H9X-MC-GBGL Statistical Analysis Plan Version 2.0

A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus

NCT03495102

Approval Date: 06-Jun-2019

1. Statistical Analysis Plan for H9X-MC-GBGL: A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus (AWARD-11)

Dulaglutide (LY2189265) Type 2 Diabetes

Study H9X-MC-GBGL is a Phase 3, randomized, double-blind trial designed to assess the efficacy and safety of once weekly investigational dulaglutide doses (4.5 mg or 3.0 mg) compared to dulaglutide 1.5 mg in patients with type 2 diabetes mellitus on metformin monotherapy.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol H9X-MC-GBGL
Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 05 March 2018
Statistical Analysis Plan Version 2.0 electronically signed and approved by Lilly on date provided below.

Approval Date: 06-Jun-2019 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

Table of Contents

Appendix **Page**

3. Revision History

SAP Version 1.0 was approved prior to first patient visit.

SAP Version 2.0 was approved prior to 36-week database lock. Key changes include:

- Clarified definition of "rescue" for efficacy estimand and health economics analyses as newly initiated antihyperglycemic medications taken for more than 14 days.
- Updated the graphical approach testing scheme.
- Removed the effect of "other antihyperglycemic medication usage (yes, no)" from all treatment-regimen estimand analyses to avoid potential confounding induced by this posttreatment intervention and to align with the model originally included in the protocol.
- Removed the tipping point analysis.
- Removed selected hyperglycemia analyses and added analyses for hypoglycemia with glucose <54 mg/dL, regardless of symptoms or rescue status.
- Removed treatment exposure analysis from the Completers and Per Protocol (PP) populations.
- Clarified baseline as the last nonmissing value taken up to the first dose date/time.
- Clarified treatment-regimen estimand missing data imputation for glycated hemoglobin A1c (HbA1c) <7.0%.
- Provided definition of the Safety Population, which has the same definition as the Intent-to-Treat (ITT) Population.
- Moved the multiple imputation based on retrieved dropouts from Section 6.9.1.2 to Section 6.1.2.1.
- Removed the summary by preferred term within system organ class for serious adverse events or adverse events leading discontinuation, including death.
- Changed the Fisher's exact test to Chi-square test for categorical patient characteristic treatment comparison to overcome the computational challenge.
- Removed sections for annual report analyses and clinical trial registry analyses, as they are not relevant for the clinical study report (CSR).
- Added clarification related to rescue therapy definition in Section 6.10.1.2.2.
- Added observed margins (OM) option in LSMEANS statement whenever this option is allowed.
- Added an appendix with a summary of the data and primary analysis for the primary and secondary efficacy endpoints by type of estimand.

4. Study Objectives

Table GBGL.1 shows the objectives and endpoints of the study.

Table GBGL.1. Objectives and Endpoints

Objectives	Endpoints
Primary To demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg as measured by change from baseline in HbA1c at 36 weeks in patients with inadequately controlled T2D on concomitant metformin therapy.	• The change in HbA1c from baseline
Secondary ***Efficacy:*** To demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg for secondary efficacy parameters at 36 weeks (controlled for Type 1 error).	• The change in body weight from baseline • Proportion of patients achieving HbA1c target <7.0% (53 mmol/mol) • The change in fasting serum glucose (FSG) from baseline
Safety: To compare each investigational dulaglutide arm (4.5 mg, 3.0 mg) to the 1.5 mg arm for selected safety parameters through 36 and 52 weeks (unless noted otherwise).	• Incidence of treatment-emergent adverse events (TEAEs) and discontinuation of study drug due to adverse events (AEs) • Adjudicated and confirmed cardiovascular and pancreatic AEs • Incidence of thyroid neoplasm AEs • Incidence of treatment-emergent (TE) dulaglutide anti-drug antibodies (ADA) and systemic hypersensitivity reactions • Changes from baseline in pulse rate • Electrocardiogram (ECG) parameters • Occurrence of hypoglycemic episodes
Pharmacokinetics (PK) and Pharmacodynamics (PD): To characterize dulaglutide PK and the dose and/or exposure-response relationships for key efficacy (eg, HbA1c and weight), and safety (eg, heart rate [HR]) endpoints.	• PK parameters (eg, maximum concentration [C_{max}], area under the curve [AUC]) at steady state • PD evaluations may include changes from baseline in HbA1c, body weight, and HR at Weeks 36 and 52

Objectives	Endpoints
Tertiary/Exploratory To compare once weekly dulaglutide 4.5 mg and 3.0 mg to the 1.5 mg arm as measured by the primary and secondary outcome measures at 52 weeks.	• The change in HbA1c from baseline • The change in body weight from baseline • Proportion of patients achieving HbA1c target <7.0% (53 mmol/mol) • The change in FSG from baseline
To compare once weekly dulaglutide 4.5 mg and 3.0 mg to the 1.5 mg arm for exploratory measures through 36 and 52 weeks (unless noted otherwise).	• Proportion of patients achieving HbA1c target ≤6.5% (48 mmol/mol) • Change from baseline in 6-point self-monitored plasma glucose (SMPG) profile • Proportion of patients achieving ≥5% body weight loss • Proportion of patients achieving ≥10% body weight loss • Proportion of patients meeting the composite endpoint of HbA1c <7.0% (53 mmol/mol), no weight gain, and no documented symptomatic or severe hypoglycemia • Proportion of patients meeting the composite endpoint of HbA1c <7.0% (53 mmol/mol), body weight loss ≥5%, and no documented symptomatic or severe hypoglycemia • Changes from baseline in fasting plasma glucagon, HOMA2-%B, HOMA2-IR, and C-peptide • Changes from baseline in serum cystatin C and cystatin C-based assessment of eGFR • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia • Changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate pressure product (RPP) • Changes from baseline in serum lipid parameters (total cholesterol, high density lipoproteins [HDL], low density lipoproteins [LDL], very low density lipoproteins [VLDL], and triglycerides) • Diabetes Injection Device Experience Questionnaire (DID-EQ) scores at Week 12 • Changes from baseline in EQ-5D-5L scores • Changes from baseline in Impact of Weight on Self-Perception Questionnaire (IW-SP) scores • Changes from baseline in Ability to Perform Physical Activities of Daily Living (APPADL) scores

Objectives and Endpoints

Abbreviations: eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life 5–Dimension 5 Level; HbA1c = glycated hemoglobin A1c; HOMA2-%B = β-cell function as measured by the Homeostasis Model Assessment-2 method; HOMA2-IR= insulin resistance as measured by the HOMA2 method; T2D = type 2 diabetes mellitus.

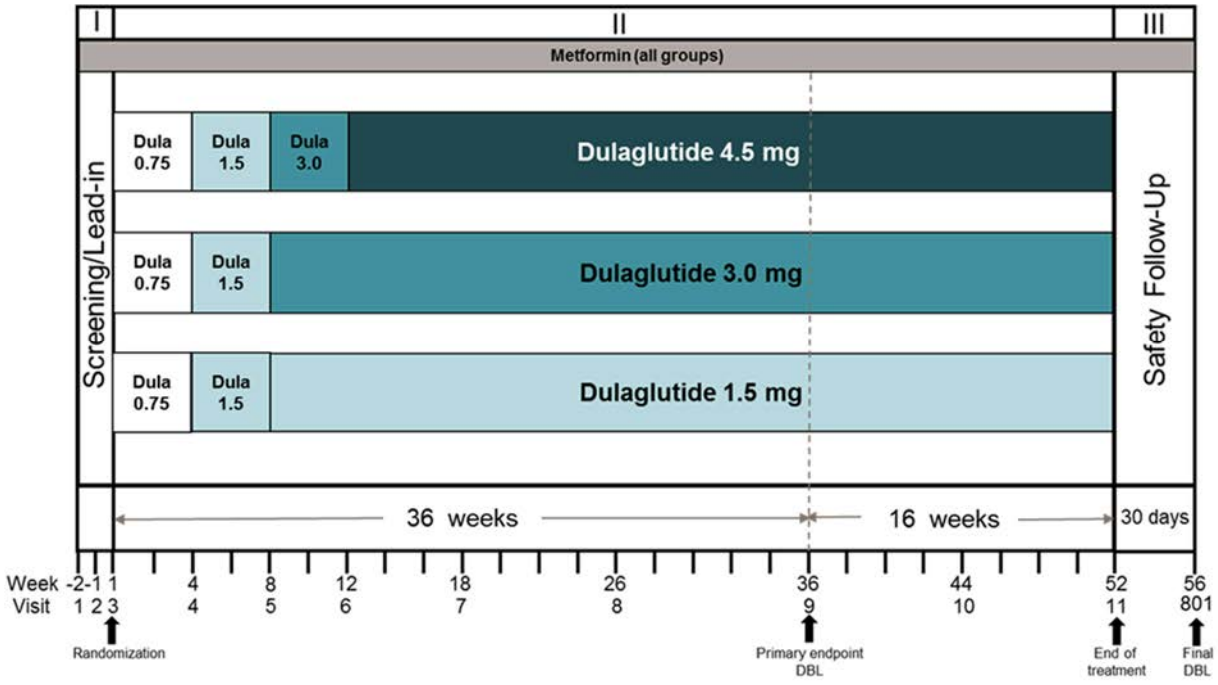
5. Study Design

5.1. Summary of Study Design

Study H9X-MC-GBGL (GBGL) is a 52-week, Phase 3, double-blind, multicenter, parallel arm study. The study is designed to assess the efficacy and safety of once weekly dulaglutide 4.5 mg and 3.0 mg in comparison to once weekly dulaglutide 1.5 mg following a primary 36-week treatment period and at the end of the 52-week Treatment Period. The primary objective of this trial is to demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg as measured by change from baseline in HbA1c at 36 weeks in patients with type 2 diabetes mellitus who are inadequately controlled on concomitant metformin therapy. Secondary objectives (controlled for Type 1 error) are to demonstrate superiority of at least 1 of the higher dulaglutide doses to dulaglutide 1.5 mg at 36 weeks on changes in body weight, proportions of patients achieving HbA1c <7.0% (53 mmol/mol), and changes in fasting serum glucose (FSG) from baseline at Week 36 (Visit 9).

The study will consist of 3 periods: an approximately 2-week Lead-In Period followed by a 52-week Treatment Period (primary efficacy endpoint at Week 36 [Visit 9]) and a 4-week Safety Follow-Up Period.

Figure GBGL.1 illustrates the study design.



Abbreviations: DBL = database lock; Dula = once weekly dulaglutide.
Note: All dulaglutide doses are once weekly.

Figure GBGL.1. Illustration of study design for Clinical Protocol H9X-MC-GBGL.

5.2. Determination of Sample Size

Assuming a screen failure rate of 40%, approximately 3000 patients will need to be screened to attain approximately 1800 patients randomized to the 3 treatment groups (600 patients/group) in a 1:1:1 ratio for dulaglutide 4.5 mg, 3.0 mg, and 1.5 mg. Assuming 15% dropout rate, this will result in approximately 510 patients per arm completing 36 weeks of treatment (the primary endpoint).

The aforementioned sample size provides ≥80% power to demonstrate superiority of at least 1 of the investigational dulaglutide doses (4.5 mg or 3.0 mg) to dulaglutide 1.5 mg with respect to the primary endpoint (change from baseline in HbA1c) at Week 36 (Visit 9). This sample size is calculated based on the assumption that there is a treatment difference (for either investigational dose) in HbA1c change from baseline of approximately -0.22%, a standard deviation (SD) of 1.1%, and a 2-sided alpha of 0.05.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized at Visit 3 to 1 of the 3 treatment arms in a 1:1:1 ratio: dulaglutide 4.5 mg, 3.0 mg, or 1.5 mg once weekly. Full dosing details, including dose escalations, are presented in GBGL Protocol Section 7.1 and GBGL Protocol Table GBGL.2.

Block randomization will be used at the country level. Randomization will be stratified by HbA1c (<8.5% [69 mmol/mol] and ≥8.5% [69 mmol/mol]).

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the CSR. Some analyses described in this SAP related to exploratory objectives may not be conducted if not warranted by data. Additional analyses of the data may be conducted as deemed appropriate without further changes made to the protocol or SAP even after the primary or final database lock (DBL).

Efficacy analyses will be conducted for the ITT Population. There will be 2 primary estimands to compare treatment groups in terms of the primary measure of HbA1c change from baseline to Week 36 (Visit 9). A table that summarizes the analyses for the 2 estimands for the primary and secondary endpoints is in Appendix 1.

One primary estimand will be an efficacy estimand (*de jure* effect), which will use the data collected up to either initiation of any new antihyperglycemic medication (regardless of whether the investigator indicated that it was for severe persistent hyperglycemia) for more than 14 days or premature treatment discontinuation (whichever occurs first) to demonstrate the effect of treatment and avoid confounding effects of other antihyperglycemic agents (Little and Kang 2015). This will also be referred to as the "on-treatment without rescue analysis" throughout this document unless otherwise specified. In addition, analyses for the treatment-regimen estimand will include all patients in the ITT Population who have a baseline measurement for the parameter of interest. The other primary estimand will be a treatment-regimen estimand (*de facto* effect), which will include data collected after initiation of other antihyperglycemic therapy and/or after premature treatment discontinuation. In addition, analyses for the efficacy estimand will include patients in the ITT Population who have a baseline and at least 1 postdose measurement for the parameter of interest.

The treatment-regimen estimand is included as primary at the request of the US Food and Drug Administration (FDA). The efficacy estimand will be considered primary for all other purposes, and will be applied to all efficacy outcomes unless otherwise specified to demonstrate the effect of treatment and avoid confounding effects with other antihyperglycemic agents.

Each of the estimands will be tested at the full significance level of 0.05.

Analyses of safety parameters will be conducted for the Safety Population unless otherwise specified.

Countries with fewer than 10 randomized patients will be pooled for statistical analyses. Pooled country will be employed for all formal statistical model-based analyses as a block factor unless otherwise denoted.

Unless otherwise specified, 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 treatments and factors of interest will be conducted at a 2-sided alpha level of 0.10. Multiplicity adjustment will be performed among the hypotheses related to the primary and secondary efficacy endpoints.

The baseline visit will be Visit 3. For all variables, including HbA1c, if baseline data are not available or are missing, the last nonmissing measurement taken up to the first dosing date/time will be used for the baseline measurement. The efficacy measure for the primary analysis is defined as the change from baseline in HbA1c to Week 36 (Visit 9).

For all statistical analyses, missing data will be treated as missing at random for all analyses unless otherwise specified.

The treatment groups mentioned in this document are based on the randomized treatment groups: dulaglutide 4.5 mg, dulaglutide 3.0 mg, and dulaglutide 1.5 mg.

All efficacy and safety data will be summarized by each treatment group at each scheduled visit unless otherwise indicated. Dulaglutide 1.5 mg will serve as the reference treatment for treatment comparison in all efficacy analyses unless otherwise specified.

The efficacy estimand analysis for a longitudinal continuous variable will employ a mixed-model repeated measure (MMRM) using restricted maximum likelihood to obtain model estimates with Kenward-Roger option to estimate denominator degrees of freedom. The model will include factors for treatment, pooled country, visit, treatment-by-visit interaction, and the baseline as a covariate. The observed margins option will be used in the LSMEANS statement whenever this option is allowed. For analyses of body weight and FSG, the baseline HbA1c strata ($\geq$8.5% [69 mmol/mol] and <8.5%) will be added in this model as a fixed effect. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the following covariance structures will be tested in order:

- toeplitz with heterogeneity
- autoregressive with heterogeneity, by visit
- compound symmetry with heterogeneous variances, by visit
- toeplitz
- autoregressive
- compound symmetry without heterogeneous variances, by visit
- compound symmetry

The first covariance structure that converges will be used.

The analysis model for nonlongitudinal continuous variables will be analysis of covariance (ANCOVA) coupled with imputation for missing endpoints unless otherwise noted.

For continuous laboratory measurements for safety, an analysis of variance (ANOVA) on ranks on change from baseline using last observation carried forward (LOCF) at Week 36 (Visit 9) and/or Week 52 (Visit 11) will be used with treatment as a fixed effect.

For all continuous measures, summary statistics will include number of patients, mean, SD, median, minimum, and maximum for both the actual and change from baseline values at each scheduled visit for each treatment unless otherwise specified. Least-squares means (LS means) and standard errors derived from the model will also be displayed for the change from baseline values at each scheduled visit for each treatment. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs between each investigational dulaglutide dose and dulaglutide 1.5 mg (treatment differences) at the same visit, along with the corresponding p-values.

Summary statistics for categorical measures will include number of subjects and percentages. The proportions of patients achieving target HbA1c <7.0% and ≤6.5% at Week 36 (Visit 9) will be analyzed using a longitudinal logistic regression with repeated measurements. In this model, pooled country, treatment, visit, and treatment-by-visit interaction will be fit as fixed effects, and baseline HbA1c as a covariate. A logistic regression model will be applied for the aforementioned HbA1c target analysis at Week 36 (Visit 9) using LOCF by removing visit-related terms from the corresponding longitudinal logistic regression model.

For the analysis of other categorical measures, Fisher's exact test will be used for treatment comparisons unless otherwise specified. Categorical variables will be summarized by sample size and the number of patients and percentages for each treatment group at each visit. Imputed data may be applied in model-based data analyses, but will not be used in data listings. The latter will only present the non-imputed raw data, including site-reported scheduled and unscheduled visits, or early termination visit data; however, only scheduled visits for the measure of interest will be included in the summary table and statistical inference unless otherwise stated.

All statistical analyses will be conducted with SAS Version 9.4® or higher unless otherwise stated.

For primary DBL, all tables, figures, and listings (TFLs) will use the data up to Week 36 (Visit 9) or the study discontinuation date, whichever is earlier, unless otherwise specified.

For the final DBL delivery, TFLs will use the data up to the end of the treatment period (Week 52 [Visit 11]) or the study discontinuation date, whichever is earlier, unless otherwise stated.

Before each DBL, all key data will be reviewed. Any decision to exclude either subjects or observations from the statistical analyses will be made and documented by the study team, and will include the rationale.

6.1.1. Adjustments for Covariates

The study is stratified by baseline HbA1c with country as a block factor; therefore, both stratification factors (baseline HbA1c <8.5% or ≥8.5% and pooled country) will be fit in the corresponding statistical model as fixed effects for the non-HbA1c measurements unless otherwise stated. For analyses of HbA1c, the strata of baseline HbA1c will be replaced with the

covariate of baseline HbA1c. For other continuous variables other than some safety laboratory measures, a corresponding baseline measure will be added as a covariate.

6.1.2. Handling of Dropouts or Missing Data

6.1.2.1. Multiple Imputation Based on Retrieved Dropouts

The primary and key secondary continuous endpoints for the treatment-regimen estimands will adopt the below missing data imputation method.

All data including those collected after rescue and/or treatment discontinuation will be included in the analyses. The missing data will be imputed based on retrieved dropouts defined as patients who had their HbA1c value measured at Week 36 (Visit 9) in the same treatment arm and the same status of premature treatment discontinuation (yes, no). Thus, for patients who prematurely discontinue treatment, missing data will be imputed based on patients who prematurely discontinued study drug, continued in the study, and had their HbA1c value measured at Week 36 (Visit 9). For patients who did not discontinue study drug but are missing their HbA1c value at Week 36 (Visit 9) (due to missing that visit, for example) and continued in the trial on treatment, the missing data will be imputed based on patients with an HbA1c value measured at Week 36 (Visit 9) on treatment.

This differs in how retrieved dropouts were originally defined in the protocol, where all missing data were imputed based on patients who prematurely discontinued treatment but still had their measurements taken at the primary endpoint Week 36 (Visit 9). While every effort will be taken to ensure patients attend all scheduled protocol visits, it is possible that some patients will be unable to attend Week 36 (Visit 9) and thus have missing HbA1c data at the primary endpoint, but continue in the trial on treatment beyond the 36-week time point. Retrieved dropouts as defined in the protocol do not adequately cover this missing pattern. Under this revised definition, it is assumed that the most likely values of the missing data would have been, if available, best imputed by information from patients who at Week 36 (Visit 9) are similar in terms of both randomized treatment assignment and treatment completion status. If the absolute value of the imputed HbA1c change from baseline is <-4.5% or >4.5%, that value will be set to -4.5% or 4.5%, respectively, to avoid unrealistic imputed values.

The pattern mixture model (PMM) depends on the probability mass function of possible missing data patterns, which would not be known a priori. This proposed multiple imputation may require post hoc changes after either of the DBLs to resolve any convergence issues due to the inadequate number of retrieved dropout patterns. The latter may lead to choosing a simpler imputation model, which may be subject to model misspecification on top of the unverifiable missing not at random (MNAR) assumption.

The proposed multiple imputation may require post hoc changes after database lock to resolve any convergence issues.

6.1.2.2. Other Imputation Methods

For analysis of patients achieving HbA1c target <7.0%, those who have missing data at Week 36 (Visit 9) will be imputed as not reaching the HbA1c target as a sensitivity analysis for the efficacy estimand. This, however, will be the primary analysis for the treatment-regimen estimand.

The LOCF method will be used to impute the missing endpoint data for the other binary efficacy endpoints such as HbA1c target and nonlongitudinal continuous variables up to Week 36 (Visit 9) and 6-point self-monitored plasma glucose (SMPG), β-cell function as measured by the Homeostasis Model Assessment-2 method (HOMA2-%B) and insulin resistance as measured by the HOMA2 method (HOMA2-IR), C-peptide, fasting insulin, fasting glucagon, and the selected safety laboratory measures.

Any missing component of date and/or time will be imputed following Lilly or dulaglutide compound level standards. For example, the missing day or month could be imputed with the first day of the month, or first month of the year.

If the first dosing date/time is missing, the nonmissing randomization date will be used to impute the first dosing date.

Other imputation may be applied if deemed necessary even after this document is approved. This addition or even change does not require an SAP revision. Rather, these detailed imputation rules will be documented.

6.1.3. Multicenter Studies

No analyses related to site are planned.

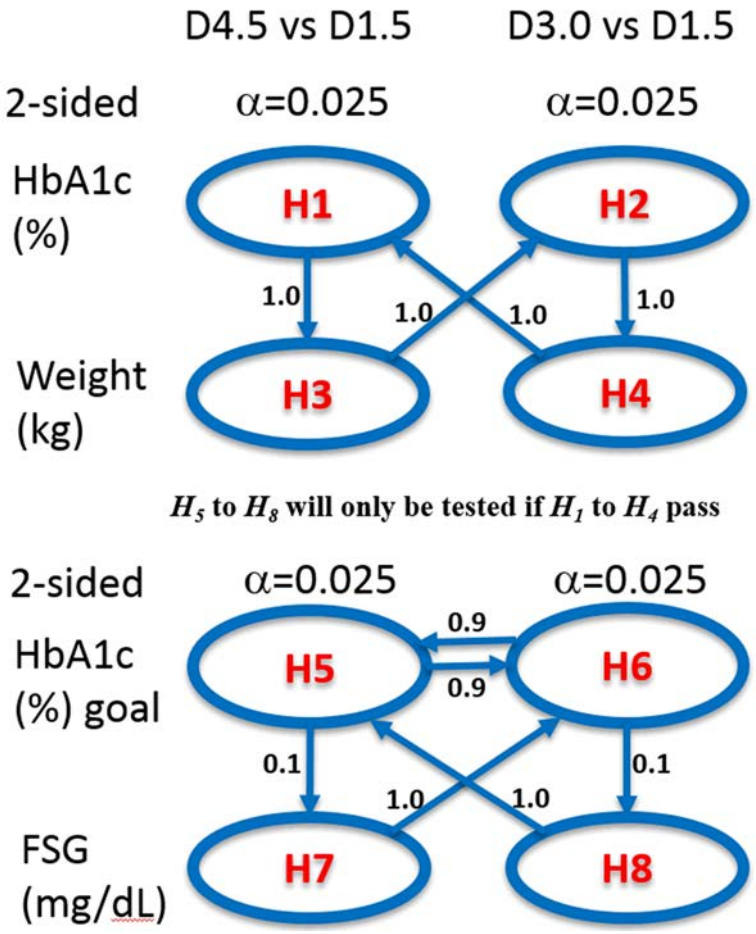
6.1.4. Multiple Comparisons/Multiplicity

To control overall Type 1 error, the graphical approach (Bretz et al. 2011) presented in Figure GBGL.2 will be used to compare the treatment effect among the pre-defined parameters of interest to address the primary and the key secondary efficacy objectives defined in the protocol at Week 36 (Visit 9) for the ITT Population. In this figure, the overall significance level of 2-sided α=0.05 will be equally split between H_1 and H_2 with 0.025 to H_1 and 0.025 to H_2. H_5 to H_8 will only be tested if H_1 to H_4 pass. The number attached for certain edges denotes the proportion of the allocated fraction of α from a prespecified hypothesis (node), if it is confirmed, that will be passed to the next hypothesis.

This graphical approach will be conducted separately for each of the 2 estimands, and each will be tested at the full significance level of 0.05:

- Treatment-regimen estimand
- Efficacy estimand

The below graphical scheme may be revised per the observed correlation matrix using blinded data among the parameters of interest at Week 36 (Visit 9) prior to the primary DBL.



Abbreviations: D1.5 = once weekly dulaglutide 1.5 mg; D3.0 = once weekly dulaglutide 3.0 mg; D4.5 = once weekly dulaglutide 4.5 mg; FSG = fasting serum glucose; H = hypothesis; HbA1c = glycated hemoglobin A1c.

Figure GBGL.2. Graphical testing scheme for Study H9X-MC-GBGL.

H_1: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in mean change from baseline in HbA1c at 36 weeks

H_2: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in mean change from baseline in HbA1c at 36 weeks

H_3: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in mean change from baseline in body weight at 36 weeks

H_4: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in mean change from baseline in body weight at 36 weeks

H_5: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in proportion of patients achieving an HbA1c <7.0% at 36 weeks

H_6: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in proportion of patients achieving an HbA1c <7.0% at 36 weeks

H_7: Superiority test of dulaglutide 4.5 mg versus dulaglutide 1.5 mg in mean change from baseline in FSG at 36 weeks

H_8: Superiority test of dulaglutide 3.0 mg versus dulaglutide 1.5 mg in mean change from baseline in FSG at 36 weeks

6.2. Patient Populations

Six patient populations are defined for the analyses in this study with detailed information listed in Table GBGL.2. Unless otherwise specified, listings will include All Randomized Patients. Efficacy analyses will be conducted for the ITT Population, and safety analyses will be conducted for the Safety Population. The primary efficacy measure (change from baseline in HbA1c) will also be evaluated in the PP and Completers populations.

In all efficacy analyses, except for treatment-regimen estimands, all data after rescue and/or treatment discontinuation (Section 6.1) will be censored. Analyses of safety parameters will be conducted for the Safety Population including the postrescue therapy data unless otherwise specified.

Table GBGL.2. Populations for Analyses

Population	Description
Entered	All patients who sign informed consent
All Randomized	All patients who are randomized
Intent to Treat (ITT)	All patients who are randomized and take at least 1 dose of study medication for an assigned treatment arm[a]
Safety	All patients who are randomized and take at least 1 dose of study medication for the assigned treatment arm
Completers	All ITT patients who have an HbA1c measure at Week 36 (Visit 9), regardless of compliance with the protocol, rescue medication, or treatment discontinuation. However, data collected after rescue and/or treatment discontinuation will be excluded
Per Protocol (PP)	All ITT patients who meet all of the following criteria: • Have no important protocol deviation that could impact the assessment of the primary endpoint (Section 6.8) • At least 75% compliant with study drug administration through Week 36 (Visit 9) • Complete the treatment period through 36 weeks (Visit 9) • Have a value of the primary efficacy measure (HbA1c) at Week 36 (Visit 9) excluding data collected after treatment discontinuation or initiation of new antihyperglycemic therapy

Abbreviation: HbA1c = glycated hemoglobin.

a Analyses using the treatment-regimen estimand will include all patients in the ITT population who have a baseline measurement for the parameter of interest, while analyses using the efficacy estimand will include patients in the ITT population who have a baseline and at least 1 postdose measurement for the parameter of interest.

6.3. Patient Disposition

The reasons for patient discontinuations from study treatment and from the study will be summarized for the All Randomized Population by treatment.

Kaplan-Meier curves by treatment for time to study treatment discontinuation due to any reason, and due to adverse event (AE) up to Week 36 (Visit 9) (primary DBL) or Week 52 (Visit 11) (final DBL) will be displayed separately. The log-rank p-value will be presented.

In addition, all entered patients will be summarized including, but not limited to, the total number of patients screened (entered) and the number of patients excluded due to screen failure. Patient disposition will be listed for the All Randomized Population.

6.4. Patient Characteristics

Demographic and baseline clinical characteristics will be summarized by treatment for the ITT, PP, and Completers populations separately. A Chi-square test will be used for treatment comparisons on categorical data analysis.

6.5. Concomitant Therapy

The prespecified concomitant medications of interest will be summarized by treatment for baseline and after randomization for the ITT Population. The concomitant therapies will be mapped using the World Health Organization Drug Dictionary in the clinical trial database and will be further classified using Anatomical Therapeutic Chemical (ATC) codes for reporting purposes.

The agents of interest for the summary report include the following groups of medication:

- antihyperglycemic agents
    - background metformin therapy
    - agents used for short-term therapy for acute condition (up to 14 days)
    - rescue therapy (only applicable after randomization)
    - agents initiated after permanent discontinuation of study drug (only applicable after randomization)
    - agents used for other reasons
- weight loss medications
- systemic glucocorticoids
- antihypertensive agents
- lipid-lowering agents
- antithrombotic agents
- anti-inflammatory agents

6.6. Treatment Compliance

Treatment compliance will be collected by sites using the compliance case report form (CRF). The compliance for each visit is defined as taking at least 75% of the scheduled injections of the study treatment for the period preceding that visit. Overall treatment compliance for each patient is defined as taking at least 75% of the injectable treatment for at least 75% of the nonmissing

visits, that is, the overall compliance percentage is at least 75% for this patient. The overall compliance in percentage for each patient will be calculated by taking the number of visits the patient was compliant divided by the total number of visits with nonmissing compliance data for this patient ×100. Treatment compliance will be summarized descriptively by treatment using the ITT Population.

6.7. Treatment Exposure

Treatment exposure is estimated using each patient's first dose and last dosing date. If the first dosing date is missing, it will be imputed with the date of randomization. If the last dosing date is missing, it will be imputed with the date the patient discontinued treatment, discontinued the study, or completed the 36-week (Visit 9) or 52-week (Visit 11) treatment period, whichever is earlier.

Exposure will be calculated for each patient. It will then be summarized descriptively by treatment for the ITT Population.

6.8. Important Protocol Deviations

Important protocol deviations will be summarized descriptively by treatment and listed for all randomized patients. All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment will be described. The rationale for choosing certain important protocol deviations as exclusionary from the PP Population will be based on their potential effect on the primary efficacy measure. The following protocol conditions as well as other conditions identified at the site and agreed upon by the study team may result in exclusion from the PP Population along with the criteria listed in Table GBGL.2:

- informed consent was never obtained
- patients who are randomized but the informed consent date is missing
- patients who have an HbA1c <7.5% or >11.0% at study entry (Visit 1)
- patients who have known type 1 diabetes
- patients who had any hematologic condition that may have interfered with HbA1c measurement (for example, hemolytic anemias, sickle-cell disease)
- excluded medication:
    - weight loss agents if the duration of use is 14 days (cumulative) during the treatment period
    - any new glucose-lowering medication initiated after randomization at Visit 3 and prior to Visit 11 (end of treatment period) for >14 days, except for study drug, rescue therapy, glucose-lowering medications initiated after study drug discontinuation, or short-term use of insulin (≤14 days) for management of medical emergencies
    - >14 consecutive days' use of systemic glucocorticoid during the treatment period

- patients who have a missing HbA1c at baseline (both Visit 1 and Visit 3) or at 36 weeks (Visit 9)
- patients who do not have an overall compliance with study drug of at least 75% up to 36 weeks

6.9. Efficacy Analyses

6.9.1. Primary Efficacy Analysis

6.9.1.1. Primary Outcome and Methodology

There will be 2 primary estimands to compare each investigational dulaglutide dose and dulaglutide 1.5 mg in terms of the primary measure of HbA1c change from baseline to Week 36 (Visit 9). See Section 6.1.

For each type of estimand, the 2 investigational doses will be tested versus dulaglutide 1.5 mg simultaneously, controlling the 2-sided alpha of 0.05. Each of the estimands will be tested separately with a full 2-sided alpha of 0.05.

For the efficacy estimand, an MMRM will be employed as the primary analysis of on-treatment without rescue data described in Section 6.1.

For the treatment-regimen estimand, an ANCOVA model will be applied as the primary analysis to the complete data using multiple imputation (Section 6.1.2.1). The model terms include pooled country and treatment as fixed effects, and baseline HbA1c as a covariate. The estimates and standard errors from the imputed datasets will be pooled (Little and Rubin 1987). The inference will be made through the pooled estimates.

6.9.1.2. Additional Analyses of the Primary Outcome

Different populations including the PP and Completers populations will be evaluated separately using the same model as described in Section 6.1. The goal for these analyses is to assess the robustness of the primary outcome.

6.9.2. Secondary Efficacy Analyses

6.9.2.1. Primary Analyses for Secondary Efficacy Endpoints

6.9.2.1.1. Efficacy Estimands

Each continuous variable (changes from baseline in body weight and in FSG) will employ the MMRM described in Section 6.9.1 by replacing baseline HbA1c with the corresponding baseline measurement as a covariate, and adding baseline HbA1c strata as a fixed effect.

The proportions of patients achieving HbA1c target <7.0% will be analyzed using the longitudinal logistic regression model described in Section 6.1. Pooled country, treatment, visit, and the treatment-by-visit interaction will be included as fixed effects with baseline HbA1c as a covariate.

6.9.2.1.2. Treatment-Regimen Estimands

An ANCOVA model will be fit to the complete data for each continuous variable (change from baseline in body weight and in FSG). In this model, pooled country, baseline HbA1c strata, and treatment will be fit as fixed effects, and corresponding baseline measure as a covariate. The missing data will be imputed (Section 6.1.2.1).

A logistic regression model will be fit to the complete data to analyze the proportions of patients reaching HbA1c target <7.0%. Pooled country and treatment will be included as fixed effects, and baseline HbA1c as a covariate. Missing data will be imputed as not achieving the target (Section 6.1.2.2).

The inference will be made through the pooled estimates using Rubin's rule (Little and Rubin 1987).

6.9.2.2. Supportive Analyses for Secondary Efficacy Endpoints

A logistic regression model will be fit with pooled country and treatment as fixed effects, and baseline HbA1c as a covariate to analyze the proportion of patients who achieved HbA1c targets. Prior to this analysis, the missing data at Week 36 (Visit 9) or the patients rescued and/or discontinued prior to Week 36 (Visit 9) will be imputed as not achieving HbA1c target.

The same logistic regression model will be applied to HbA1c targets using LOCF to impute missing data at Week 36 (Visit 9). The latter result will be generated along with the corresponding longitudinal analysis report (Section 6.9.2.1.1).

The analyses listed in the protocol using MMRM for the treatment-regimen estimand will not be carried out because they are replaced with the method described in Section 6.9.2.1.2.

6.9.3. Planned Exploratory Analyses

Some of the planned exploratory analyses are described in Section 6.1. The remaining exploratory analyses are described in this section.

The analyses of proportions of patients reaching each target: HbA1c target ≤6.5%, body weight loss ≥5%, and body weight loss ≥10% will employ the logistic regression model described in Section 6.1. The model for body weight target will be changed by replacing baseline HbA1c with baseline body weight as a covariate along with baseline HbA1c strata as a fixed effect. HbA1c target of the below 2 composite endpoints using LOCF will only apply a logistic regression model with an additional covariate of baseline body weight.

- HbA1c <7.0%, no body weight gain, and no documented symptomatic or severe hypoglycemia
- HbA1c <7.0%, body weight loss ≥5%, and no documented symptomatic or severe hypoglycemia

Longitudinal continuous variables (up to 52 weeks) such as HbA1c, body weight, FSG, and calcitonin will be analyzed using the MMRM described in Section 6.1. If the normality assumption is violated, an appropriate data transformation may be applied prior to analysis.

Nonlongitudinal continuous variables (up to 36 weeks) such as 6-point SMPG, C-peptide, fasting insulin, fasting glucagon, HOMA2-IR, and HOMA2-%B will be analyzed using LOCF by fitting a linear model with pooled country, treatment, and baseline HbA1c strata as fixed effects, and the corresponding baseline value as a covariate. A data transformation may be applied if data are not normally distributed.

The 6-point SMPG consists of measurements before and 2 hours after each of 3 meals within the same day. Each of the time points of the 6-point SMPG, mean of the premeal values, mean of the postmeal values, mean of all 6 time points, breakfast excursion, mid-day excursion, dinner excursion, and mean of all 3 excursions for each scheduled postrandomization visit will be summarized separately.

6.10. Safety Analyses

The safety parameters to be analyzed include AEs, serious AEs (SAEs), AEs of special interest (AESIs), treatment-emergent AEs (TEAEs), safety laboratory analytes, vital signs, and electrocardiograms (ECGs). Adverse events of special interest are cardiovascular (CV) events, hypoglycemia and hyperglycemia, pancreatitis, thyroid C-cell hyperplasia and C-cell neoplasms, hypersensitivity reactions, injection site reactions, supraventricular arrhythmias and cardiac conduction disorders, acute gallbladder disease, and acute renal events.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as postbaseline events that are new events or preexisting conditions that worsened in severity after randomization using MedDRA term. The maximum severity level for baseline and postbaseline for each AE will be used as a criterion to determine TEAEs. If an AE occurs on the same date as the first dosing date with missing event occurring time, that event will be counted as a postbaseline event.

Unless otherwise specified, AEs will be reported using the MedDRA Preferred Term (PT) and/or System Organ Class (SOC). Selected AEs may be reported using MedDRA High Level Terms (HLTs) in addition to the SOC and PT, for consistency with other dulaglutide studies.

6.10.1. Adverse Events

Summary statistics will be provided for the following data: medical history and/or preexisting condition AEs, TEAEs, treatment-emergent AESIs, and study and/or treatment discontinuations due to AEs or death. The numbers and proportions of patients experiencing each corresponding AE will be reported by treatment.

For each patient, the primary AE analysis will be summarized up to the end of the treatment period or premature termination of the study, whichever comes first.

As supportive analyses, SAEs, TEAEs, and treatment-emergent AESIs for each patient will be summarized through the end of the study, including the Safety Follow-up Period.

The incidence of patients with at least 1 TEAE will be summarized by PT and by treatment group, and also by the SOC and PT.

A summary of TEAEs by maximum severity will be presented descriptively by treatment group.

6.10.1.1. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

All SAEs will be summarized by treatment by PT.

Patient listings for patient narratives will be generated.

6.10.1.2. Adverse Events of Special Interest

6.10.1.2.1. Cardiovascular Events

Summaries of adjudicated and investigator-reported CV events will be provided by treatment only if ≥1% of patients have at least 1 event. The test statistics are detailed in Section 6.1.

The nonfatal CV AEs of interest are: myocardial infarction; hospitalization for unstable angina; hospitalization for heart failure; coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

6.10.1.2.2. Hypoglycemia and Hyperglycemia

The rescue therapy definition in this section is based on the response in the CRF noting rescue therapy for severe, persistent hyperglycemia, which differs from "on-treatment with rescue," as defined in Section 6.1.

6.10.1.2.2.1. Hypoglycemic Episodes

Detailed definitions for various categories of hypoglycemia are defined in the protocol (GBGL Protocol Section 9.2.2.2). For analyses purposes, the following main categories of hypoglycemia will be considered:

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a documented plasma glucose (PG) level below the defined threshold.
- **Severe hypoglycemia** is defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG level to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- **Total hypoglycemia** is defined as an episode with PG level below the defined threshold, regardless of symptoms, an episode of symptomatic hypoglycemia where PG level was not measured (ie, probable), and all severe hypoglycemia episodes.

Analyses of total and documented symptomatic hypoglycemia will include categories defined based on 2 PG cutoffs: PG ≤70 mg/dL (3.9 mmol/L) cutoff (Glucose Alert Level 1) and PG <54 mg/dL (3.0 mmol/L) cutoff (Glucose Alert Level 2) (International Hypoglycaemia Study Group 2017). Per American Diabetes Association and European Association for the Study of

Diabetes recommendations, Glucose Alert Level 2 is considered clinically important hypoglycemia for reporting in results of clinical trials of glucose-lowering drugs. Analysis of hypoglycemia episodes with a PG ≤70 mg/dL (3.9 mmol/L) also will be included for comparability to prior studies in the dulaglutide development program.

In the analyses described above, hypoglycemia data will be censored at the time of receipt of rescue medication.

Additionally, a separate analysis will report all hypoglycemia events with PG <54 mg/dL (3.0 mmol/L), regardless of symptoms, and all severe hypoglycemia episodes for the Safety Population including events that occurred after patients started new antihyperglycemic medications (including rescue medications). In recent regulatory interactions, FDA indicated that Level 2 hypoglycemia (PG <54 mg/dL or PG <3 mmol/L) represents a clinically meaningful degree of hypoglycemia and should be summarized as part of study results.

To avoid duplicate reporting, all consecutive PG values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

For each of the hypoglycemia categories, the incidence will be analyzed using the methods for analyses of categorical data described in Section 6.1, by randomized treatment. The rate of hypoglycemic episodes will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution for hypoglycemic episodes with pooled country and treatment as fixed effects and baseline HbA1c as covariate. The logarithm of days during active treatment period will be adjusted as an offset to account for possible unequal treatment duration between patients. This model will be implemented using SAS® procedure GLIMMIX using the log-link function. The predicted hypoglycemia rate per 1 year by treatment will also presented. For rare hypoglycemic episodes such as severe hypoglycemia, Wilcoxon rank sum test will be used to compare the corresponding 1-year hypoglycemia rates between each investigational dulaglutide dose and dulaglutide 1.5 mg.

6.10.1.2.2.2. Severe, Persistent Hyperglycemia

Summaries (if appropriate) will be provided for patients initiating rescue therapy for events of severe, persistent hyperglycemia by each randomized treatment. The time to initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed using PROC LIFETEST to generate Kaplan-Meier curves for each treatment. The summary reports including Kaplan-Meier curves will only be generated if ≥1% of patients receive rescue intervention.

6.10.1.2.3. Pancreatitis

Summaries of adjudicated and investigator-reported pancreatic events will be provided by treatment. However, the summary will only be generated if ≥1% of patients have pancreatic event(s). Determination of investigator-reported events will be through the “Acute pancreatitis” Standardized MedDRA Queries (SMQs) and a “Chronic pancreatitis” Lilly Search Categories (LSC) of the AE database.

6.10.1.2.4. C-cell Hyperplasia and C-cell Neoplasms

Treatment-emergent AESIs of C-cell hyperplasia and neoplasms will be identified using an LSC by HLTs of thyroid neoplasms, thyroid neoplasms malignant, and thyroid disorders. The summary report by treatment will be produced only if ≥1% of patients have any of these AESIs.

6.10.1.2.5. Hypersensitivity Reactions

If ≥1% of patients experience hypersensitivity reaction, a summary report will be generated by treatment. The hypersensitivity summary will be based on 3 SMQs: Anaphylactic reactions, Hypersensitivity, and Angioedema.

6.10.1.2.6. Injection Site Reactions

If ≥1% of patients experience injection site reaction, a summary of events in the MedDRA HLT of Injection Site Reactions will be generated by treatment.

6.10.1.2.7. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Summaries of each AESI will be produced separately by PT with decreasing frequency by treatment using SMQ.

The qualitative ECG data will be summarized by treatment separately for treatment-emergent abnormalities of conduction and rhythm.

6.10.1.2.8. Acute Gallbladder Disease

Summaries of all events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease will be generated by PT with decreasing frequency by treatment using SMQ.

6.10.1.2.9. Acute Renal Events

Summaries of all treatment-emergent renal safety events will be generated by PT with decreasing frequency by treatment separately for acute renal failure and chronic renal failure. To examine AEs indicating decrease in renal function, the SMQ for Acute Renal Failure and an LSC for chronic renal failure events will be used to search the clinical trial database for events of interest.

A summary and analysis using LOCF will be provided for renal functional laboratory measures: estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI); eGFR using CKD-EPI cystatin-C equation (Inker et al. 2012); eGFR using CKD-EPI creatinine-cystatin-C equation (Inker et al. 2012); and creatinine, urine albumin/creatinine ratio (UACR), by treatment. The ANOVA model will be fit with treatment as a fixed effect on the ranked LOCF change from baseline data.

The minimum eGFR (CKD-EPI) value and the maximum creatinine, and UACR will be used for baseline and postbaseline calculations to generate the shift table. The shift table will use eGFR cutoffs (<30, 30 to <60, 60 to <90, and ≥90 mL/min/1.73 m^2); creatinine cutoffs (≤1×upper limit of normal [ULN], >1× and ≤2×ULN, >2× and ≤4×ULN, and >4×ULN); and UACR cutoffs (<30, ≥30, and ≤300, and >300 mg/g).

6.10.1.3. Gastrointestinal Safety

Because certain gastrointestinal (GI) AEs, including nausea, vomiting, and diarrhea, are among the most common events reported in patients treated with dulaglutide, summaries and analyses for incidence will be provided for each randomized treatment to compare the treatment effect on GI tolerability.

The time courses of prevalence, incidence (newly occurring episodes), and onset (first occurrence) of GI AEs (nausea and/or vomiting and/or diarrhea) will be plotted by treatment, regardless of severity, and by severity.

The maximum severity and duration of treatment-emergent nausea and/or vomiting and/or diarrhea through the end of the treatment will be summarized by treatment.

6.10.1.4. Treatment of Overdose

Study drug overdose will be summarized only if it occurs in ≥1% of patients. Otherwise, only a data listing will be generated, including treatment overdose AE reported data.

6.10.2. Electrocardiograms

Changes from baseline in heart rate (HR), PR interval, and QT corrected for HR using Fridericia's corrected QT interval (QTcF) will be analyzed using the MMRM described in Section 6.1.

The threshold analyses will only include HR, PR interval, and QTcF, by visit and treatment. The thresholds are defined in Table GBGL.3.

Table GBGL.3. Abnormality Criteria for Heart Rate, PR Interval, and QTcF

Parameter (Unit)	Visit	Threshold Definition
HR (bpm)	Baseline (Visit 1)	>100, ≥130
	Postbaseline	>100 and CFB >15
PR interval (msec)	Baseline (Visit 1)	≥220
	Postbaseline	≥220
		≥220 and (%CFB >0 and ≤25%)
		≥220 and (%CFB >25%)
QTcF (msec)	Baseline (Visit 1)	>450 (Male) or >470 (Female)
		>480
		>500
	Postbaseline	>450 (Male) or >470 (Female)
		>480
		>500
		>30 CFB
		>60 CFB

Abbreviations: %CFB = percent change from baseline; CFB = change from baseline; HR = heart rate; QTcF = Fridericia's corrected QT interval.

The qualitative summary related to treatment-emergent cardiac conduction and rhythm abnormalities will be reported by treatment.

6.10.3. Vital Signs

Vital signs will be summarized for the Safety Population. Prior to any analyses, the arithmetic mean from the triplicates for the same parameter collected at the same visit taken from the same patient will be calculated and used for all subsequent analyses. The changes from baseline in pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate pressure product (RPP [SBP×pulse rate/1000]) will be analyzed using an MMRM similar to that described in Section 6.1. The threshold analyses will be summarized with the threshold definitions listed in Table GBGL.4.

Table GBGL.4. Abnormality Criteria for Pulse Rate, Systolic Blood Pressure, and Diastolic Blood Pressure

Parameter (Unit)	Visit	Threshold Definition
Pulse rate (bpm)	Baseline (Visit 3)	>100, ≥130
	Postbaseline	>100 and CFB >15
SBP (mm Hg)	Baseline (Visit 3)	≥160, ≤90
	Postbaseline	≥160 and CFB ≥20
		≤90 and CFB ≤-20
DBP (mm Hg)	Baseline (Visit 3)	≥100, ≤50
	Postbaseline	≥100 and CFB ≥10
		≤50 and CFB ≤-10

Abbreviations: CFB = change from baseline; DBP = diastolic blood pressure; SBP = systolic blood pressure.

6.10.4. Clinical Laboratory Evaluation

Analyses of eGFR, creatinine, and UACR are described in Section 6.10.1.2.9. For other laboratory safety parameters, summaries will be provided in this section. For continuous (numeric) laboratory analytes, including serum lipid parameters (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low density lipoprotein cholesterol, and triglycerides), the rank of the change from baseline to endpoint (Week 36 [Visit 9] for primary DBL, Week 52 [Visit 11] for final DBL) will be analyzed as detailed in Section 6.1. For qualitative laboratory analytes, the numbers and percentages of patients with normal and abnormal values will be summarized by treatment.

Each pancreatic enzyme (pancreatic amylase [p-amylase] and lipase) and the maximum postbaseline value will be summarized by treatment in a shift table using >1×ULN and ≥3×ULN separately for the Safety Population, Safety Population with normal baseline value, and Safety Population with baseline value >1×ULN.

An MMRM with pooled country, baseline HbA1c strata, treatment, visit, and treatment-by-visit interaction as fixed effects will be fit to analyze each pancreatic enzyme up to Week 52 (Visit 11). In this model, the log-transformed (post first dose measure/baseline measure) will be

the response variable, and log-transformed baseline measure will be used instead of baseline measure. The variance-covariance structure selection is detailed in Section 6.1.

An ANCOVA model for Week 36 (Visit 9) measurement using LOCF will be fit with the same model as the aforementioned MMRM but removing all terms containing visit.

A summary report and analysis for treatment-emergent abnormal laboratory values (outside the reference ranges as appropriate) will be provided for each continuous analyte by treatment. Shift tables of the change from baseline value to the maximum postbaseline value to endpoint for selected analytes using clinically meaningful thresholds will be summarized descriptively. A shift table for alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin level, and direct bilirubin will be generated using the following cutoffs: ≤1×ULN, (>1×ULN and <3×ULN), (≥3×ULN and <5×ULN), (≥5×ULN and <8×ULN), and ≥8×ULN.

6.10.5. Immunogenicity

Summaries of incidence of dulaglutide anti-drug antibodies (ADA) will be generated for treatment-emergent ADA by treatment through Week 36 (Visit 9) and through Week 56 (Visit 12).

6.11. Health Outcomes/Quality-of-Life Analyses

All parameters will be analyzed using on-treatment without rescue (Section 6.1).

6.11.1. Diabetes Injection Device Experience Questionnaire

Each item in the Diabetes Injection Device Experience Questionnaire will be summarized descriptively by treatment using LOCF at Week 12. Similarly, the device characteristic subscale and 3 global item scores (satisfaction, ease of use, and convenience) will be summarized descriptively by treatment. These items will also be analyzed using linear model with pooled country, baseline HbA1c strata, and treatment as fixed effects.

6.11.2. European Quality of Life 5-Dimension 5 Level

Each item will be summarized descriptively by treatment at each scheduled visit at which the European Quality of Life 5–Dimension 5 Level (EQ-5D-5L) questionnaire is administered. The changes from baseline in the index and visual analog scale scores will be analyzed using MMRM with pooled country, baseline HbA1c strata, treatment, visit, and treatment-by-visit interaction as fixed effects, and corresponding baseline as a covariate.

6.11.3. Impact of Weight on Self-Perceptions Questionnaire

Descriptive summaries by treatment at each scheduled visit at which the Impact of Weight on Self-Perceptions Questionnaire (IW-SP) is administered will be presented for each item. The changes from baseline in IW-SP total and transformed scores will be analyzed using an MMRM with pooled country, baseline HbA1c strata, treatment, visit, and treatment-by-visit interaction as fixed effects, and corresponding baseline as a covariate.

6.11.4. Ability to Perform Physical Activities of Daily Living

Descriptive summaries by treatment at each scheduled visit at which the Ability to Perform Physical Activities of Daily Living (APPADL) is administered will be presented for each item. The changes from baseline in APPADL total and transformed scores will be analyzed using an MMRM with pooled country, baseline HbA1c strata, treatment, visit, and treatment-by-visit interaction as fixed effects, and corresponding baseline as a covariate.

6.12. Subgroup Analyses

Subgroup analyses of the treatment interaction for important factors, including age group (<65 years, ≥65), race, gender, country, duration of diabetes (<median, ≥median), baseline HbA1c (<8.5%, ≥8.5%), body weight (<median, ≥median), and body mass index (<median, ≥median), may be conducted for the primary endpoint of HbA1c. Country will use the pooled country.

These analyses will be conducted using the MMRM with treatment, visit, subgroup, treatment-by-visit, treatment-by-subgroup, visit-by-subgroup, and treatment-by-visit-by-subgroup as fixed effects, and baseline as a covariate. If the MMRM fails to converge, the corresponding ANCOVA or ANOVA model (LOCF) will be used.

When analyzing baseline HbA1c as a subgroup, the baseline HbA1c will not be included as a covariate to avoid colinearity.

Treatment-emergent AEs occurring in >5% of patients will be summarized descriptively for the patients with the top quartile of body weight reduction from baseline by treatment group.

Other exploratory subgroup analyses may be performed as deemed appropriate.

6.13. Interim Analyses and Data Monitoring Committee

No interim analyses of efficacy are planned for this study.

An independent Data Monitoring Committee (DMC) will review unblinded interim analysis results in order to monitor the safety of the patients in the study until the last patient completes the Week 36 visit (Visit 9). The detailed analysis and communication plan for the interim analyses will be defined in a separate DMC charter. An internal Statistical Analysis Center external to the study team will perform the data analyses for the DMC. As no efficacy analyses are planned for the DMC, the family-wise error rate will not be affected by any of these analyses; hence, no alpha spending is necessary.

Study sites may receive information about interim results ONLY if these results may have an impact on the safety of patients in this trial.

The timing for DMC is described in GBGL Protocol Section 10.3.8.

6.13.1. Evaluation Criteria

For the safety-only interim analyses, the totality of the safety data on SAEs, AESIs, disposition, discontinuation due to AEs, ECGs, vital signs, and selected safety laboratory analytes may be evaluated. The analysis for each parameter will be analyzed in the same way as defined in this SAP.

7. Unblinding Plan

The purpose of the unblinding plan is to detail the process that is in place to minimize bias while preparing for or conducting any summary or analysis of the data for DMC reports, data reviews, developing/refining exposure-response analyses, and unblinding the appropriate study team members after the primary DBL. The detailed process will be documented in a separate unblinding plan per Lilly procedure.

8. References

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894-913.

Danne T, Philotheou A, Goldman D, Guo X, Ping L, Cali A, Johnston P. A randomized trial comparing the rate of hypoglycemia--assessed using continuous glucose monitoring--in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study) [erratum appears in *Pediatr Diabetes*. 2015;16(6):4 62]. *Pediatr Diabetes*. 2013;14(8):593-601.

Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C [erratum appears in *N Engl J Med*. 2012;367(7):681 and 2012;367(21):2060]. *N Engl J Med*. 2012;367(1):20-29.

International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40(1):155-157.

Little R, Kang S. Intention-to-treat analysis with treatment discontinuation and missing data in clinical trials. *Stat Med*. 2015;34(16):2381-2390.

Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. New York, NY: John Wiley & Sons; 1987.

Weinberg ME, Bacchetti P, Rushakoff RJ. Frequent repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *J Diabetes Sci Technol*. 2010;4(3):577-582.

Appendix 1.

Summary of the Data and Primary Analysis for the Primary and Secondary Efficacy Endpoints by Type of Estimand

	Efficacy Estimand	Treatment-Regimen Estimand
Data		
Data Included in the Analyses	• All patients in the ITT population with a baseline value and at least 1 postbaseline value for the measure of interest are included. • Values are excluded after treatment discontinuation or start of antihyperglycemic medications lasting >14 days.	• All patients in the ITT population with a baseline value for the measure of interest are included.
Primary Analysis for Each Endpoint		
Primary Endpoint: Change from baseline in HbA1c at Week 36	• MMRM with effects for treatment, pooled country, visit, treatment-by-visit interaction, and baseline HbA1c as a covariate,	• If the Week 36 value is missing, multiple imputation will be used to impute a value such that the reference group includes patients from the same treatment group and same treatment discontinuation status (yes, no) who had a value at Week 36. • ANCOVA with effects for treatment, pooled country, and baseline HbA1c as a covariate.
Secondary Endpoint: Change from baseline in body weight at Week 36	• MMRM with effects for treatment, pooled country, baseline HbA1c stratum (<8.5%, ≥8.5%), visit, treatment-by-visit interaction, and baseline body weight as a covariate.	• If the Week 36 value is missing, multiple imputation will be used to impute a value such that the reference group includes patients from the same treatment group and same treatment discontinuation status (yes, no) who had a value at Week 36. • ANCOVA with effects for treatment, pooled country, baseline HbA1c stratum (<8.5%, ≥8.5%), and baseline body weight as a covariate.

Summary of the Data and Primary Analysis for the Primary and Secondary Efficacy Endpoints by Type of Estimand

	Efficacy Estimand	Treatment-Regimen Estimand
Primary Analysis for Each Endpoint		
Secondary Endpoint: Change from baseline in fasting serum glucose (FSG) at Week 36	• MMRM with effects for treatment, pooled country, baseline HbA1c stratum (<8.5%, ≥8.5%), visit, treatment-by-visit interaction, and baseline FSG as a covariate.	• If the Week 36 value is missing, multiple imputation will be used to impute a value such that the reference group includes patients from the same treatment group and same treatment discontinuation status (yes, no) who had a value at Week 36. • ANCOVA with effects for treatment, pooled country, baseline HbA1c stratum (<8.5%, ≥8.5%), and baseline FSG as a covariate.
Secondary Endpoint: Achieving HbA1c goal <7% at Week 36	• Longitudinal logistic regression with effects for treatment, pooled country, visit, treatment-by-visit interaction, and baseline HbA1c as a covariate.	• If the Week 36 value is missing, the patient will be considered as not having met the goal. • Logistic regression with effects for treatment, pooled country, and baseline HbA1c as a covariate.

Abbreviations: ANCOVA = analysis of covariance; HbA1c = glycated hemoglobin A1c; ITT = intent to treat; MMRM = mixed-model repeated measure.

Leo Document ID = 9a56661a-0d45-4976-9782-d6580268a5bb

Approver: [redacted]
Approval Date & Time: 06-Jun-2019 21:14:40 GMT
Signature meaning: Approved