, and
- treatment-emergent increase from the maximum baseline in QTcF interval of greater than 30 msec, 60 msec, or 75 msec. Maximum baseline will be the maximum non-missing observation in the baseline period. The maximum value during the treatment period will be analyzed. Scheduled and unscheduled measurements will be included.

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

An MMRM analysis will be conducted to analyze changes from baseline in heart rate and PR interval, separately.

Table 4.5. 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

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; PR = pulse rate; QTcF = Fredericia's corrected QT interval.

4.6.6. Laboratory Data

4.6.6.1. Central Laboratory Measures

All laboratory data will be reported in the International System of Units. Selected laboratory measures will also be reported using conventional units. Limits from the performing lab will be used to define low (L) and high (H). 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 may be displayed in plots for participants who have both a baseline and at least 1 postbaseline planned measurement. Baseline will be the last non-missing observation prior to taking first study drug. Unplanned measurements will be excluded from plots.

A shift table will be provided including unplanned measurements. The shift table will include the number and percentage of participants within each baseline category (low, normal, high, or missing) versus each postbaseline category (low, normal, high, or missing) by treatment. The

proportion of participants shifted will be compared between treatment groups using Fisher's exact test.

For qualitative laboratory analytes, the number and percentage of participants 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 participant identification, treatment group, laboratory collection date, study day, analyte name, and analyte finding.

The MMRM model or ANCOVA (if MMRM model is not applicable) will be used for the analysis during the treatment period for the continuous measurements for selected lab tests.

4.6.7. Special Safety Topics

4.6.7.1. Exocrine Pancreas Safety

4.6.7.1.1. Pancreatic Enzyme

Observed pancreatic enzyme data (p-amylase and lipase) will be summarized by treatment group and nominal visit, in a model with strata (country, baseline HbA1c stratum [≤8%, >8%]) as fixed effects.

The counts and percentages of participants with maximum postbaseline pancreatic enzyme value exceeding the following thresholds will be provided by baseline pancreatic enzyme value (≤ upper limit of normal [ULN], > ULN), and treatment: ≤1x ULN, (>1 to ≤3) x ULN, (>3 to ≤5) x ULN, (>5 to ≤10) x ULN, >10x ULN.

An MMRM analysis will be used to analyze each pancreatic enzyme with a log transformed (postbaseline measure/baseline measure) response variable and treatment, nominal visit, strata (country, baseline HbA1c stratum [≤8%, >8%]), treatment-by-nominal visit interaction as fixed effects.

4.6.7.1.2. Pancreatic Events

Summaries of adjudicated and investigator-reported pancreatic events will be provided by treatment group. Detailed searching criteria can be found in Appendix 6 (Section 7.6).

4.6.7.2. Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE) reported by investigators are adjudicated by an independent clinical endpoint committee (CEC) in a blinded fashion.

The cardiovascular (CV) AEs to be adjudicated include 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).

Only adjudicated MACE will be considered as adverse events of special interest (AESI). The counts and percentages of participants with adjudicated MACE may be summarized by treatment.

In addition, MACE reported by investigator may also be summarized although a major adverse cardiovascular event reported by investigator is not considered as AESI.

A listing of participants reporting MACE events, either reported by investigator or identified by the CEC, will be provided. The listing will include treatment, participants 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 participant has discontinued study drug prior to the event).

4.6.7.3. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent supraventricular arrhythmias and cardiac conduction disorders will be considered as AESI. The cardiovascular events will include clinically relevant rhythm and conduction disorders.

The treatment-emergent supraventricular arrhythmias and cardiac conduction disorders events will be included using the MedDRA PTs. Detailed searching criteria can be found in Appendix 6 (Section 7.6).

The counts and percentages of participants with treatment emergent supraventricular arrhythmias and cardiac conduction disorders will be summarized by treatment and PT nested within Standardized MedDRA Queries (SMQ). The PT will be ordered with decreasing frequency within SMQ. A listing of participants with treatment-emergent supraventricular arrhythmias and cardiac conduction disorders may be provided if deemed necessary.

4.6.7.4. Hepatic Safety

4.6.7.4.1. Hepatobiliary Disorders

Hepatobiliary disorders will be considered as AESI. The counts and percentages of participants with treatment-emergent potentially drug-related hepatic disorders will be summarized by treatment and PT within SMQ. Detailed searching criteria can be found in Appendix 6 (Section 7.6).

4.6.7.4.2. Liver Enzymes

Analyses for laboratory analyte measurements are described in Section 4.6.6. This section describes additional analyses of liver enzymes.

The counts and percentages of participants with the following elevations in hepatic laboratory tests at any time during the treatment period and during the entire study including follow up period will be summarized between treatment groups:

- ALT: The number and percentage of participants with a measurement greater than or equal to 1 time (1x), 3 times (3x), 5 times (5x), 10 times (10x), and 20 times (20x) the performing lab upper limit of normal (ULN) during the treatment period will be summarized for all participants with a postbaseline value.
- AST: The number and percentage of participants with a measurement greater than or equal to 1 time (1x), 3 times (3x), 5 times (5x), 10 times (10x), and 20 times (20x) the performing lab upper limit of normal (ULN) during the treatment period will be summarized for all participants with a postbaseline value.

- ALP: The number and percentage of participants with a measurement greater than or equal to 2 times (2x) and 3 times (3x) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.
- TBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2x), 5 times (5x), and 8 times (8x) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.
- DBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2x) and 5 times (5x) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.

Two plots will be provided as follows:

- Hepatocellular Drug-Induced Liver Injury (DILI) Screening Plot (TBL versus ALT or AST): Each participant is plotted (that is, scatterplot) based on their maximum post-baseline TBL (y-axis) versus transaminase (ALT or AST, whichever is higher), regardless of the time between the two maximum values. Dashed lines represent TBL and transaminase cut-offs of 2x ULN and 3x ULN (default) respectively. A potential Hy's Law case is circled and defined as having a maximum post-baseline TBL ≥2x ULN within 30 days after maximum post-baseline ALT or AST ≥3x ULN, without findings of cholestasis (defined as ALP <2x ULN). Include all scheduled and unscheduled laboratory test values.
- Cholestatic DILI Screening Plot (TBL versus ALP): Each participant is plotted (that is, scatterplot) based on their maximum post-baseline total bilirubin (y-axis) versus ALP (x-axis), regardless of the time between the two maximum values. Dashed lines represent TBL and ALP cut-offs of 2x ULN and 3x ULN (default) respectively. A potential cholestatic liver injury case is circled and defined as having a maximum post-baseline TBL ≥2x ULN within 30 days after maximum post-baseline ALP ≥2x ULN. Include all scheduled and unscheduled laboratory test values.

The counts and percentages of participants in each quadrant and overall of the respective plots will be provided by treatment group of LY3502970, dulaglutide and placebo, if data warrant. For the potential hepatocellular DILI plot, the quadrants will be: Potential Hy's Law (right upper), Cholestasis (left upper), Temple's corollary (right lower). For the potential cholestatic DILI plot, the quadrants will be: TBL ≥2x ULN and ALP ≥2x ULN (right upper), TBL ≥2x ULN and ALP <2x ULN (left upper), TBL <2x ULN and ALP <2x ULN (left lower), TBL <2x ULN and ALP ≥2x ULN (right lower).

4.6.7.5. Hypoglycemia

Per the study protocol, investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the blood glucose values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2020 American Diabetes Association position statement on glycemic targets (ADA 2020) as below. Level 2 and Level 3 hypoglycemia events are considered as safety topics of special interest.

- **Level 1 Hypoglycemia (Level 1):**
  Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
- **Level 2 Hypoglycemia (Level 2):**
  Glucose <54 mg/dL (3.0 mmol/L)
- **Severe Hypoglycemia (Level 3):**
  Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
    - The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
    - If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.
- **Other hypoglycemia categories:**
  Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

To avoid duplicate reporting, all consecutive hypoglycemic events occurring within a 1-hour period will be considered as a single hypoglycemic event.

Both the incidence (percent of participants experiencing ≥1 episode) and the rate (episodes/participant/year) of level 2 or level 3 hypoglycemia, and level 1 hypoglycemia will be reported by treatment group.

Severe hypoglycemia will be considered as AESIs. The summaries of severe hypoglycemia will be provided by treatment group. A listing of all events of severe hypoglycemia may be provided, if deemed necessary. This listing will provide treatment allocation, clinical characteristics of the hypoglycemic event, and concomitant medications.

For these hypoglycemia analyses, only hypoglycemia events prior to permanent discontinuation of study drug or initiation of rescue medication will be included.

4.6.7.6. Severe Persistent Hyperglycemia

In this study, investigators will be trained on how to apply decision criteria for the timing and method of intervention in participants who do not reach glycemic targets during the 26-week treatment period (Protocol 6.8.3). If any of the criteria is met, then participants may begin treatment with another antihyperglycemic agent as determined by their physician. This will be defined as severe persistent hyperglycemia for analysis. Severe persistent hyperglycemia will be considered as AESI.

Summaries of participants who had hyperglycemia rescue medicine (that is, severe persistent hyperglycemia) will be provided by treatment group.

4.6.7.7. Thyroid Safety Monitoring

4.6.7.7.1. Calcitonin

Observed calcitonin data (a thyroid-specific laboratory assessment) will be summarized by treatment group and nominal visit.

The counts and percentages of participants with a maximum postbaseline calcitonin value in the following thresholds will be provided by treatment and maximum baseline calcitonin value (≤20 ng/L, >20 ng/L to ≤35 ng/L, >35 ng/L). Postbaseline: ≤20 ng/L, >20 ng/L to ≤35 ng/L, >35 ng/L to ≤50 ng/L, >50 ng/L to ≤100 ng/L, and >100 ng/L.

4.6.7.7.2. C-Cell Hyperplasia and Thyroid Malignancies

Thyroid malignancies and C-Cell hyperplasia will be considered as AESI. Treatment-emergent thyroid malignancies and C-Cell hyperplasia will be identified using MedDRA High Level Term (HLT) for Thyroid neoplasms and PT for Thyroid C-cell hyperplasia.

The counts and percentages of participants with treatment-emergent thyroid C-cell hyperplasia and malignancies will be summarized by treatment and PT ordered with decreasing frequency. In addition, a listing of participants with treatment-emergent thyroid C-cell hyperplasia and neoplasms may be provided if deemed necessary.

4.6.7.8. Gastrointestinal Safety

4.6.7.8.1. Nausea, Vomiting, Diarrhea and Constipation

Summaries and analyses for incidence and severity of nausea, vomiting, diarrhea, constipation and the 4 events combined, will be provided by each treatment group by week and overall.

Summary of the prevalence over time for nausea, vomiting, diarrhea, constipation and the 4 events combined will also be presented through plots.

Time to the onset of nausea, vomiting, diarrhea and constipation will be plotted.

4.6.7.8.2. Severe Gastrointestinal Events

Severe GI adverse events (GI SOC) will be captured with AE-CRF form and serious cases will be captured with the SAE form. The PTs in the GI SOC MedDRA will be used to identify GI AEs, and only the PTs with serious/severe cases will be considered as AESIs.

The counts and percentages of participants with severe GI events will be summarized by treatment group.

4.6.7.9. Renal Safety

Laboratory measures related to renal safety will be analyzed as specified for laboratory measurements in Section 4.6.6.

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/1.73 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).

Mixed model repeated measure analyses for eGFR and UACR will be provided. Log transformation will be performed for UACR.

4.6.7.9.1. Acute Renal Events

Because severe GI events may lead to dehydration, which could cause a deterioration in renal function including acute renal failure, dehydration events will be analyzed. Acute renal events associated with chronic renal failure exacerbation will also be captured.

Acute renal events will be considered as AESI.

The counts and percentages of participants with acute renal events will be summarized by treatment by using the MedDRA PTs contained in any of the following SMQs:

- Acute renal failure: Narrow terms in Acute renal failure SMQ (20000003) and
- Chronic kidney disease: Narrow terms in Chronic kidney disease SMQ (20000213).

In addition, a listing of participants with treatment-emergent acute renal events may be provided, if deemed necessary.

4.6.7.9.2. Dehydration

Dehydration events will be captured in the Narrow terms in Dehydration SMQ (20000232).

A listing of participants with treatment-emergent dehydration events will be provided.

4.6.7.10. Hypersensitivity Events

Hypersensitivity reactions and related information reported in eCRF will be listed and summarized by treatment group.

Analyses of both time periods use the current SMQs, to search for relevant events.

Summaries of all potential hypersensitivity reactions will be generated by PT with decreasing frequency by treatment group. 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 6 (Section 7.6). Within query, individual PTs that satisfied the queries will be summarized. Also, a single event may satisfy multiple SMQs, in which case the event contributes to every applicable SMQ.

The number and proportion of participants experiencing treatment-emergent potential systemic hypersensitivity reactions will be summarized and compared by treatment group using Fisher's exact test.

4.6.7.11. Abuse Liability

The counts and percentages of participants with treatment-emergent potential abuse liability events and treatment-emergent drug abuse and dependence will be summarized by treatment group with decreasing frequency. Detailed searching criteria can be found in Section 7.6.

4.7. Other Analyses

4.7.1. Subgroup Analyses

Subgroup analyses of the primary endpoint *(HbA1c) will be made to assess consistency of the intervention effect across the following subgroups using the "efficacy estimand":*

- Age group: <65 versus ≥65 years
- Sex: female versus male
- Baseline HbA1c (≤8.0%, >8.0%)
- Baseline BMI (≤30 kg/m^2, >30 kg/m^2)
- Race
- Ethnicity
- Country/Region
- Prior Use of Metformin (Yes, No)
- Duration of Type 2 Diabetes (<median duration, >=median duration)

If the number of participa*nts is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study.*

For HbA1c and change from baseline in HbA1c, for each subgroup analyses aforementioned, the following 2 models will be conducted:

- Conduct MMRM model on the subgroup only with terms of treatment group, visit, treatment group-by-visit-interaction, country, HbA1c stratum, and baseline as a covariate. Variance-covariance structure for within-participant errors will be same as Section 4.1.
- Full MMRM model: treatment group, visit, subgroup, treatment group-by-visit-interaction, treatment-by-subgroup-interaction, subgroup-by-visit-interaction, treatment-visit -subgroup-interaction, country and HbA1c stratum as fixed effects, and baseline as a covariate. Variance-covariance structure for within-participant errors will be same as Section 4.1.

Additional subgroup analyses may also be performed.

4.8. Interim Analyses

An interim efficacy and safety assessment after all participants complete Visit 12 (Week 16) of the treatment period may be conducted to provide information for dose escalation schemes and clinical trial material packaging for future studies. If conducted, an internal Assessment Committee (AC) will be formed to review the interim analyses for the safety and efficacy reports in an unblinded manner. Additional interim analyses may be conducted. Details on the timing of the interim analyses, operational support, and unblinding will be specified in the AC charter and in the study unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded for

the final data base lock. Study sites will receive information about interim results only if deemed necessary for the safety of the participants. The trial will not be stopped based on the superiority of LY3502970 versus placebo or dulaglutide 1.5 mg. Therefore, there will be no inflation of the type 1 error rate and no need to employ an alpha spending function or multiplicity adjustment.

The database lock and primary data analysis for Study GZGE will occur when all participants have completed the study. Participants and investigators will remain blinded until the completion of the study.

The cancellation or addition of an interim analysis can be determined at any time during the study and will not require a protocol amendment.

Unblinding details are specified in a separate unblinding plan document.

The AC charter will describe the planned interim analyses for AC and the analyses for corresponding endpoints will follow the SAP described analysis method.

4.9. Changes to Protocol-Planned Analyses

No changes have been made from protocol planned analyses.

5. Sample Size Determination

Approximately 370 participants will be randomly assigned to study drug in a randomization ratio of 5:5:5:5:5:3:3:3:3, including 50 participants per treatment group to placebo, dulaglutide, LY1, LY2 and LY3 treatment groups, and 30 participants per treatment group to LY4-1, LY4-2, LY5-1, and LY5-2 treatment groups.

The sample size calculation is based on the primary efficacy estimand and its endpoint (change from baseline to Week 26 in HbA1c). Assuming a SD of 1.1%, a 2-sided alpha level of 0.05, 40 completers for one LY3502970 treatment group and 40 completers for the placebo group can provide >90% power to detect a treatment difference of -0.9% between the LY3502970 treatment group and placebo (LY3502970– Placebo) in change from baseline HbA1c at Week 26. Taking into consideration a potentially higher dropout rate due to gastrointestinal events in the higher doses of LY, 50 participants for placebo arm and 60 participants per treatment group (or 30 participants per dose escalation regimen) for LY4 and LY5 should be randomized. Assuming a same 20% dropout rate for dulaglutide, LY1, LY2, and LY3, 50 participants per treatment group should be randomized.

6. Novel Coronavirus (COVID-19) Impact

The following additional statistical analyses may be performed at the final database lock to assess the impact of COVID-19 pandemic for all randomized participants if data warrant.

- Listing of all randomized participants who discontinue study due to COVID-19 pandemic.
- Listing of adverse events or deaths related to COVID-19 pandemic.
- Listing of Participants using Extended Visit Window due to COVID-19

In case there is a larger impact of COVID-19 on the study, due to a shut-down or any other reason, more details for additional analyses may be provided.

For the primary endpoints and key secondary endpoints, missing data due to COVID-19 will be handled as described in Section 4.3.3.

7. Supporting Documentation

7.1. Appendix 1: Demographic and Baseline Characteristics

All demographic and baseline clinical characteristics will be summarized by treatment groups and dose escalation subgroups (placebo, dulaglutide, LY1, LY2, LY3, LY4-1, LY4-2, LY5-1, LY5-2) for all randomized participants.

The following variables will be included but not limited to: age (years), age groups (<65 and ≥65 years), sex, country, ethnicity, race, height (cm), body weight, HbA1c at baseline (% and mmol/mol), Hba1c stratum at baseline (≤8.0% and >8.0%), fasting glucose at baseline, BMI at baseline, BMI groups at baseline (≤30 and >30 kg/m^2; <25, ≥25 to <30, ≥30 to <35, ≥35 to <40 and ≥40 kg/m^2), fasting blood (serum) glucose (mg/dL and mmol/L), Metformin prior use (yes, no), eGFR, eGFR groups (estimated glomerular filtration rate based on the modified Modification of Diet in Renal Disease equation): <30, ≥30 to <45, ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2), duration of diabetes (years), type 2 diabetes duration group, tobacco use, baseline SBP, baseline DBP, and baseline pulse rate. A listing of participant demographic and baseline characteristics will be provided for all randomized participants.

A listing of participants whose stratification factor value(s) that are entered into the IWRS (for treatment group assignment) is different from the clinical database will also be provided.

Number of randomized participants and number of randomized participants discontinued per investigator within country for each treatment group will be summarized. In addition, number of enrolled participants per investigator within each country will also be summarized.

7.2. Appendix 2: Historical Illnesses and Pre-existing Conditions

The count and percentages of participants with historical illnesses and pre-existing conditions will be summarized by treatment group using the MedDRA PTs nested within SOC. The SOC will be in alphabetical order. Conditions (that is, PTs) will be ordered by decreasing frequency within SOC. This will be summarized for all randomized participants. Historical illnesses are illnesses that end prior to inform consent and preexisting conditions are conditions that are still ongoing at inform consent. Events will be ordered by decreasing frequency. No statistical comparisons between treatment groups will be performed.

7.3. Appendix 3: Treatment Compliance

If data warrant, the counts and percentages of participants who follow the planned dose escalation scheme (IWRS data), have missed doses of study drug (eCRF data) ≥ 7 days, or have dose de-escalation (IWRS data) will be summarized for each treatment group for all randomized participants. Listings of such participants will be also provided.

Non-compliance is defined as having ≥75% of days of missed doses before permanent study drug discontinuation, will also be summarized by treatment group and dose escalation subgroups.

7.4. Appendix 4: Concomitant Medications

Concomitant medications will be summarized by treatment group. The percentages of participants who took concomitant medication will be summarized by treatment using PT nested

within Anatomical Therapeutic Chemical (ATC) Level 3 codes. The concomitant medications will be ordered by decreasing frequency within each ATC level.

Concomitant medication will be summarized by PTs by treatment groups by decreasing frequency for all randomized participants.

Additionally, medications of interest (as defined below) will be summarized by treatment groups and dose escalation subgroups for all randomized participants.

Concomitant medications of interest include the following:

- baseline antihypertensive therapy, by type/class
- baseline lipid lowering therapy, by type/class
- changes to baseline medication in post-randomization (in term of type/class and dose):
    - antihypertensive therapy, and
    - lipid lowering therapy.
- utilization after randomization of:
    - antihyperglycemic medication
    - antidiarrheal medication, and
    - antiemetic medication
    - constipation medication.

7.5. Appendix 5: Important Protocol Deviations

Important protocol deviations are identified in the Trial Issues Management Plan. A listing of important protocol deviations by treatment will be provided at the end of the study (for all randomized participants).

7.6. Appendix 6: Searching Criteria for Additional Safety Assessments

Pancreatitis Events

Determination of investigator-reported events will be through the “Acute pancreatitis” SMQ (20000022, narrow scope) and a “Chronic pancreatitis” PT search of the AE database, while adjudication-confirmed pancreatitis are found from adjudication forms.

Hepatic Treatment-Emergent Adverse Events

Treatment-emergent potentially drug-related hepatic disorders will be summarized by treatment using the MedDRA PTs contained in any of the following SMQs:

- Broad and narrow terms in the Liver related investigations, signs, and symptoms SMQ (20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009)
- Broad and narrow terms in the Hepatitis non-infections SMQ (20000010)
- Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)
- Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015)

- Narrow PTs in Gallbladder related disorders SMQ (20000124)
- Narrow PTs in Biliary tract disorders SMQ (20000125); and
- Narrow PTs in Gallstone related disorders SMQ (20000127).

Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent supraventricular arrhythmias, arrhythmias and cardiac conduction disorders will be considered as an AESI. The cardiovascular events will include clinically relevant rhythm and conduction disorders. The treatment-emergent supraventricular arrhythmias and cardiac conduction disorders events will be included using the MedDRA PT contained in any of the following SMQs:

1) Supraventricular Arrhythmias:

- For symptoms: Arrhythmia related investigations, signs, and symptoms SMQ (20000051), narrow and broad terms
- For supraventricular arrhythmias: In Cardiac arrhythmia SMQ, under tachyarrhythmias sub SMQ
    - Supraventricular tachyarrhythmias SMQ (20000057), broad and narrow terms
    - Tachyarrhythmia terms, nonspecific SMQ (20000164), narrow terms only; and
    - Ventricular tachyarrhythmias SMQ (20000058), narrow terms only.

2) Cardiac Conduction Disorders

- Conduction defects SMQ (20000056), narrow terms only; and
  Cardiac conduction disorders High Level Term (HLT; 10000032), all PTs.

Hypersensitivity Events

The hypersensitivity TEAE are characterized as follows:

- Anaphylactic reaction SMQ (20000021; narrow, algorithm per SMQ guide, and broad)
- Hypersensitivity SMQ (20000214; narrow and broad)
- Angioedema SMQ (20000024; narrow and broad)
- Event maps to PT of Injection related reaction (10071152).

The number and percentage of patients who experienced a TEAE for the following will be analyzed:

- Any narrow or algorithmic term from any one of the 4 SMQs indicated above (that is, combined search across narrow and algorithmic portions of all 4 SMQs)
- Any narrow scope term within each SMQ, separately (that is, narrow SMQ search)
- Any term within each SMQ, separately (that is, broad SMQ search).

Abuse Liability

To identify AE terms suggestive of potential abuse liability, a list of MedDRA PTs referred to as Abuse Term list will be used. In addition, narrow and broad terms from SMQ of Drug abuse, dependence, and withdrawal (20000101 and 20000102) will be used.

8. References

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Approval	PPD 24-Oct-2022 15:25:22 GMT+0000

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Approved on 24 Oct 2022 GMT