

H9X-MC-GBGE Statistical Analysis Plan V2

A Randomized, Parallel-Arm, Double-Blind Study of Efficacy and Safety of Dulaglutide When Added to SGLT2 Inhibitors in Patients With Type 2 Diabetes Mellitus

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Redacted Version

**1. Statistical Analysis Plan**  
**A Randomized, Parallel-Arm, Double-Blind Study of**  
**Efficacy and Safety of Dulaglutide When Added to SGLT2**  
**Inhibitors in Patients with Type 2 Diabetes Mellitus**  
**(AWARD-10: Assessment of Weekly AdministRation of**  
**LY2189265 in Diabetes – 10)**

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Dulaglutide (LY2189265)

Study H9X-MC-GBGE is a Phase 3b, randomized, double-blind, placebo-controlled trial that investigates the effect of the addition of once-weekly dulaglutide 1.5 mg or 0.75 mg to SGLT2 inhibitors, with or without concomitant use of metformin, on change from baseline in hemoglobin A1c (HbA1c) at 24 weeks in patients with type 2 diabetes mellitus.

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Protocol H9X-MC-GBGE  
Phase 3b

Statistical Analysis Plan Version 1.0 electronically signed and approved by Lilly: 19 November 2015.

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 01-Apr-2016 GMT

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### 3. Revision History

The protocol for this study was approved on 29-Jul-2015. Protocol amendment (a) was approved on 21-Aug-2015. Version 1 of this Statistical Analysis Plan (SAP) was approved prior to first patient visit (FPV). Version 2 of the SAP was developed based on the request from FDA that the ITT estimand (treatment regimen estimand, including the post-rescuedata) be used for the primary analysis. This revision was approved before the last patient visit. The following changes were made in this revision: 1) sample size due to protocol amendment; 2) the definition of the completers population for consistency with other dulaglutide studies; 3) hypoglycemia rate analysis using linear mixed model instead of GEE for better control of the type I error rate; 4) including baseline HbA1c-by-visit interaction term in the HbA1c target analysis to improve model convergence.

## 4. Study Objectives

Table GBGE.4.1 shows the objectives and endpoints of the study.

**Table GBGE.4.1. Objectives and Endpoints**

Objectives	Endpoints
<p><b>Primary</b> To demonstrate that once-weekly dulaglutide (1.5 mg and/or 0.75 mg) is superior to placebo as measured by HbA1c at 24 weeks (change from baseline) in patients with inadequately controlled T2D on concomitant SGLT2 inhibitor therapy.</p>	<ul style="list-style-type: none"> <li>• The change in HbA1c from baseline to 24 weeks</li> </ul>
<p><b>Secondary</b> Key secondary efficacy objectives (controlled for type 1 error) are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks</p> <p>Other secondary efficacy objectives are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks</p> <p>Secondary safety objectives are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks</p>	<ul style="list-style-type: none"> <li>• Proportion of patients with HbA1c target values of &lt;7.0% at 24 weeks</li> <li>• The change in FBG (central laboratory) from baseline to 24 weeks</li> <li>• The change in body weight from baseline to 24 weeks</li> </ul> <ul style="list-style-type: none"> <li>• Proportion of patients with HbA1c target values of ≤6.5% at 24 weeks</li> <li>• The change in 6-point SMPG profile from baseline to 24 weeks</li> <li>• The change in fasting glucagon from baseline to 24 weeks</li> </ul> <p>Incidence of:</p> <ul style="list-style-type: none"> <li>• Treatment-emergent adverse events (TEAEs)</li> <li>• Early discontinuations due to AEs</li> <li>• Adjudicated cardiovascular and pancreatic AEs</li> <li>• Thyroid neoplasms AEs</li> <li>• AEs related to kidney failure, eGFR</li> <li>• Systemic hypersensitivity AEs</li> <li>• Local injection site reactions</li> <li>• The change in systolic and diastolic blood pressure, heart rate, and lipids from baseline to 24 weeks</li> <li>• Incidence and rate of hypoglycemic episodes</li> <li>• Ketoacidosis, and initiation of rescue therapy for severe persistent hyperglycemia</li> </ul>



**Objectives and Endpoints**

Objectives	Endpoints
<p><b>Exploratory</b> Exploratory efficacy objectives are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks</p>	<ul style="list-style-type: none"> <li>• Proportion of patients meeting the composite endpoint of HbA1c &lt;7.0%, no weight gain, and no documented symptomatic hypoglycemia</li> <li>• Proportion of patients meeting the composite endpoint of HbA1c &lt;7.0%, body weight loss &gt;5%, and no documented symptomatic hypoglycemia</li> </ul>

Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; SGLT2 = sodium-glucose co-transporter 2; SMPG = self-monitored plasma glucose; T2D = type 2 diabetes.

## 5. A Priori Statistical Methods

### 5.1. Determination of Sample Size

With 120 completers per arm, the study will have 90% power for demonstrating superiority of either dulaglutide 1.5 mg or 0.75 mg versus placebo in change from baseline in mean hemoglobin A1c (HbA1c) at 24 weeks, assuming a standard deviation (SD) of 1.2%, a difference between dulaglutide and placebo of 0.55%, and a 2-sided significance level of 0.025. Assuming that the dropout rate is 15% for the entire study period, the study will need to enroll at least approximately 142 patients in each arm for a total of 426 patients enrolled. Assuming a screen fail rate of 40%, a total of approximately 710 patients will be screened to meet these enrollment number requirements.

### 5.2. 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 SAP or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The primary analysis population will be the intent-to-treat (ITT) population, defined as all patients randomized who have received at least 1 dose. This is also the safety population. A select number of measurements (HbA1c, percent to goal in HbA1c, fasting blood glucose [FBG], and body weight) will also be evaluated in the per-protocol (PP) population and completer population. The PP population will include patients without important protocol deviations, took no concomitant medications that would confound the interpretation of results (such as systemic steroids or non-study glucose-lowering agents used >14 days), and have an HbA1c measurement at the primary visit endpoint ([Table GBGE.5.1](#)). The completer population will be based on patients who completed the treatment period ([Table GBGE.5.1](#)).

There will be 2 primary estimands to compare the placebo and the dulaglutide arms in terms of the primary measure of HbA1c change from baseline to 24 weeks. One primary estimand will be an efficacy estimand which will not use post-rescue data; the other primary estimand, requested by the US Food and Drug Administration (FDA), will be an ITT estimand (treatment regimen estimand) which will use post-rescue data. The efficacy estimand compares the benefit of the initially randomized treatments assuming all patients remained in the study and did not take additional or alternative antihyperglycemic medication. The estimate of mean change from baseline to endpoint reflects what would have been observed if patients stayed on their initially randomized treatments. The treatment-regimen estimand compares the benefit of treatment regimens as they are actually taken. The estimate of mean change from baseline to endpoint reflects what was actually observed regardless of use of any additional or alternative antihyperglycemic agents. Both estimands will use the same primary analysis model, and each will be tested at the full significance level of 0.05.

Analyses of the key secondary efficacy outcomes (percent to goal in HbA1c, FBG, body weight) and hypoglycemia will be performed on the full dataset with and without censoring data collected after rescue medication for any reason.

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

The baseline will be Visit 5, except for HbA1c. Patients who do not need stabilization will have blood drawn for baseline HbA1c at Visit 2, and those who need stabilization at Visit 4. For all variables except HbA1c, if baseline data are missing, the last nonmissing measurement taken prior to Visit 5 will be used for the baseline measurement. For HbA1c, if baseline data are missing, the imputation will be conducted only if an additional value between Visit 2 and randomization (patients not needing stabilization) or Visit 4 and randomization (patients needing stabilization) is collected. The endpoint for the primary analysis is defined as the change from baseline in HbA1c at 24 weeks (Visit 11). Key secondary endpoints are percent to goal in HbA1c (<7.0%) at 24 weeks and change from baseline in FBG (central laboratory) and body weight at 24 weeks.

Two analysis models will be used for the primary and key secondary continuous efficacy measures. The primary analysis will be mixed-model repeated measure (MMRM) analysis using restricted maximum likelihood (REML). 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

The first covariance structure that converges will be used.

The secondary analysis for the primary and key secondary continuous endpoints will be analysis of covariance (ANCOVA). Missing endpoints will be imputed with the last (postbaseline) observation carried forward (LOCF). The percentage of patients achieving the target HbA1c of <7.0% at 24 weeks will be analyzed using a longitudinal logistic regression with repeated measurements.

A graphical testing approach will be used to strongly control for type 1 error to test for superiority of each of the dulaglutide doses versus placebo at 24 weeks for the following

measures: (1) change from baseline in HbA1c, (2) change from baseline in FBG (central laboratory), (3) percent achieving HbA1c <7.0%, and (4) change from baseline in body weight.

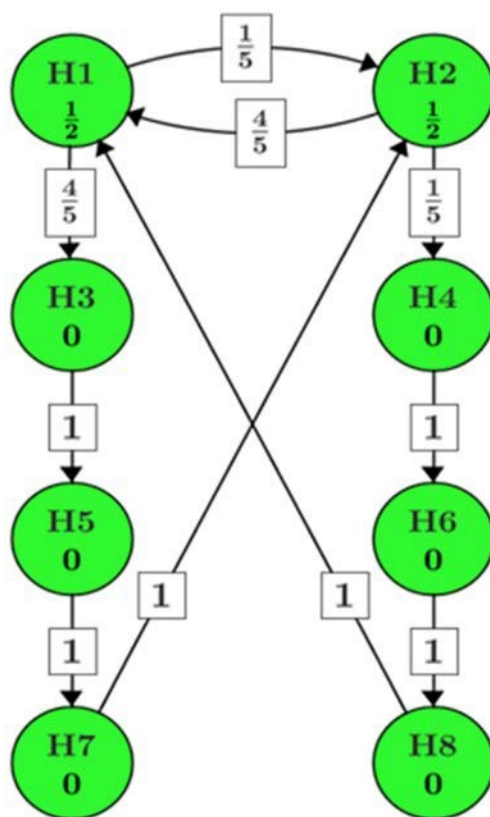
For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and change from baseline measurements. Least-squares mean (LS mean) and standard errors derived from the model will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS mean and the 95% CIs for the treatment differences (dulaglutide – placebo), along with the p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test will be used for treatment comparisons, unless 80% of cells have an expected value of at least 5, in which case the chi-square test will be used.

### 5.3. Graphical Testing Scheme

To control type I error, a graphical testing scheme (Bretz et al. 2011) presented in [Figure GBGE.5.1](#) will be used to compare treatments regarding selected secondary objectives once the primary objective has been achieved. In [Figure GBGE.5.1](#) the numbers in the circles indicate the fraction of alpha used for the first hypothesis tests. The numbers along the arrows represent the fraction of alpha from a hypothesis, if it is rejected, to allocate to the next hypothesis.

The graphical testing scheme will be performed for the efficacy estimand and the treatment regimen estimand (see [Section 5.1](#)) separately.



**Figure GBGE.5.1. Graphical testing scheme for Study H9X-MC-GBGE.**

H1: Primary objective, superiority test of dulaglutide 1.5 mg versus placebo on hemoglobin A1c (HbA1c) change from baseline at 24 weeks.

H2: Primary objective, superiority test of dulaglutide 0.75 mg versus placebo on HbA1c change from baseline at 24 weeks.

H3: Superiority test of dulaglutide 1.5 mg versus placebo on HbA1c target 7.0% at 24 weeks.

H4: Superiority test of dulaglutide 0.75 mg versus placebo on HbA1c target 7.0% at 24 weeks.

H5: Superiority test of dulaglutide 1.5 mg versus placebo on body weight change from baseline at 24 weeks.

H6: Superiority test of dulaglutide 0.75 mg versus placebo on body weight change from baseline at 24 weeks.

H7: Superiority test of dulaglutide 1.5 mg versus placebo on FBG change from baseline at 24 weeks.

H8: Superiority test of dulaglutide 0.75 mg versus placebo on FBG change from baseline at 24 weeks.

## 5.4. Patient Population

The following patient populations described in [Table GBGE.5.1](#) will be used to analyze the data. The data collected in this study will be presented as listings by investigator site, patient, and treatment.

**Table GBGE.5.1. Analysis Populations**

Population	Definition
All Entered	All patients who signed informed consent forms (ICF)
All Randomized	All patients who were randomized to a treatment arm
Non-randomized	All patients who entered, but not randomized, to a treatment arm
Intent-to-treat (ITT)	All randomized patients who have taken at least one dose of the study medication
Per-protocol (PP)	All patients in ITT and who also meet the following criteria: <ul style="list-style-type: none"> <li>• Have no important protocol deviations (Section 5.7)</li> <li>• Completed the treatment phase (24 week [Visit 11]) for primary end point (ie, did not discontinue from the study early)</li> <li>• Are at least 75% compliant with study drug for at least 75% of the visits</li> </ul>
Completer Population	The completers population will be defined as those who: <ul style="list-style-type: none"> <li>• Completed the treatment period (ie, did not discontinue early from the study)</li> </ul>

The complete list of protocol deviations leading to exclusion from the PP population is provided in Section 5.7.

## 5.5. Patient Disposition

A listing of patient discontinuation will be presented for all randomized patients. Frequency counts and percentages of all patients entered, randomized/enrolled, completing and discontinuing from the study and study treatment will be presented for all treatment groups. A summary of discontinuations will also be presented by visit. The overall percent discontinued comparisons among the treatments will be performed using a Chi-square test or Fisher's exact test.

## 5.6. Patient Characteristics

Demographic and baseline characteristics will be summarized by treatment group for ITT, PP and completer populations. For continuous measures, summary statistics will include sample size (n), mean, median, min, max, and SD. Treatment differences will be analyzed using analysis of variance (ANOVA) model with treatment as the factor. For categorical measures, summary statistics will include sample size, frequency and percent. Treatment difference will be compared using Fisher's exact test or Chi-square test.

## 5.7. Protocol Deviations

Important protocol deviations will be listed for all randomized patients. The rationale for choosing the important protocol deviations was based on their potential to impact the primary analysis. The following protocol deviations will be considered important and patients with these protocol deviations will be excluded from the PP population:

- Patients violating the following Inclusion/Exclusion criteria:

- Have HbA1c <7.0% or >9.5% at study entry (Visit 1) or at Visit 2 for patients without stabilization; HbA1c <7.0% or >9.5% at study entry (Visit 1) or at Visit 4 for patients with stabilization;
- Patients with Type 1 diabetes
- Have any hematologic condition that may interfere with HbA1c measurement (for example, hemolytic anemia, sickle-cell disease)
- Use of weight loss drugs within 3 months prior to study entry or use of systemic glucocorticoids 1 month prior to study entry, or use of these medications between study entry and Visit 5;
- Use of ANY other oral antihyperglycemic medications (OAMs) (other than sodium-glucose cotransporter 2 [SGLT2] inhibitors and metformin), GLP-1 receptor agonist (RA), pramlintide or insulin 3 months prior to study entry, or between study entry and Visit 5; or initiation of metformin between study entry and Visit 5; short-term use of insulin for acute care ( $\leq 14$  days) during the 3-month period prior to entry is not protocol deviation;
- Missing HbA1c at baseline (Visit 5) or at 24 weeks (Visit 11)
- Patients who do not have an overall compliance with study drug at least 75% for at least 75% of the visits during the study
- Patients who took medications that were prohibited per protocol for >14 days (cumulative) after randomization (Visit 5-Visit 11), including:
  - Excluded antihyperglycemia medications; including insulin use for acute care; Note: use of rescue therapy medications is not considered protocol deviation;
  - Other protocol-prohibited medications (systemic glucocorticoids or weight loss medications);
- Informed consent was never obtained
- Patients who are randomized but the informed consent data is missing.

## 5.8. Concomitant Medications

Glucose lowering agents will be summarized by treatment at entry, baseline (Visit 5), and for the entire 24-week treatment period. Doses of SGLT2 inhibitors and metformin will be summarized at baseline (Visit 5) and at study end (Visit 11). Other pre-specified concomitant medications of interest (antihypertensives, lipid lowering agents, antithrombotic agents, anti-inflammatory agents, and cardiac therapy) will be summarized by treatment at baseline (Visit 5).

Antihypertensive medications will be additionally summarized for the entire 24-week treatment period by treatment group including frequency and reasons for dose change. Frequency of use of non-study glucose-lowering medications will be summarized at baseline (Visit 5) and for the entire 24-week treatment period by treatment group.

## 5.9. Study Drug Compliance

Study drug compliance for each visit is defined as taking at least 75% of the scheduled injections of the study drug for the period preceding that visit. Overall treatment compliance for each patient is defined as taking at least 75% of the injectable study drug for at least 75% of the 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 non-missing compliance data for this patient \*100. Study drug compliance will be listed and summarized using ITT population. The compliance will be summarized and presented in descriptive statistics that include the sample size (n), mean, SD, median, min, and max. The frequency and percent of patients who are compliant will be compared between the treatment groups using Chi-square test or Fisher's exact test at each visit and overall.

## 5.10. Treatment Exposure

Treatment exposure is defined as the time from when the patient is randomized at Visit 5 and receives study drug until the patient either discontinues from treatment or completes the treatment period as planned.

The duration of treatment exposure will be listed and summarized by treatment group for ITT, PP, and completer populations. Duration of exposure will be categorized into the following groups:  $\leq 14$  days,  $>14$  to  $\leq 28$  days,  $>28$  to  $\leq 56$  days,  $>56$  to  $\leq 84$  days,  $>84$  to  $\leq 126$  days,  $>126$  to  $\leq 168$  days and  $>168$  days. These categories will be summarized as frequency by treatment group. Summary statistics will include mean per patient exposure in days, SD, median, min, and max. The duration of treatment exposure will be analyzed using one-way ANOVA with treatment as fixed effect.

## 5.11. Primary Efficacy Analysis

The primary outcome is the difference in HbA1c mean change from baseline to 24 weeks in the ITT population. The primary hypothesis of interest in this placebo-controlled study is whether dulaglutide has superior efficacy compared to placebo, in patients already treated with SGLT2 inhibitors.

The primary analysis model will be an MMRM for HbA1c change from baseline to 24 weeks in the ITT population (Visit 11) with treatment, country, SGLT2 inhibitor dose ("low" versus "high"), metformin use ("yes" versus "no"), visit and treatment-by-visit as fixed effects, baseline HbA1c as a covariate, and patient as a random effect.

### 5.11.1. Additional Analyses for Primary Endpoint

The primary analysis model, MMRM, will be repeated for the PP population and the completer population as sensitivity analyses. If the conclusion differs from the analysis of the ITT population, the data and analyses will be further investigated.

The secondary analysis model will be an ANCOVA (only for excluding rescue data) for HbA1c change from baseline to 24 weeks (Visit 11), using a similar model as described above with



treatment, country, SGLT2 inhibitor dose (“low” versus “high”), and metformin use (“yes” versus “no”) as factors and baseline HbA1c as a covariate. Missing endpoints will be imputed with the LOCF using postbaseline data only using ITT population.

To investigate departure from the Missing At Random (MAR) assumption for the primary analysis for both efficacy and treatment regimen estimands, a sensitivity analysis using a particular missing not at random (MNAR) assumption will be performed. Specifically, a placebo multiple imputation (pMI) will be performed (Ayele et al. 2014), which assumes that the drug effect in missing data and post-rescue data in both the placebo arm and dulaglutide arm was like the observed effect in the placebo arm (excluding post-rescue data). This is essentially the “copy reference” approach as described in Carpenter et al. 2013. This approach is in essence assuming that the drug effect will decay over time, in accordance with the correlation structure implied by the data. Data imputed this way will be analyzed with the same MMRM model as the primary analysis. This particular MNAR assumption can be viewed as a “worst reasonable case” assessment of the two estimands..

For both the efficacy estimand and the treatment regimen estimand, a tipping point analysis will be performed in which the missing data are imputed with a MAR assumption. However, prior to analysis, in the dulaglutide arm the imputed values will be replaced by the imputed value plus delta. Multiple values of delta will be tried until the value at which the conclusion from the MMRM analysis changes.

## **5.12. Key Secondary Efficacy Analysis**

To control type I error, a graphical testing scheme as described in Section 5.3 will be used to compare treatments regarding the following selected secondary objectives (body weight, fasting blood glucose, and HbA1c target of <7.0%) once the primary objective has been achieved.

### **5.12.1. Analysis of Body Weight**

The evaluation of change from baseline in body weight will be performed using MMRM and ANCOVA models on the ITT population. The MMRM model, which will be primary for the change in weight, will include treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), visit, baseline HbA1c strata ( $\leq 8.0\%$ , and  $> 8.0\%$ ), treatment-by-visit interactions as fixed effects, and baseline body weight as a covariate and patient as a random effect. The ANCOVA model with LOCF includes treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), baseline HbA1c strata ( $\leq 8.0\%$ , and  $> 8.0\%$ ) as fixed effects, and baseline body weight as covariate. LS means, 95% CI, and the p-value will be presented for the treatment comparison.

### **5.12.2. Analysis of Fasting Blood Glucose**

Change from baseline in FBG will be summarized using the ITT population. This variable will be analyzed using the ANCOVA model with LOCF which includes treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), baseline HbA1c strata ( $\leq 8.0\%$  and  $> 8.0\%$ ) as fixed effects, and baseline (FBG) as covariate.

### **5.12.3. Percentage of Patients Achieving a Target HbA1c <7.0%**

For percentages of patients achieving target HbA1c of <7.0 at 24 weeks, longitudinal logistic regression with repeated measurements (generalized linear mixed models, Liu and Zhan 2011) will be used. The model will include independent variables for treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), visit, baseline HbA1c - by-visit interaction, and the treatment-by-visit interaction as fixed effects, and baseline HbA1c as a covariate. These analyses will be performed with post-rescue data excluded (considered missing), and separately with all post-rescue data included. In addition, an analysis of percentage of patients on HbA1c targets will be performed where patients who have been rescued or have no post-baseline data will be considered (imputed) as not having achieved the target.

## **5.13. Other Secondary Efficacy Analysis**

### **5.13.1. Analysis of Fasting Glucagon**

Change of fasting glucagon will be summarized using ITT population. Change from baseline of fasting glucagon will be analyzed using ANCOVA model with LOCF includes treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), baseline HbA1c strata ( $\leq 8.0\%$  and  $> 8.0\%$ ) as fixed effects, and baseline (fasting glucagon as a covariate (with and without post rescue data).

### **5.13.2. Percentage of Patients Achieving a Target HbA1c $\leq 6.5\%$**

For percentages of patients achieving target HbA1c of  $\leq 6.5\%$  at 24 weeks, longitudinal logistic regression with repeated measurements (generalized linear mixed models, Liu and Zhan 2011) will be used. The model will include independent variables for treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), visit, baseline HbA1c - by-visit interaction, and treatment-by-visit interaction as fixed effects, and baseline HbA1c as a covariate. These analyses will be performed with post-rescue data excluded (considered missing), and separately with all post-rescue data included. In addition, an analysis of percentage of patients on HbA1c targets will be performed where patients who have been rescued or have no post-baseline data will be considered (imputed) as not having achieved the target.

### **5.13.3. Analysis of 6-point SMPG profile**

The 6-point self-monitored plasma glucose (SMPG) profiles consist of pre-meal and 2-hour postprandial SMPG measurements for the morning, midday, and evening meals.

The following variables for 6-point SMPG profile will be analyzed using MMRM:

1. Pre morning meal plasma glucose (PG) (mg/dL)
2. 2-hour postprandial measurement for morning meal PG (mg/dL)
3. Pre midday meal PG (mg/dL)
4. 2-hour postprandial measurement for midday meal PG (mg/dL)

5. Pre evening meal PG (mg/dL)
6. 2-hour postprandial measurement for evening meals PG (mg/dL)
7. Mean of all pre-meals PG (mg/dL)
8. Mean of all postprandial PG (mg/dL)
9. Mean of all meals 2-hr excursion (mg/dL)
10. Mean of all 6-point PG (mg/dL)

For mean of all pre-meals PG (Report 7), the pre-meal daily mean is calculated as the average PG values collected for before morning, midday and evening meals on a particular day. The change from baseline is calculated as the mean of all pre-meals PG at Week 12 and Week 24 minus the mean of all pre-meals PG at baseline.

For mean of all postprandial PG (Report 8), the post-meal daily mean is calculated as the average of 2-hour postprandial PG values of morning, midday and evening meals on a particular day. The change from baseline is calculated as the mean of all postprandial PG at Week 12 and Week 24 minus the mean of all postprandial PG at baseline.

For mean of all meals 2-hour excursion at each visit (Report 9), the daily mean for all meals is calculated as the average of glucose excursion for morning, midday and evening meals on a particular day. The change from baseline is calculated as the mean of all meals 2-hour excursion at Week 12 and Week 24 minus the mean of all meals 2-hour excursion at baseline.

For mean of all 6-point PG (Report 10), the daily mean is calculated as the average of 6 PG values collected on a particular day. The change from baseline is calculated as the mean of all 6-point PG at Week 12 and Week 24 minus the mean of all 6-point PG at baseline.

Change from baseline of 6-point SMPG values will be summarized using the ITT population, and analyzed using MMRM with treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), visit, baseline HbA1c strata ( $\leq 8.0\%$  and  $> 8.0\%$ ) and treatment-by-visit interaction as fixed effects, baseline 6-point SMPG as a covariate and patient as a random effect. An unstructured covariance structure will be used to model the within-patient variability and implicitly adjusts for missing data. If this analysis fails to converge, then other covariance structures will be tested in the order mentioned in Section 5.2.

#### **5.14. Pharmacokinetic/Pharmacodynamic Analyses**

Not Applicable for this study.

#### **5.15. Safety Analyses**

The safety analysis will include the assessment of adverse events (AEs), serious adverse events (SAEs), special safety topics, laboratory analytes, vital signs, and electrocardiograms (ECGs). Unless otherwise specified, the ITT population will be used for analyses of the safety measurements.

### 5.15.1. Adverse Events

An adverse event (AE) is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to a drug. Adverse events will be coded from the actual term described by the investigator using the Medical Dictionary for Regulatory Activities (MedDRA). Unless otherwise specified, AEs will be reported using the MedDRA system organ class (SOC) and preferred term (PT). Selected AEs may be reported using MedDRA high-level terms (HLT).

All AEs will be listed by investigator by patient using MedDRA PT.

Treatment-emergent adverse events (TEAEs) are defined as an event that first occurs or worsens (increases in severity) after the first dose on Visit 5.

Summary statistics will be provided for TEAEs, SAEs, and study discontinuation due to AEs or death during the treatment period. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and chi-square tests will be used to compare the treatment groups.

Since gastrointestinal (GI) AEs, like nausea and vomiting, are among the most common events reported in patients treated with dulaglutide, summaries and analyses for onset, duration, and severity of nausea and vomiting will be provided.

Listings of patients experiencing allergic and hypersensitivity reactions, as well as those discontinuing the study due to AE will be produced.

### 5.15.2. Special Safety Topics

#### 5.15.2.1. Hypoglycemic Episodes

Hypoglycemia will be classified as follows (ADA 2005):

- Documented Symptomatic Hypoglycemia: Any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a plasma glucose level of  $\leq 70$  mg/dL (3.9 mmol/L), or PG  $< 54$  mg/dL (3 mmol/L). Therefore, the category of interest will be:
  - Documented Symptomatic Hypoglycemia with PG  $\leq 70$  mg/dL
  - Documented Symptomatic Hypoglycemia with PG  $< 54$  mg/dL
- Asymptomatic Hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia, but with measured plasma glucose of  $\leq 70$  mg/dL (3.9 mmol/L), or PG  $< 54$  mg/dL (3 mmol/L). Therefore, the category of interest will be:
  - Asymptomatic Hypoglycemia with PG  $\leq 70$  mg/dL
  - Asymptomatic Hypoglycemia with PG  $< 54$  mg/dL

- Severe Hypoglycemia: 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 plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. Severe hypoglycemia will be further divided in the following four subcategories:
  - Severe Hypoglycemia with PG  $\leq 70$  mg/dL
  - Severe Hypoglycemia with PG  $< 54$  mg/dL
  - Severe Hypoglycemia with PG  $> 70$  mg/dL
  - Severe Hypoglycemia with PG missing
- Nocturnal Hypoglycemia: Any hypoglycemic event that occurs between bedtime and waking. Therefore, the category of interest will be:
  - Nocturnal Hypoglycemia, events with PG  $\leq 70$  mg/dL included
  - Nocturnal Hypoglycemia, events with PG  $< 54$  mg/dL included
- Probable Symptomatic Hypoglycemia: An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration of  $\leq 70$  mg/dL [3.9 mmol/L]), or PG  $< 54$  mg/dL (3 mmol/L). Therefore, the category of interest will be:
  - Probable Symptomatic Hypoglycemia, events with PG  $\leq 70$  mg/dL
  - Probable Symptomatic Hypoglycemia, events with PG  $< 54$  mg/dL

Cases of relative hypoglycemia will also be collected, but will not be included in the category of overall hypoglycemia:

- Relative Hypoglycemia: is defined as symptomatic events during which the person reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration of  $> 70$  mg/dL (3.9 mmol/L). Therefore, the category of interest will be:
  - Probable Symptomatic Hypoglycemia, events with PG  $> 70$  mg/dL
  - Probable Symptomatic Hypoglycemia, events with PG  $\geq 54$  mg/dL

Total hypoglycemia includes any event that meets criteria for documented symptomatic hypoglycemia (including severe hypoglycemia), asymptomatic hypoglycemia, or probable symptomatic hypoglycemia. Those categories that are defined by PG will be analyzed by the PG  $\leq 70$  mg/dL threshold and by the PG  $< 54$  mg/dL threshold separately. Therefore, total hypoglycemia category will have the following two subcategories:

- Total Hypoglycemia (events with PG  $\leq 70$  mg/dL included)
- Total Hypoglycemia (events with PG  $< 54$  mg/dL included)

A listing of the individual hypoglycemic episodes, by patient, will be presented using all randomized population.

The incidence of hypoglycemic episodes will be summarized using frequency and percent. The frequency and percent at each visit are calculated as the number of patients and percent of patients reporting hypoglycemic episodes at that visit. The overall frequency and percent will also be reported. The overall frequency and percent are calculated as the total number of patients and percent of patients reporting hypoglycemic episodes during the entire study treatment period. The summary report will be conducted using ITT patients. Fisher's exact test or Chi-square test will be used for treatment comparison.

The hypoglycemia rates (episodes/patient/30 days, episodes/patient/year) for each visit, and overall will be analyzed using a negative binomial model with the generalized linear mixed model. The model will include treatment, country, SGLT2 inhibitor dose ("low" versus "high"), metformin use ("yes" versus "no"), visit, baseline HbA1c strata ( $\leq 8.0\%$  and  $> 8.0\%$ ) and treatment-by-visit interaction as fixed effect, and baseline hypoglycemia rate as a covariate. For the above mentioned analysis, PROC GLIMMIX in SAS will be used with random statement. The logarithm of days between visits will be adjusted as an offset to account for possible unequal duration between visits and between patients. The predicted hypoglycemia rate per 30 days and per year by treatment and visit will also be presented. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following covariance structures will be tested in this order: compound symmetry, then, autoregressive.

Additional exploratory analyses may be performed if deemed necessary.

#### **5.15.2.2. Percentage of Patients Receiving Rescue Medication due to Severe, Persistent Hyperglycemia**

Frequency counts and percentage of patients receiving rescue medication due to severe persistent hyperglycemia will be presented using ITT population. Fisher's exact test will be applied to compare treatments on the proportion of patients receiving rescue medication due to severe persistent hyperglycemia. Time to receiving rescue medication due to severe persistent hyperglycemia will be analyzed to compare treatment groups using a semi-parametric proportional hazard Cox regression model with treatment, country, SGLT2 inhibitor dose ("low" versus "high"), metformin use ("yes" versus "no"), baseline HbA1c strata ( $\leq 8.0\%$  and  $> 8.0\%$ ) as fixed effects, and baseline HbA1c as a covariate. A Kaplan-Meier curve will be plotted for both treatments on the same graph, for presentation purposes. These same reports will be also provided for patients meeting criteria for severe persistent hyperglycemia, irrespective of whether they received rescue therapy while in the trial or not.

#### **5.15.2.3. Pancreas Safety**

Listing and summary will be provided for all events that submitted for adjudication. Listing and summary of adjudicated pancreatic events will also be provided.

#### **5.15.2.4. Cardiovascular Safety**

Listing and summary of events submitted for adjudication will be provided. Listing and summary of adjudicated cardiovascular (CV) events will also be provided. Heart rate and

systolic and diastolic blood pressure from vital signs will be summarized as well as ECG data (see Section 5.15.2.4.1 and Section 5.15.2.4.2 for details). In addition to the summary of AEs from the CV SOC, an additional summary of AEs suggestive of hypotension will be provided.

#### **51524.1. Vital Signs**

All vital signs will be listed using the all randomized population. The average value (mean of two measurements) will also be listed.

The measurements will be averaged for each patient at each visit. The average values will be used in the descriptive summaries and analyses.

Descriptive statistics for the change from baseline for sitting systolic, diastolic blood pressures and heart rates (HR) will be presented and will be analyzed using an MMRM model described in Section 5.2. Summaries and analyses will be conducted using the ITT population. The selection of the variance-covariance structure is discussed in Section 5.2. There will be no multiplicity adjustments for analyses of vital signs. Corresponding figures will be presented.

#### **51524.2 Electrocardiogram**

A listing of the individual and averaged ECG measurements (Heart Rate, QT, RR, QRS, PR and corrected QTs [QTc]) by patient will be produced using the all randomized patient population. Also, a listing of abnormal selected ECG parameters by patient will be produced using the all randomized patients population.

Descriptive statistics for the actual measurements and change from baseline, by treatment arm and visit, for selected ECG parameters will be presented using ITT population. The parameters that are included in the summary and analysis with an ANCOVA model are ECG heart rate and the QT, QTcF, QTcB, RR, PR, and QRS intervals.

The ANCOVA approach suggested by Dmitrienko and Smith (2002, 2003) will be the primary method of correcting QT interval for RR interval.

A mixed-effect ANCOVA model for QT change from baseline with the RR change from baseline and baseline QT as covariates will be used where treatment, country, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), baseline HbA1c strata ( $\leq 8.0\%$  and  $> 8.0\%$ ) as fixed effect, and patient will be the random effect. Least-squares mean obtained from this model by primary treatment group and visit, along with the standard error (SE) of the LS mean for the change from baseline measurements will be displayed. Treatment comparisons will be displayed, showing the treatment difference LS mean and the 95% CI of the treatment difference along with the p-value for treatment comparison.

Additional correction methods such as Fridericia’s and Bazett’s corrections will also be used to correct the QT interval.

For quantitative ECG variables, summaries and analysis of treatment emergent abnormal values will also be provided.

Selected thresholds for HR, PR interval, and QTc interval shown in the following [Table GBGE.5.2](#) will be used to summarize clinically relevant abnormal values for these variables.

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**Table GBGE.5.2. Thresholds for HR, PR, and QTc Interval**

ECG Variable (unit)	Threshold
QTcF actual measurement (msec)	>450 for males, >470 for females > 480, >500
QTcF Change from Baseline (msec)	>60, >30, <-60, <-30
ECG heart rate (bpm)	>=130, >100, <50 >100 and increase from baseline >=15 <50 and decrease from baseline <= -15
PR interval (msec)	≥220 ≥220 and increase >20 ≥220 and increase >40 ≥220 and 0 < Increase <= 25% from baseline ≥220 and Increase > 25% from baseline

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; HR = heart rate; PR = pulse rate.

For qualitative ECG outcomes, treatment-emergent abnormalities will be summarized and compared using the likelihood-ratio test. Abnormalities will also be grouped hierarchically into categories. The top level categories include rhythm, conduction, axis, morphology, ischemia, infarction, injury, ST segment, T wave, U wave and other. Percent of patients in each category will be compared using Pearson chi-square test. Other qualitative analyses may be conducted, if deemed necessary.

#### 5.15.2.5. Thyroid Safety

Listings of AEs of interest associated with the thyroid gland (benign and malignant neoplasms) will be produced, as well as a listing of biopsy reports. For calcitonin, summaries and analysis for changes from baseline and treatment emergent abnormal values will be provided as well as listing of abnormal values. Shift tables may be provided if appropriate.

#### 5.15.2.6. Renal Safety

To assess renal safety, summary and analyses for changes from baseline will be provided for estimated glomerular filtration rate (eGFR), as well as shift tables. Treatment emergent abnormal values will be summarized and analyzed. Listing of AEs suggestive of acute and chronic kidney failure will also be provided. Other reports may also be generated if deemed appropriate.

#### 5.15.2.7. Allergic/Hypersensitivity Reactions

Listing and summary of allergic and other hypersensitivity AEs will be provided.

### 5.15.3. Analysis of Laboratory Analyte

All laboratory measurements including scheduled and unscheduled will be listed by patient by visit using all randomized patients. An additional listing will be presented for all laboratory

measurements that are outside the normal range. Certain laboratory measurements will be listed using clinical relevant thresholds other than laboratory limits.

All summary analyses will be conducted by treatment group using ITT population.

Descriptive statistics will be presented, by treatment group and visit, for the laboratory measurements. For each continuous laboratory measurement, the change from baseline, at each visit, will be analyzed using ANOVA on the ranks, with treatment as a fixed effect. Last-observation-carried-forward will be used to impute missing post baseline values for the last visit. Continuous lab measures will also be compared to reference range to determine whether they are abnormally high, low or normal. The incidence and percent of high, low and normal values will be listed for each of the treatment arms and compared using the Fisher's exact test or Chi-square test. Shift table will also be presented for each continuous measure.

For subjective (qualitative) laboratory assessments, count and percent of normal and abnormal values will be analyzed using Fisher's exact test or Chi-square test.

Counts and percentages for patients with pancreatic enzymes above upper limit of normal (ULN) and greater than or equal to  $3 \times \text{ULN}$  will be summarized at baseline and by visit for each treatment group.

A summary of changes (shift tables using normal and abnormal categories) in amylase (total, pancreatic) and lipase evaluation from baseline to the maximum postbaseline will be produced.

Additional analyses will be conducted if deemed necessary.

### 5.16. Subgroup Analyses

Population subgroups of interest will be analyzed for the variables of HbA1c and body weight. Other variables may also be evaluated.

The following are candidate subgroups that might be analyzed. This list is not necessarily all-inclusive:

- baseline age group (<65 years,  $\geq 65$  years)
- race
- ethnicity
- country
- duration of diabetes at baseline (<median duration and  $\geq$ median duration)
- BMI (<median and  $\geq$ median)
- concomitant metformin
- baseline HbA1c ( $\leq 8.0\%$  and  $> 8.0\%$ )
- baseline glucagon (<median and  $\geq$ median)

An analysis will be performed examining the treatment-by-subgroup interaction term at Week 24 using the MMRM model with country, treatment, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), visit, subgroup, subgroup-by-treatment interaction, treatment-by-visit interaction, subgroup-by-visit interaction, and subgroup-by-treatment-by-visit interaction as fixed effects and baseline (HbA1c or body weight) as a covariate. For the subgroup analysis of baseline HbA1c strata ( $\leq 8.0\%$  and  $> 8.0\%$ ), the model will include country, treatment, SGLT2 inhibitor dose (“low” versus “high”), metformin use (“yes” versus “no”), visit, subgroup, subgroup-by-treatment interaction, treatment-by-visit interaction, subgroup-by-visit interaction, and subgroup-by-treatment-by-visit interaction as fixed effects. Baseline HbA1c will not be included as a covariate. The interaction effects at Week 24 will be evaluated using a significance level of 0.10, unadjusted.

### 5.17. Exploratory Analyses

The following exploratory analyses will be conducted to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks using a similar longitudinal logistic regression with repeated measurements as described in Section 5.12.3:

- Proportion of patients meeting the composite endpoint of HbA1c  $< 7.0\%$ , no weight gain, and no documented symptomatic hypoglycemia
- Proportion of patients meeting the composite endpoint of HbA1c  $< 7.0\%$ , body weight loss  $> 5\%$ , and no documented symptomatic hypoglycemia

## 6. Unblinding Plan

### 6.1. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist will be consulted to determine whether it is necessary to amend the protocol.

### 6.2. Site Level Unblinding

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. The treatment assignments will be blinded to patients and investigators until the end of the study.

Emergency un-blinding for AEs may be performed through the interactive web response system (IWRS). This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls/ website visits resulting in an un-blinding event are recorded and reported by the IWRS.

The investigator should make every effort to contact the Lilly clinical research physician (CRP) prior to un-blinding a patient's treatment assignment. If a patient's treatment assignment is un-blinded, Lilly must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or patient is un-blinded, the patient must be discontinued from the study (Protocol Section 8.3.1.3). In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

### 6.3. Sponsor/Trial Level Unblinding

The study team will remain blinded to treatment assignments until all patients have completed the study and the database has been finalized and locked for analysis.

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