H9X-JE-GBGQ Statistical Analysis Plan Version 1

A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Two Doses of Dulaglutide in Combination with a Single Oral Antihyperglycemic Medication or as Monotherapy in Japanese Patients with Type 2 Diabetes Mellitus (AWARD-JPN: Assessment of Weekly Administration of LY2189265 in Diabetes – JAPAN)

NCT04809220

Approval Date: 14-Oct-2022

Title Page

Protocol Title: A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Two Doses of Dulaglutide in Combination with a Single Oral Antihyperglycemic Medication or as Monotherapy in Japanese Patients with Type 2 Diabetes Mellitus

Protocol Number: H9X-JE-GBGQ

Compound Number: LY2189265

Short Title: Assessment of Weekly Administration of LY2189265 in Diabetes – JAPAN

Acronym: AWARD-JPN

Sponsor Name: Eli Lilly Japan K.K.

Legal Registered Address: Eli Lilly Japan K.K., Kobe Hyogo Japan

Regulatory Agency Identifier Number(s)

Registry	ID
Not available	

Table of Contents

Tables

Approved on 14 Oct 2022 GMT

Figures

Version history

This Statistical Analysis Plan (SAP) Version 1 for Study H9X-JE-GBGQ (GBGQ) is based on the protocol dated 15 December 2020 and approved prior to any unblinding.

1. Introduction

This SAP includes the analysis plan for efficacy and safety.

The table, figure, and listing (TFL) specifications are contained in a separate document.

1.1. Objectives, Endpoints, and Estimands

Table GBGQ.1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To demonstrate that once-weekly dulaglutide 1.5 mg is superior to dulaglutide 0.75 mg for change from baseline in HbA1c at 26 weeks	• Change from baseline in HbA1c at 26 weeks
Secondary	
Efficacy • To compare dulaglutide 1.5 mg to 0.75 mg for efficacy parameters through 26 and 52 weeks	• Change from baseline in HbA1c • Proportion of participants achieving HbA1c target of ≤6.5% and <7.0% • Change from baseline in FSG • Change from baseline in 6-point SMBG • Change from baseline in body weight
Safety • To compare dulaglutide 1.5 mg to 0.75 mg for safety parameters through 26 and 52 weeks	• Incidence of TEAEs • Discontinuation of study intervention due to AEs • Incidence of hypoglycemic episodes • Change from baseline in vital signs (SBP, DBP, and pulse rate) • Change from baseline in laboratory tests[a]

Abbreviations: AEs = adverse events; DBP = diastolic blood pressure; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; SMBG = self-monitored blood glucose; TEAEs = treatment-emergent adverse events.

[a] Specified in the protocol Section 10.2 (Appendix 2).

1.1.1. Estimands

This section describes efficacy estimands.

1.1.1.1. Primary and Supportive Estimands

There will be one estimand of interest in analyzing primary endpoint for the Treatment Period. Intercurrent events which lead to study treatment discontinuation are defined in PROTOCOL Section 7. There will be no supportive estimands.

1.1.1.1.1. Primary Estimand for Continuous Multiple Endpoints: (Hypothetical)

The primary estimand is a hypothetical estimand representing the primary clinical question of interest: what is the difference between treatment conditions, i.e., Dulaglutide 1.5mg vs

Dulaglutide 0.75mg, in the target participant population, in successful means after Week 26 (or Week 52 for the final database lock) achieved without the intercurrent events specified above and all participants adhered to the treatment?

The primary estimand is described by the following attributes:

[A] Population: defined through appropriate I/E criteria to reflect the targeted participant population for approval

[B] Endpoint: change from baseline in HbA1c at Week 26

[C] How to account for intercurrent events (ICEs):

For participants who require any use of rescue medication or discontinued the study treatment due to the various reasons prior to Week 26 (or Week 52 for the final database lock), a hypothetical strategy will be used to estimate what the treatment effect would have been if the rescue medication was not available and all participants adhered to the treatment.

[D] Population-level summary: difference in means between treatment conditions

Analysis of the other continuous efficacy will use the above estimand.

The table below summarizes the analytical strategies that will be conducted on the intercurrent events for the estimand.

Table GBGQ.1.2. Description of Primary Estimand for Efficacy Analysis

Estimand	Analysis Strategy for Intercurrent Events: Rescue Medication/ Treatment Discontinuation	Missing Data Imputation Method	Analysis
Primary Estimand for Continuous Multiple Endpoints (Hypothetical)	Hypothetical: Set to missing	No imputation (MMRM)	HbA1c, FSG

Abbreviations: FSG = fasting serum glucose; HbA1c = hemoglobin A1c; MMRM = mixed-effects model for repeated measures.

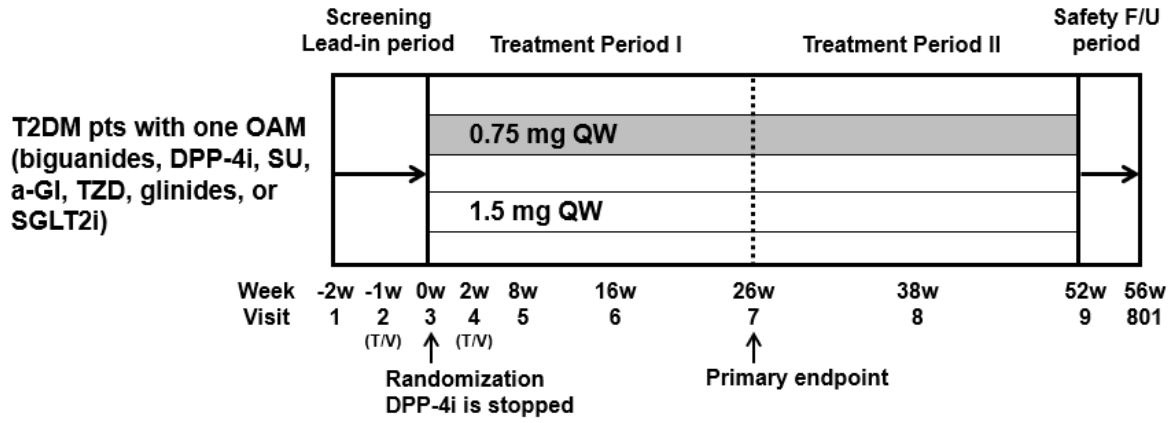
1.2. Study Design

Study Design

Study H9X-JE-GBGQ is a Phase 3, multicenter, randomized, double-blind, parallel-group study in participants with T2D with inadequate glycemic control on a single OAM. The OAMs include:

- Sulfonylureas (SU)
- biguanides
- alpha-glucosidase inhibitors (a-GI)
- thiazolidinedione (TZD)
- glinides
- sodium-glucose cotransporter type 2 inhibitors (SGLT2i), and
- DPP-4 inhibitors (DPP-4i).

Participants will be randomized at Visit 3 in a 2:1 ratio to weekly subcutaneous injections of dulaglutide 1.5 mg or 0.75 mg.



Abbreviations: a-GI = alpha-glucosidase inhibitors; DPP-4i = dipeptidyl peptidase-4 inhibitor; F/U = follow up; OAM = oral antihyperglycemic medications; pts = patients; SGLT2i = sodium-glucose cotransporter type 2 inhibitors; SU = sulfonylureas; T2D = type 2 diabetes; T/V = telephone visit; TZD = thiazolidinedione; w = week; QW = once weekly.

Note: Visit 2 (Week -1) and Visit 4 (Week 2) will be conducted as a telephone visit.

Figure GBGQ.1.1. Study design.

Study Periods

The study will consist of 3 periods:

[1] an approximately 2-week screening/lead-in period

During the screening/lead-in period, participants are required to continue their pre-study OAM therapy and should not change the type of OAMs used or their doses in order to allow reliable assessment of HbA1c at Visit 3.

[2] a 52-week treatment period including Treatment Period I (26-week for the primary endpoint) and Treatment Period II (26-week)

Participants are required to continue using their concomitant OAMs, except for DPP-4i, throughout the treatment period. If a participant uses daily DPP-4i, it is required that the participants stop using daily DPP-4i at randomization.

Discontinuation or dose changes of concomitant OAMs are not permitted, except in certain situations (Protocol Section 6.5). Participants will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study intervention (Protocol Section 6.5).

Randomization:

Approximately 732 participants will be screened to achieve 585 participants randomly assigned in a 2:1 ratio to dulaglutide 1.5 mg group and dulaglutide 0.75 mg group (390 and 195 participants, respectively).

Randomization at Visit 3 will be stratified by pre-study OAM class and HbA1c at Visit 1.

For participants taking DPP-4i prior to randomization, target numbers of participants randomized for 1.5 mg and 0.75 mg are 150 and 75 (total 225 participants).

For participants taking other OAMs, target numbers of participants randomized for 1.5 mg and 0.75 mg are 240 (40 per OAM class) and 120 (20 per OAM class). In total, 360 participants (60 per OAM class) will be randomized for other OAMs.

The stratification factors are as follows.

Table GBGQ.1.3. The Stratification Factors

Stratification factors	Groups
pre-study OAM class	SU biguanides TZD a-GI glinides SGLT2i DPP-4i
HbA1c at Visit 1	low (<8.5% for DPP-4i class and <9.0% for other OAM classes) high (≥8.5% for DPP-4i class and ≥9.0% for other OAM classes)

Abbreviations: a-GI = alpha-glucosidase inhibitors; DPP-4i = DPP-4 inhibitor; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medications; SGLT2i = sodium-glucose, cotransporter type 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinedione.

Early Termination (ET) Visit:

Every attempt will be made to keep participants in the study irrespective of their adherence to treatment with study intervention.

At any time after Visit 3 (randomization), a participant who is to discontinue from the study before Visit 9 (Week 52) will have an ET visit conducted. At this visit, procedures will occur as shown in the Schedule of Activities (SoA, Protocol Section 1.3). Participants should be instructed to return any remaining used or unused study intervention supplies and diaries to the study site at this visit. Participants will be asked to perform the Safety Follow-Up visit (Visit 801) approximately 4 weeks after the ET visit, so that the Safety Follow-Up visit (Visit 801) will be their final visit. If the participant is not able to perform the Safety Follow-Up visit (Visit 801), the ET visit will be the final study visit. A participant summary electronic case report form (eCRF) will be completed.

[3] a 4-week safety follow-up period

All participants who complete the treatment period (both I and II) are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after the last visit of the treatment period. During the safety follow-up period, participants will not receive study intervention. The safety follow-up period will also be applied to participants who discontinue from the study. In this case, the Safety Follow-Up visit (Visit 801) will occur approximately 4 weeks after the ET visit.

Other details are defined in Protocol Section 4.1.

2. Statistical Hypotheses

The alternative hypothesis for the primary objective is:

Dulaglutide 1.5 mg is superior to dulaglutide 0.75 mg, relative to the mean change in HbA1c from baseline at Week 26.

2.1. Multiplicity Adjustment

There is no multiplicity adjustment.

3. Analysis Sets

The following analysis populations and analysis sets are defined:

Table GBGQ.3.1. Populations and Analysis Sets

Populations or Analysis Sets	Description
Entered	All participants who sign the ICF.
Randomized	All participants who are randomized to a treatment arm.
Nonrandomized	All participants entered, but not randomized to a treatment arm.
Intention-to-treat (ITT) Population	All randomly assigned participants who are exposed to at least 1 dose of study intervention for an assigned treatment arm. Participants will be included in the treatment group they were randomized to.
Efficacy analysis set for Period I (EAS1)	Data obtained during Treatment Period I (26-week) from the ITT population, excluding data after initiating rescue antihyperglycemic medication or discontinuing study intervention (last dose date + 7 days). In the event of a treatment error, participants will be analyzed according to the treatment they were randomly assigned to receive.
Safety analysis set for Period I (SS1)	Data obtained during Treatment Period I from the ITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.
Efficacy analysis set for Period I and II (EAS2)	Data obtained during Treatment Period I and II (52-week) from the ITT population, excluding data after initiating rescue antihyperglycemic medication or discontinuing study intervention (last dose date + 7 days). In the event of a treatment error, participants will be analyzed according to the treatment they were randomly assigned to receive.
Safety analysis set for Period I and II (SS2)	Data obtained during both Treatment Period I, II and safety F/U period from the ITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.

Abbreviations: ICF = informed consent form; F/U = follow-up.

Approved on 14 Oct 2022 GMT

Treatment Groups and Comparisons for Each Study Period and Analysis Population are defined as follows.

Table GBGQ.3.2. Treatment Groups and Comparisons for Each Study Period and Analysis Population

Study Period	Analysis Population	Treatment Groups	Abbreviation	Comparisons When Applicable
Treatment Period I (Week 26)	EAS1 SS1	dulaglutide 1.5 mg dulaglutide 0.75 mg Total	DULA1.5 DULA0.75 TOTAL	DULA1.5 vs DULA0.75;
Treatment Period II (Week 52)	EAS2	dulaglutide 1.5 mg dulaglutide 0.75 mg Total	DULA1.5 DULA0.75 TOTAL	DULA1.5 vs DULA0.75;
Overall Period (Week 56)	SS2	dulaglutide 1.5 mg dulaglutide 0.75 mg Total	DULA1.5 DULA0.75 TOTAL	DULA1.5 vs DULA0.75;

Abbreviations: EAS[X]=Efficacy analysis set for Period X (1 or 2); SS[X]=Safety analysis set for Period X (1 or 2)

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly Japan K.K. (Lilly). The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used.

Analyses and summaries from assessment of endpoints described in the protocol are planned to be included in a clinical study report (CSR). Analyses and summaries for key safety data are also planned to be included in the CSR. Results from additional efficacy analysis and other safety analyses may also be provided in the CSR as deemed appropriate.

Not all displays described in the SAP will necessarily be included in the CSRs. Any display described and not provided in the CSR would be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display created interactively will be included in the CSR if deemed relevant to the discussion.

All statistical processing will be performed using SAS® unless otherwise stated. Except where noted (e.g., interaction test), all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

The Schedule of Visits and Procedures outlined in the protocol specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis, unless specified otherwise (e.g., MMRM or GLM analysis).

Any change to the data analysis methods described in the protocol will require a protocol amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the CSR.

For variables that are not collected at each post-baseline visit, data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM or GLM analysis (Andersen and Millen 2013). Also, for by-visit summaries/displays such as boxplots, the weeks when data was not scheduled to be collected may not be displayed. However, unscheduled assessments within any defined study period will still be used in the shift analyses, and for imputing values for the change from baseline to last observation carried forward (LOCF) endpoint analyses.

If there are no patients in planned TFLs, they may not be created. (e.g., specific AESI TFLs.)

Baseline definition

Baseline will be defined as the last available value before the first injection for efficacy. In most cases, this will be the measure recorded at Baseline Visit 3 (Week 0). If the participant does not take any injection, the last available value on or prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value.

For the safety analyses, the following baselines will be used. For safety analyses using a baseline period, the baseline period is defined as the time from Screening Visit (Visit 1) to the date/time of the first injection.

- Treatment-emergent adverse events (TEAEs): baseline will be all results (including medical histories which are ongoing at the date of informed consent) recorded during the baseline period.
- Treatment-emergent abnormal laboratory and vital signs results: baseline will be all results recorded during the baseline period.
- Change from baseline to last post-baseline observation or to each scheduled post-baseline visit for laboratory and vital signs results: baseline will be the last scheduled non-missing assessment recorded during the baseline period.

Stratification factors

The randomization to treatment groups is stratified by pre-study OAM class and HbA1c at Visit 1 (Low/High) (Table GBGQ.1.3). Unless otherwise specified, the statistical analysis models will include them as input variables.

Continuous variables

For continuous variables, baseline and postbaseline values, actual values will be summarized by sample size/mean (SD)/min/median/max (add Q1/Q3 if appropriate).

For baseline, LSmean (SE) will be estimated by ANOVA model (TYPE III sum of squares) with treatment as input variable, unless otherwise specified.

For postbaseline at each scheduled visit, actual value and change from baseline will be summarized by mean (SD)/min/median/max, and N (total number of patients with non-missing value at baseline and at least one post-baseline result within each treatment arm).

In addition, depending on number of scheduled timepoints, one of the following analyses will be conducted.

[Case 1] Single post-baseline time point (e.g., 6-point SMBG at Week 26, Lab analysis from baseline through Week 26)

Change from baseline will be analyzed using analysis of covariance (ANCOVA) with the following terms in the model:

- treatment group, baseline value, pre-study OAM class, and baseline HbA1c stratum.

Type III tests for least squares (LS) means will be used for **statistical comparison between treatment groups.** The LS mean difference, standard error (SE), p-value, and 95% CI, unless otherwise specified, will also be reported. In addition, **within treatment comparison** (the post-baseline value v.s. baseline value) will be conducted with the same model. P-value will be reported.

[Case 2] Multiple post-baseline time point (e.g., Lab analysis from baseline through Week 52 and follow-up period)

Change from baseline will be analyzed using mixed model for repeated measures (MMRM). Except for the HbA1c analysis (primary analysis), the model includes

- treatment, baseline value, visit, the interaction of treatment-by-visit, pre-study OAM class, and baseline HbA1c stratum,

as fixed effects.

The HbA1c analysis excludes the HbA1c stratification factor from the MMRM model because HbA1c is included as a continuous baseline variable.

The covariance structure to model the within-participant errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The restricted maximum likelihood (REML) will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom.

Type III tests for the LS means will be used for the **treatment comparison**; LS mean difference, SE, p-value, and 95% CI will also be reported. In addition, **within treatment comparison** (the post-baseline value v.s. baseline value) will be conducted with the same model. P-value will be reported.

The same MMRM model will be used to estimate actual value at each visit.

For continuous laboratory analysis, the model specified above will be used for treatment comparison. However, actual visit values and change from baseline are based on descriptive statistics, not from the statistical models (LSmeans). There will be no within treatment comparison.

Discrete variables (binary)

For **efficacy binary endpoints** (achieving HbA1c levels <7.0% or ≤6.5%), multiple post-baseline time point will be analyzed using a longitudinal logistic regression with repeated measurements, (generalized linear mixed model (GLM)), without imputation. The model term includes

- treatment, baseline value, visit, the interaction of treatment-by-visit, and pre-study OAM class.

Proportion of responders (denominator, numerator, %) at each time point will be shown (no statistical tests). Missing data is excluded from the denominator.

If convergence issue happens, simple logistic regression (week 26 at interim DBL, week 52 at final DBL) will be used with model terms

- treatment, baseline value, and pre-study OAM class.

Approved on 14 Oct 2022 GMT

For **safety binary endpoints,** including AE rate and qualitative laboratory analysis, Fisher's exact test will be used, unless otherwise specified.

For analyzing incidence of hypoglycemic episodes, treatment differences in the incidence of hypoglycemic episodes will be assessed using Fisher's exact tests, unless otherwise specified. Treatment differences in rates of hypoglycemic episodes (week 26 at interim DBL, week 52 at final DBL) will be analyzed using a **generalized linear model** assuming negative binomial distribution if data warrant; otherwise, the Wilcoxon rank-sum test will be used. The generalized linear model will include

- offset, treatment, baseline hypoglycemia rate, pre-study OAM class, and baseline HbA1c stratum,

The logarithm of days during active treatment period (exposure in days divided by 365.25) will be included as the offset to account for possible unequal duration between visits and between participants.

Note that in the protocol **generalized linear mixed-effects model** was planned. However due to low rate of the events, a convergence issue happened. Therefore, analysis was changed from the multi-visit analysis to the single visit analysis.

Time to event analysis

The Kaplan-Meier product limit method will be used to estimate cumulative event-free survival rates. Figure will be created. Cox proportional hazards regression analysis will be used to compare hazard rates between treatments using Wald test. The model term includes treatment group, pre-study OAM class, and baseline HbA1c stratum. Median confidence interval will be derived by log-transformed Greenwood formula.

4.1.1. General Considerations for Follow-Up Period

No efficacy analysis will be conducted for follow-up period. Safety analysis will include all data in follow-up period, unless otherwise specified.

4.1.2. Handling of Dropouts or Missing Data

Depending on the estimand being addressed, different methods will be used to manage missing data. Description of the estimands can be found in Section 1.1.1.

4.1.2.1. Handling of Dropouts or Missing Data

For efficacy analysis relative to the estimand for continuous endpoints collected multiple times post-baseline, a Mixed-effects Model for Repeated Measures (MMRM) will be performed without explicit imputation. The description of MMRM can be found in Section 4.1.2.1.1.

For efficacy analysis relative to the estimand for continuous endpoints collected only once post-baseline (or at each timepoint), missing data including those as a result of intercurrent events will be imputed using Last Observation Carried Forward (LOCF). The description of LOCF can be found in Section 4.1.2.1.2.

The table below describes the planned imputation methods for efficacy endpoints.

Table GBGQ.4.1. Imputation Techniques for Various Variables

Type of Endpoints	Efficacy Endpoints	Missing Data Imputation Method (Analysis Method)
Continuos	Continuous endpoints at multiple post-baseline timepoints	No imputation (MMRM)
	Continuous endpoints collected only once post-baseline (or at each timepoint)	LOCF (ANCOVA)

Abbreviations: ANCOVA = analysis of covariance; LOCF = last observation carried forward; MMRM = mixed-effects model for repeated measures.

4.1.2.1.1. Mixed-effects Model for Repeated Measures (MMRM)

Mixed-effects model for repeated measures analyses will be performed on continuous endpoints to mitigate the impact of missing data. This approach assumes missing observations are missing-at-random (missingness is related to observed data) and borrows information from participants in the same treatment arm taking into account both the missingness of data through the correlation of the repeated measurements.

The values subsequent to rescue medication use or treatment discontinuation will be made missing before applying the MMRM model. The MMRM model is described in Section 4.1.

4.1.2.1.2. Last Observation Carried Forward (LOCF)

In this analysis, the values subsequent to rescue medication use or treatment discontinuation will be made missing. All missing values will be imputed using LOCF. If there is no post-baseline observation, then the patient will be excluded from the analysis.

4.2. Participant Dispositions

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study intervention (dulaglutide 1.5 mg or 0.75 mg), will be presented by treatment arm.

In particular, following TFLs will be created:

- Summary of Analysis Population which includes (see definition in the GBGQ PROTOCOL Table 1)
  - entered patients
  - non-randomized patients
  - randomized patients
  - ITT population
- Listing of Analysis Population
- Summary of Patient Disposition Prior to Randomization which includes
  - number of patients who discontinued prior to randomization
  - reason for discontinuation (denominator is patients who discontinued prior to randomization)

- Summary of Patient Disposition by Visit
- Listing of the Screen Failures
- Summary of Patient Disposition which includes followings (All randomized population as denominator):
  - study disposition status
  - study treatment status
  - reasons for study discontinuation
  - reasons for study treatment discontinuation
- Listing of Patient Disposition
- Summary of Patient Allocation (by investigator)
- Listing of Date of Visit

A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment arm will be provided. Cox proportional hazards regression analysis will be used to compare hazard rates between treatments using Wald test. The model term includes

- treatment group, baseline value, pre-study OAM class, and baseline HbA1c stratum.

4.3. Primary Endpoints Analysis

4.3.1. Definition of endpoints

The primary efficacy measure will be evaluated at 26 weeks:

- Change from baseline in HbA1c.

4.3.2. Main analytical approach

The primary efficacy of dulaglutide 1.5 mg versus dulaglutide 0.75 mg 26 weeks will be guided by the "efficacy" estimand using the efficacy analysis set 1 (EAS1). The "efficacy" estimand, represents efficacy prior to discontinuation of investigational product and prior to initiation of rescue therapy, which is without confounding effects of rescue therapy for persistent severe hyperglycemia.

4.3.3. Sensitivity Analyses

None.

4.3.4. Supplementary analyses

None.

4.4. Secondary Endpoints Analysis

The following secondary efficacy measures will be evaluated through 26 and 52 weeks:

- Change from baseline in HbA1c (% and mmol/mol)
- Proportion of participants achieving HbA1c target of $\leq$6.5% and <7.0%
- Change from baseline in FSG (mg/dL and mmol/L)
- Change from baseline in 6-point SMBG (mg/dL and mmol/L)

- Change from baseline in body weight (kg)

In addition, following TFLs will be created:

- Estimated LS Means of HbA1c (%) (Figure)
- Estimated LS Means of Fasting Serum Glucose (Figure)
- Summary of 6-point SMBG (mg/dL and mmol/L): 2-hr Excursion for Each Meal and Means of All Meals 2-hr Excursion Values
- Summary of 6-point SMBG (mg/dL and mmol/L): Mean of 6-point BG, All-premeals BG and All-PPBG
- Summary of 6-point SMBG (mg/dL and mmol/L): Circadian Variation in 6-point BG
- Listing of 6-point SMBG (mg/dL and mmol/L)
- Summary of All Types of 6-point SMBG (mg/dL and mmol/L) Change from Baseline Values
- Estimated LS Means of Body Weight (kg) (Figure)

4.5. Tertiary/Exploratory Endpoints Analysis

None.

4.6. Safety Analyses

All safety analyses will be conducted using both the SS1 and SS2 to assess the safety parameters through 26 and 52 weeks, unless otherwise stated.

In this study AESIs defined in the PROTOCOL (Section 8.3.3) are as follows:

a. Hypoglycemia

b. Severe, persistent hyperglycemia

c. Pancreatitis

d. C-cell hyperplasia and C-cell neoplasms

e. Cardiovascular events

f. Hypersensitivity reactions

4.6.1. Extent of Exposure

Treatment exposure is defined as the time from when the patient is randomized at Visit 3 and receives study drug until the patient either permanently discontinues from investigational product or completes the treatment period.

Treatment exposure will be calculated for each participant and summarized by treatment group.

Treatment exposure will be summarized and listed using safety analysis set.

The summary includes duration of exposure which will be categorized into the following groups: >0 weeks, ≥26 weeks, > 0 to < 26 weeks, (for final DBL, add ≥26 to <52 weeks, and ≥52 weeks). These categories will be summarized as frequency by treatment.

Listing of Randomization Scheme, and lot numbers of study drug will be created. Lot number will be provided upon request.

4.6.2. Adverse Events

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported by preferred term and system organ class (SOC). Selected notable AEs of interest may be reported using high-level terms. All AEs and TEAEs, defined as post-baseline events that are new events or preexisting conditions that worsened in severity after randomization, will be listed by participant and visit. Information on treatment, actual term, preferred term, severity, seriousness, and relationship to study intervention will also be reported.

Summary statistics will be provided for incidence of TEAEs, SAEs, and study discontinuation due to AEs or death during the treatment period. Counts and proportions of participants experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

For each PT in Summary of TEAEs by Severity, Fisher's exact test will be used for overall (mild + moderate + severe) and for severe.

TFLs Related to Adverse Events

Analysis	Additional Information
Summary of AEs	Overview By Treatment Group
Summary of TEAEs	By PT and Treatment Group
Summary of TEAEs	By SOC, PT and Treatment Group
Summary of TEAEs by Severity	By PT and Treatment Group
Summary of TEAEs Possibly Related to Study Drug	By PT and Treatment Group
Summary of SAEs	By PT and Treatment Group
Summary of AEs Leading to Discontinuation of Study Drug	By PT and Treatment Group
Summary of AEs Leading to Discontinuation of Study	By PT and Treatment Group
Listing of SAEs	
Listing of Deaths	
Listing of AEs Leading to Discontinuation of Study and/or Study Drug	

Abbreviations: AEs= adverse events; PT= preferred term; SAEs= serious adverse events; SOC = System Organ Class; TEAE = treatment-emergent adverse events.

4.6.2.1. Deaths, Other Serious Adverse Events, and other Notable Adverse Events

The number and percentage of participants reported with an SAE during the treatment period will be summarized by treatment using MedDRA PT. A listing of SAEs will be provided.

The number and percentage of participants

[1] who permanently discontinued from study treatment due to an AE

[2] who discontinue study due to an AE (including AEs that led to death)

will be summarized by treatment using MedDRA PT. Events will be ordered by decreasing frequency in total population.

4.6.3. Additional Safety Assessments

4.6.3.1. Clinical Laboratory Evaluation

The clinical laboratory evaluations will be summarized as described in the table below. Continuous values are shown with descriptive summary (without LSmeans) and p values based on the model in Section 4.1.

TFLs Related to Clinical Laboratory Evaluations

Analysis	Additional Information
Listing of Patients with Treatment Emergent Abnormal (3*ULN) Laboratory Results	
Listing of Patients with Treatment Emergent Abnormal (ULN and LLN) Laboratory Results	
Summary and Analysis of Numeric Laboratory Tests	By Treatment Group and Visit
Summary and Analysis of Abnormal Laboratory Results	By Treatment Group and Visit
Shift of Calcitonin from Maximum Baseline to Maximum Postbaseline	By Treatment Group
Summary of Percent Change in Lipid Measurements	By Treatment Group and Visit

Abbreviations: LLN=Lower Limit Normal; ULN=Upper Limit Normal.

Listing of Individual Laboratory Values would be created upon request.

4.6.3.2. Vital Signs and Other Physical Findings

Vital signs will be summarized as described in the table below.

TFLs Related to Vital Signs

Analysis	Additional Information
Summary of Vital Signs	By Treatment and Visit
Listing of Patients with Abnormal Vital Signs	

Listing of Vital Signs	

4.6.3.3. Hypoglycemia

TFLs Related to Hypoglycemia

Analysis	Additional Information
Listing of Individual Hypoglycemic Episodes	
Listing of Severe/Serious Hypoglycemia Episodes	
Summary of Level 1 hypoglycemia: Glucose <70 mg/dL (3.9 mmol/L) and >= 54 mg/dL (3.0 mmol/L)	Overall Period
Summary of Level 2 hypoglycemia: Glucose <54 mg/dL (3.0 mmol/L)	Overall Period
Summary of Level 3 hypoglycemia: Severe hypoglycemia	Overall Period
Summary of Nocturnal hypoglycemia	Overall Period
Summary of Clinically significant hypoglycemia (Level 2 or 3)	Overall Period

4.6.3.4. Electrocardiograms (ECG)

Descriptive summary of ECG results (PR, QRS, QT, RR, mean heart rate, and corrected QT interval (QTcF)) will be created.

TFLs Related to ECG

Analysis	Additional Information
Summary of ECG Results	By Treatment and Visit

Abbreviations: ECG = electrocardiogram.

4.6.3.5. Special Safety Topics including Adverse Events of Special Interest

4.6.3.5.1. Severe, Persistent Hyperglycemia

Following TFLs will be created. Note that if a reported AE term contains the word "severe, persistent hyperglycemia ", then it is considered as **"severe, persistent hyperglycemia"**:

TFLs Related to Severe, Persistent Hyperglycemia

Analysis	Additional Information
Listing of Severe, Persistent Hyperglycemia	
Summary of Severe, Persistent Hyperglycemia Leading to Rescue Therapy	By Treatment Group
Summary of Severe, Persistent Hyperglycemia	By Treatment Group

Listing of Insulin Therapy for Severe, Persistent Hyperglycemia	
Summary of Insulin Therapy for Severe, Persistent Hyperglycemia	By Treatment Group

4.6.3.5.2. Pancreatitis

Pancreatic event is captured by the eCRF (Pancreatic Event CRF). Following summary will be created. Note that "Summary of Pancreatitis Adverse Events "and "Listing of Pancreatitis Adverse Events" only include events confirmed by adjudication. Therefore, these will not be based on MedDRA PT.

TFLs Related to pancreatitis

Analysis	Additional Information
Summary of Pancreatic Enzyme Thresholds - Amylase	By Treatment Group and Visit
Summary of Pancreatic Enzyme Thresholds - Lipase	By Treatment Group and Visit
Listing of Events That Were Sent for Adjudication. Possible Cases of Pancreatitis	
Summary of Pancreatitis Adverse Events	By Treatment Group and PT
Listing of Pancreatitis Adverse Events	

Abbreviations: PT= preferred term.

4.6.3.5.3. C-cell Hyperplasia and C-cell Neoplasms

This will be determined by the following terms:

High Level Terms: Anaplastic thyroid cancer, Follicular thyroid cancer, Huerthle cell carcinoma, Medullary thyroid cancer, Papillary thyroid cancer, Poorly differentiated thyroid carcinoma, Thyroid cancer, Thyroid cancer metastatic, Thyroid cancer recurrent, Thyroid cancer stage 0, Thyroid cancer stage I, Thyroid cancer stage II, Thyroid cancer stage III, Thyroid cancer stage IV.

PT: Thyroid c-cell hyperplasia.

TFLs Related to C-cell Hyperplasia and C-cell Neoplasms

Analysis	Additional Information
Summary of C-cell Hyperplasia and C-cell Neoplasms	By Treatment Group
Listing of C-cell Hyperplasia and C-cell Neoplasms	

4.6.3.5.4. CardioVascular (CV) Events

CV events will be identified based on MACE events and SAE which will be reviewed by medical.

TFLs Related to CV

Analysis	Additional Information
Summary of Cardiovascular Adverse Events	By Treatment Group and PT
Listing of Cardiovascular Adverse Events	

Abbreviations: PT= preferred term.

4.6.3.5.5. Hypersensitivity Reactions

If preferred term is in below list, they are considered as hypersensitivity events:

1. Narrow terms in the Anaphylactic Reaction SMQ (20000021)
2. Narrow terms in the Angioedema SMQ (20000024)
3. Narrow terms in the Severe Cutaneous Adverse Reactions SMQ (20000020)
4. Narrow terms in the Hypersensitivity SMQ (20000214).

TFLs Related to hypersensitivity

Analysis	Additional Information
Summary of Allergic/hypersensitivity Adverse Events	By Treatment Group and PT
Listing of Allergic/hypersensitivity Adverse Events	

Abbreviations: PT= preferred term.

4.6.3.5.6. Gastrointestinal

The events (Constipation, Diarrhoea, Nausea and Vomiting) will be captured by the corresponding PTs. Following TFLs will be created.

TFLs Related to gastrointestinal

Analysis	Additional Information
Incidence and Prevalence of Gastrointestinal Adverse Events (Constipation, Diarrhoea, Nausea and Vomiting) (Table)	By Treatment Group and Weeks
Time to First Onset of Gastrointestinal Adverse Events (Constipation, Diarrhoea, Nausea and Vomiting) (Figure)	By Treatment Group and Weeks
Duration of Treatment-Emergent Gastrointestinal Adverse Events (Constipation, Diarrhoea, Nausea and Vomiting) (Table)	By Treatment Group and Days

Incidences and prevalence are categorized into the following periods:

Interim analysis (weeks): 0, 4, 8, 12, 16, 20, **26 (**4-week interval except the last category)

final analysis (weeks): 0, 4, 8, 12, 16, 20, **24,** 28, 32, 36, 40, 44, 48, 52 (4-week interval)

For example, at the interim analysis, following categories are used:

[0 <= weeks <=4], [4 < weeks <=8] …, [20 < weeks <=26], [26 < weeks],

Kaplan-Meier analysis will be conducted (censored at the time when patients discontinue study.)

4.6.3.5.7. Acute Gallbladder Disease

Acute Gallbladder Disease is defined as one of the following conditions (contains both narrow and broad terms):

[1] SMQ= Gallbladder related disorders

[2] SMQ CODE = 20000124

Table and listing will be created.

4.7. Other Analyses

4.7.1. Subgroup analyses

Subgroup-by-treatment interaction will be tested with 2-sided alpha level of 0.10.

Binary outputs (at Week 26 for interim DBL, at Week 52 for final DBL) will be evaluated based on odds ratio with 95% confidence interval.

4.7.1.1. Efficacy Subgroup Analyses

Following subgroup will be used:

[SUB1] Baseline HbA1c (%) (2 groups: value < 8.5, 8.5 <= value)

[SUB2] Age subgroup 1 (years) (2 groups: value < 65, 65<= value)

[SUB3] Age subgroup 2 (years) (3 groups: value < 65, 65<= value < 75, 75 <= value)

[SUB4] Sex (2 groups: male, female)

[SUB5] Duration of Diabetes (years) (2 groups: value < median, median <= value)

[SUB6] Baseline Body Weight (kg) (2 groups: value < median, median <= value)

[SUB7] Baseline BMI (2 groups: value < 25, 25 <= value)

[SUB8] Monotherapy or OAM combination (2 groups: Monotherapy, SU/BG/a-GI/TZD/Glinides/ SGLT-2i)

Note that the medians are based on ITT population.

For [SUB1]-[SUB8] following analysis will be conducted:

[SUB_EFF1] Change from baseline in HbA1c (%)

[SUB_EFF2] Proportion of participants achieving HbA1c target of ≤6.5%

[SUB_EFF3] Proportion of participants achieving HbA1c target of <7.0%

[SUB_EFF4] Change from baseline in body weight (kg)

Table GBGQ.4.2. Statistical Model Term Summary for the Subgroup Analysis

	A	B	C	D	E	F	G	H
1		Analysis:	CFB A1c (%)	CFB Weight (kg)	CFB Pulse (bpm)	A1c < 7%, <=6.5%	Nausea, Diarrhoea	Hypo Level 1, Hypo Level 2 (Incidence)
2		Outcome type	Continuous (mult-visits)			Binary (single)	Binary (single)	Binary (single)
3		Model	MMRM			Logistic	Logistic	
4		Basic model (each subgroup)	TMT, BASE, visit, TMT*visit			TMT, BASE	TMT	
5		Basic model (combined subgroup)	TMT, BASE, visit, TMT*visit, SUB, SUB*TMT, SUB*visit, SUB*TMT*visit			TMT, BASE, SUB, SUB*TMT,	TMT, SUB, SUB*TMT,	
6	Subgroup	BASE in the model	A1c (conti.)	Weight (conti.)	Pulse (conti.)	A1c (conti.)	None	
7	SUB1	Term adjust	OAM Delete:BASE	OAM	OAM	OAM Delete:BASE	OAM	
8	SUB2-5	Term adjust	OAM	OAM + A1c(stratum)		OAM	OAM + A1c(stratum)	
9	SUB6/7	Term adjust	OAM	OAM + A1c(stratum) Delete: BASE	OAM + A1c(stratum)	OAM	OAM + A1c(stratum)	
10	SUB8	Term adjust	None	A1c(stratum)		None	A1c(stratum)	

Abbreviation: A1c = hemoglobin A1c; BASE=baseline; CFB = change from baseline; cont. = continuous; Hypo = hypoglycemia; Logistic = logistic regression; MMRM = mixed-effects model for repeated measures; OAM = oral antihyperglycemic medication; SUB = subgroup; TMT = treatment

Two statistical models will be used:

[Model 1] Estimation model for each subgroup (denoted as “each subgroup” in Table GBGQ.4.2).

[Model 2] Interaction tests model for combined subgroup (denoted as “combined subgroup” in Table GBGQ.4.2).

Model 1 and Model 2 have different covariates. They are summarized in Table GBGQ.4.2.

Example: [SUB1] [SUB_EFF3] (A1c <7% analysis) each subgroup model will have

[Model 1] (TMT+BASE) + (OAM -BASE) = TMT +OAM.

[Model 2] (TMT+ BASE+ SUB+SUB*TMT) + (OAM-BASE) = TMT+SUB+ SUB*TMT + OAM.

4.7.1.2. Safety Subgroup Analyses

For [SUB1]-[SUB8], following analysis will be conducted

[SUB_SAF1] Proportion of participants who have TEAE Nausea

[SUB_SAF2] Proportion of participants who have TEAE Diarrhoea

[SUB_SAF3] Summary of Level 1 hypoglycemia: Glucose <70 mg/dL (3.9 mmol/L) and >= 54 mg/dL (3.0 mmol/L)

- Note: The response variable is incidence, not aggregated rate per year. Statistical model is logistic regression.

[SUB_SAF4] Summary of Level 2 hypoglycemia: Glucose <54 mg/dL (3.0 mmol/L)

- Note: The response variable is incidence, not aggregated rate per year. Statistical model is logistic regression.

[SUB_SAF5] Change from baseline in pulse rate (bpm)

Model terms and analysis are summarized in the Table GBGQ.4.2.

4.7.1.3. OAM Subgroup Analyses

All Table/Figure analysis (e.g., demographic, treatment compliance, efficacy, safety) will be conducted for the following OAM subgroups unless otherwise specified.

- DPP-4 inhibitors (DPP-4i)

  Note: This is a monotherapy of dulaglutide.
- Sulfonylureas (SU)
- Biguanides (BG)
- Alpha-glucosidase inhibitors (a-GI)
- Thiazolidinedione (TZD)
- Glinides
- Sodium-glucose cotransporter type 2 inhibitors (SGLT-2i)
- Combination therapy (SU, BG, a-GI, TZD, Glinides, or SGLT-2i)

When statistical models are used (e.g., MMRM, ANCOVA, logistic regression) “pre-study OAM class” model term will be excluded.

For example, for SU subgroup, MMRM model of **Analysis of HbA1c (%)** will include following terms:

- treatment, baseline value, visit, the interaction of treatment-by-visit

The statistical models do not include the OAM subgroup-treatment interaction as a model term. Therefore, no interaction will be tested (using p-value).

The subgroup analysis specified in Section 4.7.1.1 or Section 4.7.1.2 (e.g. Age, Sex) will not be conducted for the OAM subgroups.

If OAM subgroup results are redundant, they will not be created, for example, “Summary of Dose Modification of Oral Anti-Diabetic Medication” and “Summary of OAM Mean Daily Doses (mg/day)”.

For Kaplan-Meier analysis, odds ratio and p-value will not be produced if estimates are unavailable due to small events or sample size, or figure may not be created.

4.8. Interim Analyses

The first database lock (DBL) and unblinding will occur, and the interim analysis, including all data up to Week 26. It does not include follow-up period data for safety analysis.

If an AE is continuing at the timing of the interim (week 26), its end day of the AE is temporarily assumed to be Week 26 (Week 26 imputation method). This will minimize the AE duration length estimation bias. If we eliminate these events from the duration analysis, the duration will be shorter than the Week 26 imputation method, which is not ideal. At the final DBL, an actual AE end day will be replaced.

Suppose a patient discontinues the study before Visit 7 (their last visit will be Visit 801) and he does not have Visit 7. Then the interim analysis will include the data captured by the maximum scheduled visit in Study Period 1.

The interim analysis only includes maximum scheduled visit data in Study Period 1. Hence the unscheduled one (e.g., Visit 7.1) will be out of scope.

Visit 801 (early termination visit) may be included in some TFLs, for example, disposition.

The final database lock will then be conducted after all participants have completed the Follow-Up Period.

If an AE is continuing at the timing of the final database lock, its end day of the AE is assumed to be the end of his/her study completion day.

Unblinding details are specified in a separated unblinding plan.

4.8.1. Data Monitoring Committee (DMC)

NA.

4.9. Changes to Protocol-Planned Analyses

NA.

5. Sample Size Determination

Approximately 732 participants will be screened to achieve 585 participants randomly assigned in a 2:1 ratio to dulaglutide 1.5 mg group and dulaglutide 0.75 mg group (390 and 195 participants, respectively). Assuming a drop-out rate of 10%, 528 participants will be evaluable for an estimated total of 352 evaluable participants in the dulaglutide 1.5 mg group and 176 evaluable participants in the dulaglutide 0.75 mg group.

This sample size provides at least 90% power for demonstrating superiority of dulaglutide 1.5 mg to dulaglutide 0.75 mg in the HbA1c change from baseline at Week 26. This assumes a true treatment difference of -0.3% with a common standard deviation (SD) of 1.0% for the change in HbA1c from baseline.

For participants taking DPP-4i prior to randomization, target numbers of participants randomized for 1.5 mg and 0.75 mg are 150 and 75 (total 225 participants).

For participants taking other OAMs, target numbers of participants randomized for 1.5 mg and 0.75 mg are 240 (40 per OAM class) and 120 (20 per OAM class). In total, 360 participants (60 per OAM class) will be randomized for other OAMs.

6. Supporting Documentation

6.1. Appendix 1: Description and Derivation of Efficacy and Health Outcome Endpoints

Table GBGQ.6.1. Description and Derivation of Efficacy/Health Outcome Measures and Endpoints

Measure	Description	Variable	Derivation/Comment	Imputation Approach if Missing Components (postbaseline visit)
HbA1c		Continuous HbA1c (% and mmol/mol)	Observed score and change from baseline	Missing if baseline or observed value is missing.
HbA1c		Categorical HbA1c (%) value: Value <= 6.5% Value < 7.0%	Postbaseline	Missing if baseline or observed value is missing.
FSG		FSG (mg/dL and mmol/L)	Observed score and change from baseline	Missing if baseline or observed value is missing.
Body weight		Body weight (kg)	Observed score and change from baseline	Missing if baseline or observed value is missing.
6-point SMBG		Use (mg/dL) [A1] Pre-Morning Meal BG [A2] Morning Meal 2-hr PPBG [A3] Pre-Midday Meal BG [A4] Midday Meal 2-hr PPBG [A5] Pre-Evening Meal BG [A6] Evening Meal 2-hr PPBG	Observed score and change from baseline	Missing if baseline or observed value is missing.
6-point SMBG		Use (mg/dL) [B1] Morning pre meal to 2-hr excursion [B2] Midday pre meal to 2-hr excursion [B3] Evening pre meal to 2-hr excursion	Observed score and change from baseline [B1] = [A2]-[A1] [B2] = [A4]-[A3] [B3] = [A6]-[A5]	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if Missing Components (postbaseline visit)
6-point SMBG		Use (mg/dL) [C1] Mean of all pre meals to 2-hr excursion [C2] Mean of all 6-point BG [C3] Mean of all pre-meals BG [C4] Mean of all postprandial meals BG	[C1] = Average([B1], [B2], [B3]) [C2] = Average([A1], [A2], [A3], [A4], [A5], [A6]) [C3] = Average([A1], [A3], [A5]) [C4] = Average([A2], [A4], [A6])	When taking average, use non-missing values and take their average. If all values are missing, then the mean is considered as "missing." If baseline or observed value is "missing," then it is missing. E.g., If [A5] is missing, then [C3] =Average([A1], [A3])
6-point SMBG		Use (mg/dL) Daily Circadian Variation in 6-point BG	Observed score and change from baseline Max([A1], [A2], [A3], [A4], [A5], [A6]) - Min([A1], [A2], [A3], [A4], [A5], [A6])	Missing if all [A1]-[A6] are missing. When taking max or min, use non-missing values.

Abbreviations: BG = blood glucose; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; PPBG = postprandial blood glucose; SMBG = self-monitored blood glucose.

6.2. Appendix 2: Description of Efficacy and Health Outcome Analyses

Table GBGQ.6.2. Description of Efficacy and Health Outcome Analyses

Measure	Variable	Estimand (Section 1.1.1)	Analysis Method (Section 4.1)	Analysis Set (Section 3)	Comparison/Time Point	Analysis Type
HbA1c	Change from baseline	Primary Estimand (Hypothetical)	MMRM	ITT	DULA1.5 vs DULA0.75. Interim: Week 8, 16, 26 Final: Week 8, 16, 26, 38, 52	Week 26: primary analysis: Other weeks: secondary analysis
HbA1c	Proportion of participants achieving HbA1c target of ≤6.5% and <7.0%	Hypothetical	GLM	ITT	DULA1.5 vs DULA0.75. Interim: Week 8, 16, 26 Final: Week 8, 16, 26, 38, 52	Secondary analysis
FSG	Change from baseline	Primary Estimand (Hypothetical)	MMRM	ITT	DULA1.5 vs DULA0.75. Interim: Week 8, 16, 26 Final: Week 8, 16, 26, 38, 52	Secondary analysis
Body weight	Change from baseline	Primary Estimand (Hypothetical)	MMRM	ITT	DULA1.5 vs DULA0.75. Interim: Week 8, 16, 26 Final: Week 8, 16, 26, 38, 52	Secondary analysis

Approved on 14 Oct 2022 GMT

Measure	Variable	Estimand (Section 1.1.1)	Analysis Method (Section 4.1)	Analysis Set (Section 3)	Comparison/Time Point	Analysis Type
6-point SMBG	Change from baseline: [A1] Pre-Morning Meal BG [A2] Morning Meal 2-hr PPBG [A3] Pre-Midday Meal BG [A4] Midday Meal 2-hr PPBG [A5] Pre-Evening Meal BG [A6] Evening Meal 2-hr PPBG [B1] Morning pre meal to 2-hr excursion [B2] Midday pre meal to 2-hr excursion [B3] Evening pre meal to 2-hr excursion [C1] Mean of all pre meals to 2-hr excursion [C2] Mean of all 6-point BG [C3] Mean of all pre-meals BG [C4] Mean of all postprandial meals BG	Hypothetical	ANCOVA	ITT	DULA1.5 vs DULA0.75. Interim: Week 26 Final: Week 26 (No data at Week 52)	Secondary analysis
6-point SMBG	Change from baseline: Circadian Variation in 6-point BG	Hypothetical	ANCOVA	ITT	DULA1.5 vs DULA0.75. Interim: Week 26 Final: Week 26 (No data at Week 52)	Secondary analysis

Abbreviations: ANCOVA = analysis of covariance; BG = blood glucose; DULA0.75 = Dulaglutide 0.75 mg arm; DULA1.5 = Dulaglutide 1.5 mg arm; FSG = fasting serum glucose; GLM= generalized linear model; HbA1c = hemoglobin A1c; ITT = Intention-to-treat population; MMRM = mixed-effects model for repeated measures; PPBG = postprandial blood glucose; SMBG = self-monitored blood glucose.

6.3. Appendix 3: Demographic and Baseline Characteristics

Participant demographic variables and baseline characteristics will be summarized (All Randomized population). The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No formal statistical comparisons will be made between treatment groups unless otherwise specified.

The following demographic information will be included:

- Age/Sex/Race/Country
- Body Weight (kg) / Height (cm) / BMI
- HbA1c (%, mmol/mol)
- HbA1c Category (Low/High defined as stratification factor in Table GBGQ.1.3, value < 8.5, 8.5 <= value, value < 9.0, 9.0 <= value)
- Fasting Blood Glucose (mg/dL, mmol/L) (show mean/SD/median/ min/max)
- eGFR Group (Stage G1/G2/G3a/G3b/G4/G5)
- Duration of Diabetes (years) (show mean/SD/median/ min/max)
- Duration of Diabetes (< Median, >= Median)
- Duration of Diabetes (< 5 years, >= 5 to < 10 years, >= 10 years)
- Systolic BP (mm Hg)/ Diastolic BP (mm Hg)/ Pulse (bpm)
- Age subgroup 1 (years) (2 groups: value < 65, 65<= value)
- Age subgroup 2 (years) (3 groups: value < 65, 65<= value < 75, 75 <= value)
- Body Weight (kg) (2 groups: value < median, median <= value)
- Baseline BMI (2 groups: value < 25, 25 <= value)

By-participant listings of basic demographic information will be provided.

6.4. Appendix 4: Medical History

Historical illnesses are defined as the conditions/events with an **end date prior** to the informed consent date.

Pre-existing conditions are defined as the conditions/events with a **start date prior** to the informed consent date and with **an end date on or after** the informed consent date.

Following TFLs will be created

- Summary of Pre-existing Conditions
- Listing of Historical Illnesses
- Listing of Pre-existing Conditions and Adverse Events
- Listing of Pre-existing Conditions

6.5. Appendix 5: Treatment Compliance

"Treatment compliant to study intervention" is defined as "treatment compliance >= 75%" where,

$$Treatment\ compliance\ (\%) = 100 \times \frac{Number\ of\ injections\ administered}{Number\ of\ injections\ administered + not\ administered}$$

The numerator and denominator are based on CRF (Exposure: Dulaglutide).

Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment arm using the ITT population. Its listing will be created.

Of the participants in the ITT population, frequency counts and percentages of participants prematurely discontinuing study interventions, including the reason for premature discontinuation, will be presented by treatment arm.

A Kaplan-Meier analysis of time from randomization to premature study intervention discontinuation by treatment arm will be provided.

6.6. Appendix 6: Prior and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to the date of first dose of treatment in each treatment period to allow medications to be classified as concomitant for each treatment period.

Prior medications are those medications that start prior to the date of first dose and stop prior to or on the date of first dose of study intervention.

Concomitant medications are those medications that start before, on, or after the first day of study intervention of the defined treatment period and continue into the treatment period.

Following Prior and/or Concomitant medication TFLs will be created:

- Summary of General Concomitant Medication
- Listing of General Concomitant Medication
- Listing of Prior/Concomitant Oral Antidiabetic Agents
- Summary of Oral Anti-Diabetic Medication (Prior Medications)
- Summary of Dose Modification of Oral Anti-Diabetic Medication **During the Study Period**
  - It is based on the baseline OAM. For example, if a patient with baseline OAM biguanide starts DPP-4 inhibitors after randomization, it will not appear in this table.
  - The modification is categorized as Decreased/Increased/Stopped.
  - Fisher Exact test is used for the treatment comparison (Decreased events).
- Summary of OAM Mean Daily Doses (mg/day)
- Listing of Insulin Therapy for Severe, Persistent Hyperglycemia (See Section 4.6.3.5.1)

- Summary of Insulin Therapy for Severe, Persistent Hyperglycemia During the Treatment Period (See Section 4.6.3.5.1)
  - Note: Fisher Exact test is used for the treatment comparison.

6.7. Appendix 7: Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations are defined as those deviations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

Refer to a separate document called "GBGQ Trial Issues Management Plan" for the important protocol deviations with categorizations.

The number and percentage of participants having IPD(s) will be summarized within

- Protocol Deviation Category,
- Study Specific Deviation Term

by treatment group.

A by-participant listing of important protocol deviations will be provided.

6.8. Appendix 8: Impact of COVID-19

Impact of pandemic (e.g., COVID-19) on analyses will be collected Disposition CRF (for disposition). Protocol deviation/mitigation will be collected through Clinical Trial Management System (CTMS). Those are identified as having the text "COVID-19:" at the beginning of their descriptions.

Impact of pandemic (e.g., COVID-19) on analyses will be systemically addressed.

Following TFLs will be created:

- Listing of Patient Disposition Affected by COVID-19
- Summary of Protocol Deviations/Mitigation Related to COVID-19
  - Note: It include following categories:
    - Protocol Deviation Category,
    - Study Specific Deviation Term.
- Listing of Protocol Deviations/Mitigation Related to COVID-19

6.9. Appendix 9: Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.10. Appendix 10: Clinical Trial Registry Analyses

Additional analyses will be performed (if not already available from the study CSR) for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset, will be converted to an XML file. Both serious adverse events (SAEs) and 'Other' AEs are summarized by treatment group and by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event,
    - the number of participants who experienced each event term, and
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participants in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

6.11. Appendix 11: Unblinding Plan

Unblinding details are specified in a separated unblinding/blinding plan.

7. References

Andersen SW, Millen BA. On the practical application of mixed effects models for repeated measures to clinical trial data. *Pharm Stat*. 2013;12(1):7–16. https://doi.org/10.1002/pst.1548

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Approval	PPD Statistician 14-Oct-2022 06:22:17 GMT+0000

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Approved on 14 Oct 2022 GMT