

H9X-MC-GBGJ Statistical Analysis Plan Version 1

A Phase 2, Double-Blind, Placebo-Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy

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1. Statistical Analysis Plan: H9X-MC-GBGJ: A Phase 2, Double-Blind, Placebo- Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy

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Dulaglutide (LY2189265) T2D

Study H9X-MC-GBGJ is a Phase 2, randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of once-weekly investigational dulaglutide doses compared to placebo at 18 weeks in patients with type 2 diabetes mellitus on metformin monotherapy.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol H9X-MC-GBGJ
Phase 2

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

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2. Table of Contents

1.	Statistical Analysis Plan: H9X-MC-GBGJ: A Phase 2, Double-Blind, Placebo-Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy	1
2.	Table of Contents	2
3.	Revision History	8
4.	Study Objectives and Endpoints	9
5.	Study Design	12
5.1.	Summary of Study Design	12
5.2.	Determination of Sample Size	13
5.3.	Method of Assignment to Treatment	13
6.	A Priori Statistical Methods	15
6.1.	General Considerations	15
6.2.	Adjustments for Covariates	17
6.3.	Handling of Dropouts or Missing Data	17
6.4.	Multicenter Studies	18
6.5.	Multiple Comparisons/Multiplicity	18
6.6.	Patient Population	18
6.7.	Patient Disposition	19
6.8.	Patient Characteristics	19
6.9.	Treatment Compliance	20
6.10.	Concomitant Therapy	20
6.11.	Efficacy Analyses	21
6.11.1.	Primary Outcome and Methodology	21
6.11.2.	Additional Analyses of the Primary Outcome	21
6.11.2.1.	MMRM in different populations	21
6.11.2.2.	Missing data imputation	21
6.11.2.3.	Bayesian Analyses For Exploratory Objectives	21
6.11.3.	Secondary Efficacy Analyses	22
6.11.3.1.	The Primary Analyses for Secondary Efficacy Endpoints	22
6.11.3.2.	Supporting Analyses For Secondary Efficacy Endpoints	23
6.11.3.3.	Bayesian Analyses For Exploratory Objectives	23
6.12.	Pharmacokinetic/Pharmacodynamic (PK/PD) Methods	23
6.13.	Safety Analyses	23
6.13.1.	Extent of Exposure	24
6.13.2.	Adverse Events	24

- 6.13.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events 25
- 6.13.4. Adverse Events of Special Interest 25
 - 6.13.4.1. Hypoglycemic Episodes 25
 - 6.13.4.2. Severe, Persistent Hyperglycemia 27
 - 6.13.4.3. Pancreatitis 27
 - 6.13.4.4. C-cell hyperplasia and C-cell Neoplasms 28
 - 6.13.4.5. Allergic/Hypersensitivity Reactions 28
 - 6.13.4.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders 28
- 6.13.5. Gastrointestinal Safety 28
- 6.13.6. Treatment of Overdose 29
- 6.13.7. Cardiovascular Safety 29
 - 6.13.7.1. Cardiovascular Events 29
 - 6.13.7.2. Electrocardiograms 29
 - 6.13.7.3. Vital Signs 31
- 6.13.8. Renal Safety 32
- 6.13.9. Immunogenicity 33
- 6.13.10. Clinical Laboratory Evaluation 33
- 6.14. Subgroup Analyses 33
- 6.15. Important Protocol Deviations 34
- 6.16. Interim Analyses and Assessment Committee 35
 - 6.16.1. Assessment Committee 35
 - 6.16.2. Interim Analyses 35
 - 6.16.2.1. Timing of the Interim Analysis 35
 - 6.16.2.2. Evaluation Criteria 35
- 6.17. Planned Exploratory Analyses 36
- 6.18. Annual Report Analyses 36
- 6.19. Clinical Trial Registry Analyses 37
- 7. Unblinding Plan 38
 - 7.1. Operational Procedures 38
 - 7.2. Site Level Unblinding 39
 - 7.3. Trial Level Safety Reviews 40
 - 7.4. Assessment Committee Reports 40
 - 7.4.1. Safety Only Reports 41
 - 7.4.2. Efficacy/Safety Interim Report 41
 - 7.4.2.1. Model Development 41
 - 7.4.2.2. Reports Delivery 41

7.5. Clinical Study Report 42

 7.5.1. Prelock Unblinding 42

 7.5.2. End of Study Unblinding 42

8. References 43

9. Appendices 44

List of Tables

Table		Page
Table GBGJ.1.	Objectives and Endpoints	9
Table GBGJ.2.	Populations for Analyses	19
Table GBGJ.3.	Heart Rate, PR-Interval, and QTcF Abnormal Data	31
Table GBGJ.4.	Abnormality Data for Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure.....	32
Table GBGJ.5.	Study H9X-MC-GBGJ Group Name and Membership.....	39

List of Figures

Figure

Page

Figure GBGJ.1. Illustration of study design for Clinical Protocol H9X-MC-GBGJ.....13

List of Appendices

Appendix

Page

Appendix 1. [Analysis Windows for the Selected Parameters.....](#)45

3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to unblinding (or the first visit when a subject receives study drug or any other protocol intervention if the clinical trial is open-label).

4. Study Objectives and Endpoints

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

Table GBGJ.1. Objectives and Endpoints

Objectives	Endpoints
<p>Primary To demonstrate that once weekly dulaglutide (4.5 mg, 3.0 mg, 1.5 mg) is superior to placebo in HbA1c reduction at 18 weeks in patients with T2D on concomitant metformin monotherapy.</p>	<ul style="list-style-type: none"> The change in HbA1c from baseline
<p>Secondary <u>Efficacy</u></p> <ul style="list-style-type: none"> To compare each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) to the placebo arm at 18 weeks for secondary efficacy parameters <p><u>Safety</u></p> <ul style="list-style-type: none"> To compare each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) to the placebo arm for selected safety parameters at 18 weeks <p><u>Pharmacokinetics and Pharmacodynamics</u></p> <ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) of dulaglutide and establish the relationships between dose/exposure and key safety and efficacy measures 	<ul style="list-style-type: none"> Proportion of patients achieving HbA1c target of <7.0% The change in fasting serum glucose (FSG; central laboratory) from baseline The change in body weight from baseline Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) Discontinuation of study drug due to adverse events (AEs) Incidence and rate of hypoglycemia (severe, total, documented symptomatic, and nocturnal) PK parameters (eg, C_{max}, AUC) Pharmacodynamic evaluations will include HbA1c, FSG, body weight, QTcF interval, and heart rate
<p>Tertiary/Exploratory <u>Efficacy</u></p> <ul style="list-style-type: none"> To compare each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) to the placebo arm for additional efficacy measures at 18 weeks 	<ul style="list-style-type: none"> Proportion of patients achieving HbA1c target ≤6.5% The change in 6-point self-monitored plasma glucose (SMPG) profiles from baseline The change in fasting plasma glucagon from baseline The change from baseline in insulin resistance (HOMA-IR) and β-cell function (HOMA-%B) as measured by the HOMA2 Method (Caumo et al. 2006)

Objectives and Endpoints

Objectives	Endpoints
<p>Tertiary/Exploratory (continued)</p> <p><u>Efficacy</u></p> <ul style="list-style-type: none"> To compare the investigational dose dulaglutide arms (4.5 mg and 3.0 mg) to the 1.5 mg arm for efficacy measures at 18 weeks <p><u>Safety</u></p> <ul style="list-style-type: none"> To compare the investigational dose dulaglutide arms (4.5 mg and 3.0 mg) to the placebo arm for additional safety measures at 18 weeks To compare the investigational dose dulaglutide arms (4.5 mg and 3.0 mg) to the 1.5 mg arm for safety measures at 18 weeks 	<ul style="list-style-type: none"> Change from baseline in HbA1c Proportion of patients achieving HbA1c target <7.0% or ≤6.5% The change in FSG (by central laboratory) from baseline The change in body weight from baseline The change in 6-point SMPG profiles from baseline The change in fasting plasma glucagon from baseline The change in HOMA-IR and HOMA-%B from baseline Selected gastrointestinal tolerability AEs (nausea, vomiting, and diarrhea) Pancreatic safety assessed by incidence of cases of adjudicated pancreatitis CV safety assessed by the incidence of adjudicated deaths and nonfatal major CV events Thyroid-related safety assessed by the incidence of cases of thyroid neoplasms Vital signs (PR, BP) ECG (HR, QTcF, supraventricular arrhythmias and cardiac conduction abnormalities) Immune system-related safety, including the incidence of dulaglutide antidrug antibodies (ADA) and the incidence of allergic and hypersensitivity reactions Injection site reactions Incidence of rescue therapy initiation due to severe, persistent hyperglycemia TEAEs and SAEs Discontinuation of study drug due to AEs Incidence and rate of hypoglycemia (severe, total, documented symptomatic, and nocturnal) Selected gastrointestinal tolerability AEs (nausea, vomiting, and diarrhea) Pancreatic safety assessed by incidence of cases of adjudicated pancreatitis CV safety assessed by the incidence of adjudicated deaths and nonfatal major CV events

Objectives and Endpoints

Objectives	Endpoints
<p data-bbox="181 268 574 298">Tertiary/Exploratory (concluded)</p> <p data-bbox="181 779 261 808"><u>Safety</u></p> <ul data-bbox="235 810 795 1003" style="list-style-type: none"> To compare the titration algorithms (Algorithm 1 vs. Algorithm 2) within the investigational dose dulaglutide arms (4.5 mg and 3.0 mg) and across the investigational dose arms versus dulaglutide 1.5 mg and placebo at 6 and 18 weeks 	<ul data-bbox="868 268 1412 913" style="list-style-type: none"> Thyroid-related safety assessed by the incidence of cases of thyroid neoplasms Vital signs (PR, BP) ECG parameters (HR, QTcF, supraventricular arrhythmias and cardiac conduction abnormalities) Immune system-related safety, including the incidence of dulaglutide ADA and the incidence of allergic and hypersensitivity reactions Injection site reactions Incidence of rescue therapy initiation due to severe, persistent hyperglycemia Incidence of selected GI AEs (nausea, vomiting, and diarrhea) Vital signs (PR, BP)

Abbreviations: ADA = antidrug antibodies; AE = adverse event; AUC = area under concentration-time curve; BP = blood pressure; C_{max} = maximum concentration; CV = cardiovascular; ECG = electrocardiogram; FSG = fasting serum glucose; GI = gastrointestinal; HbA_{1c} = hemoglobin A_{1c}; HOMA = Homeostasis Model Assessment; HR = heart rate; PR = pulse rate; QTcF = Fridericia’s corrected QT interval; T2D = type 2 diabetes mellitus; SAEs = serious adverse events; SMPG = self-monitored plasma glucose; TEAS = treatment emergent adverse events.

5. Study Design

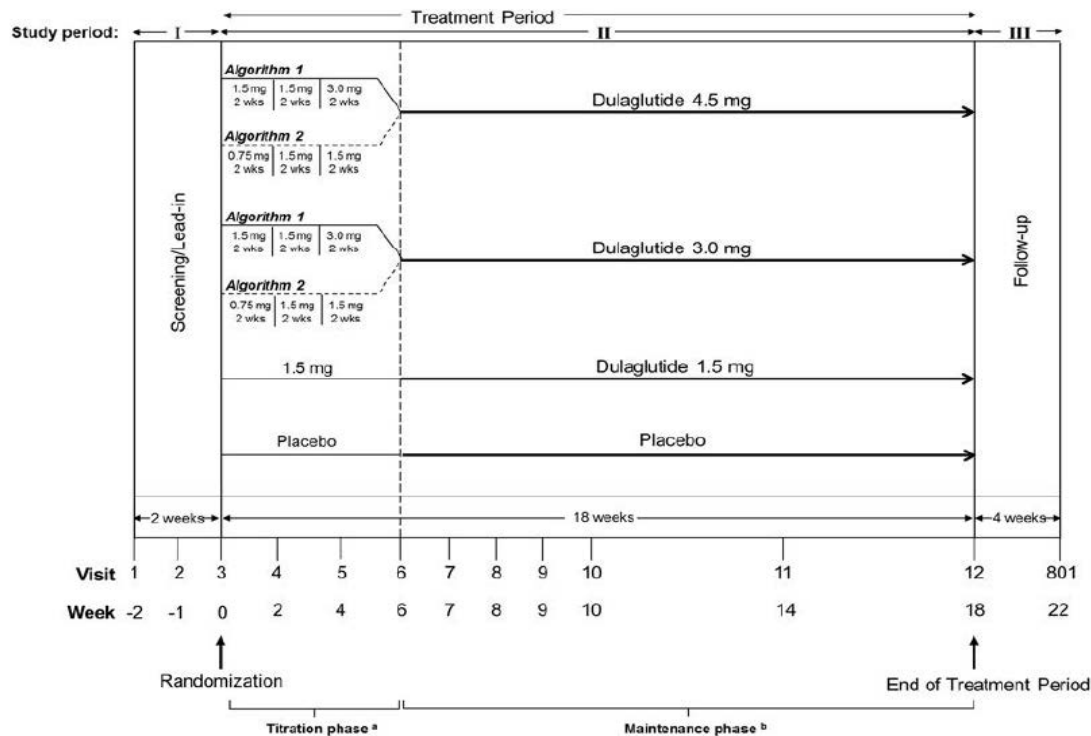
5.1. Summary of Study Design

Study H9X-MC-GBGJ (GBGJ) is a randomized, multicenter, placebo-controlled, double-blind Phase 2 trial in T2D patients on metformin monotherapy. The study is designed to assess the efficacy and safety of once weekly dulaglutide 3.0 mg and 4.5 mg in comparison to placebo. In addition, the trial will explore how these dulaglutide doses compare to the approved dulaglutide 1.5 mg dose to support dose selection for further development in Phase 3 trials, and to guide design of these additional trials. Study GBGJ will also explore the effect of 2 dulaglutide dose titration algorithms on gastrointestinal (GI) tolerability with investigational doses to guide design of the definitive algorithm to be evaluated in Phase 3 trials. The primary objective of this trial is to show superiority of the 3 dulaglutide doses (4.5 mg, 3.0 mg, 1.5 mg) to placebo in change in hemoglobin A1c (HbA1c) at 18 weeks.

During the trial, an unblinded internal assessment committee (AC) will review data on safety and tolerability in study participants according to a prespecified schedule in order to assure the safety of randomized patients. An efficacy/safety interim analysis will be conducted after approximately 120 patients have completed the 18-week therapy.

The study will consist of 3 periods: an approximately 2-week lead-in period, followed by an 18-week treatment period, and a 4-week safety follow-up period.

Figure GBGJ.1 illustrates the study design.



- a Patients will administer 1 injection per week in the first 4 weeks of the titration phase, and 2 injections per week in the remainder of the titration phase.
- b During the maintenance phase, the assigned dose will require 3 injections.

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

5.2. Determination of Sample Size

Assuming a screen failure rate of 30%, approximately 429 patients will need to be screened to attain approximately 300 patients randomized to the 4 treatment arms in a 1:1:1:1 ratio for 4.5 mg, 3.0 mg, 1.5 mg dulaglutide, or placebo weekly (~75 patients per arm). For the investigational dulaglutide dose arms (4.5 mg and 3.0 mg), approximately 38 patients will be assigned to each titration algorithm (Algorithms 1 and 2). Assuming a 20% dropout, this will result in approximately 60 patients per arm and 30 patients per algorithm (in each of the investigational-dose dulaglutide arms) completing the study.

The aforementioned sample size provides $\geq 90\%$ power to demonstrate superiority for the dulaglutide doses (4.5 mg, 3.0 mg, and 1.5 mg) to placebo with respect to HbA1c change from baseline to 18 weeks. This assumes a true glycemic effect difference of -1% HbA1c for each dulaglutide dose versus placebo, and a standard deviation (SD) of 1.2% with a 2-sided alpha of 0.05.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to one of the study treatment arms at Visit 3. Assignment to treatment arms will be determined by a computer-generated random sequence using an Interactive Web Response System (IWRS). The IWRS will be used

to assign cartons containing double-blinded study drug to each patient. Site personnel will confirm that they have located the correct cartons by entering a confirmation number found on the label into the IWRS.

Block randomization will be used at the country level. Patients will be randomized in a 1:1:1:1 ratio (dulaglutide 4.5 mg, dulaglutide 3.0 mg, dulaglutide 1.5 mg, placebo). Within the dulaglutide 4.5 mg and 3.0 mg arms, patients will be randomly assigned (1:1) to Algorithm 1 or Algorithm 2. Randomization will be stratified by HbA1c (<8%, ≥8%).

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company 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 clinical study report (CSR). Additional exploratory analyses of the data may be conducted as deemed appropriate without further changes made to the protocol or SAP even after the datalock.

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. No adjustments for multiplicity will be performed.

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 prior to this visit 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 18 (Visit 12).

For all statistical analyses, missing data will be treated as missing at random unless otherwise specified; therefore, no imputation is needed unless otherwise stated.

The treatment groups mentioned in this document are based on the randomized treatment groups: dulaglutide 4.5 mg, dulaglutide 3.0 mg, dulaglutide 1.5 mg, placebo. For the purposes of tables, figures, the treatment groups will be: Dula 4.5, Dula 3.0, Dula 1.5, and Placebo. For data listings, the treatment groups will be presented as Placebo, Dula 1.5, Dula 3.0/A1 representing dulaglutide 3.0 mg/algorithm 1, Dula 3.0/A2 representing dulaglutide 3.0 mg/algorithm 2, Dula 4.5/A1 representing dulaglutide 4.5 mg/algorithm 1, Dula 4.5/A2 representing dulaglutide 4.5 mg/algorithm 2.

Incidence of nausea, vomiting, and diarrhea, vital signs (pulse rate, blood pressure [PR, BP]), electrocardiogram (ECG) variables (heart rate [HR], PR interval, and Fridericia's corrected QT interval [QTcF]), and pancreatic enzyme (amylase and lipase) will be summarized by the randomized treatments, and by algorithm within the same investigational dulaglutide dose, and by algorithm across the investigational dulaglutide doses.

Placebo will serve as the reference treatment for each dulaglutide dose, while dulaglutide 1.5 mg as the active comparator for each investigational dulaglutide dose.

All efficacy and safety data will be summarized by each treatment group at each scheduled visit unless otherwise indicated. A scheduled visit is based on the analysis window for the selected

parameters of interest ([Appendix 1](#), Table APP1.1) not the actual visit number reported by the site. For the other measures, the actual scheduled visit reported by the sites will be used.

A mixed-model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. In this model, restricted maximum likelihood will be used to obtain model estimates with Kenward-Roger (KR) option to estimate denominator degrees of freedom. The corresponding baseline value will be used as a covariate, and the stratification factors (pooled country, HbA1c strata [screening HbA1c at Visit 1: <8.0%, ≥8.0%]), treatment (dulaglutide 4.5 mg, dulaglutide 3.0 mg, dulaglutide 1.5 mg, placebo), visit, and treatment-by-visit interaction will be fixed effects. For HbA1c change from baseline analysis or HbA1c target analysis, HbA1c strata will be replaced with continuous baseline HbA1c as a covariate from the aforementioned model. 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 of covariance (ANCOVA) as a sensitivity analysis for the primary and secondary continuous efficacy endpoints using the last observation carried forward (LOCF) described in Section 10.3.1 of the protocol H9X-MC-GBGJ(a) will not be used for analyses of secondary continuous efficacy endpoints as the analysis was shown to produce biased results (Lachin 2016) with little inferential value.

For continuous laboratory measurements for safety, an analysis of variance (ANOVA) on ranks 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 mean (LS mean) and standard errors (SEs) 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 mean and the 95% CIs between each dose and placebo, and between each investigational dulaglutide dose and 1.5 mg at the same visit, along with the corresponding p-values.

Summary statistics for categorical measures will include number of subjects and percentages. The percentage of patients achieving target HbA1c <7.0% at Week 18 will be analyzed using a longitudinal logistic regression with repeated measurements with treatment, visit, treatment-by-visit interaction, and baseline HbA1c-by-visit interaction as fixed effects and baseline HbA1c as a covariate. For the analysis of other categorical measures, 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 unless otherwise stated. Unless otherwise stated, categorical variables will be summarized by sample size, the number of patients and percentages for each treatment group at each visit.

Imputed data may be applied in model-based data analysis, but will not be used in data listing.

The latter will only present the non-imputed raw data including site reported scheduled, site reported unscheduled, or early termination visit data; however, only scheduled visits for the measure of interest ([Appendix 1](#), Table APP1.1) will be included in the summary table and statistical inference unless otherwise stated.

Additional analyses may be performed even after datalock if deemed needed.

All statistical analyses will be conducted with Statistical Analysis System (SAS) Version 9.4® or higher unless otherwise stated.

6.2. Adjustments for Covariates

The study is stratified by baseline HbA1c with country as a block factor; therefore, both stratification factors will be fitted in the corresponding statistical model as fixed effects for the non-HbA1c measurements unless otherwise stated. For HbA1c analysis, 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.

6.3. Handling of Dropouts or Missing Data

Missing data will be imputed as a sensitivity analysis for the primary and key secondary continuous endpoints using a tipping point approach, and copy reference approach. The reference is from those patients on the same treatment who received rescue medication and/or stopped study medication, but had the measurement for the corresponding endpoints.

For HbA1c target of <7.0% and ≤6.5%, those who have missing data at Week 18 (Visit 12) or who receive rescue therapy prior to the Week 18 visit will be imputed as not reaching HbA1c target.

Last observation carried forward (LOCF) to impute the missing endpoint data will be used for the non-longitudinal continuous variables such as 6-point self-monitored plasma glucose (SMPG), Homeostasis Model Assessment (HOMA-IR), and HOMA-%B, c-peptide, fasting insulin, 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 non-missing randomization date will be used to impute the first dosing date and the time will be placed with 0800 hours. The 0800 hours is the most common first injection time per historical dulaglutide studies. This imputation is only applicable for PK related exposure analysis.

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, those detailed imputation rules will be documented in a separated file such as statistical decision log or track change log.

6.4. Multicenter Studies

No planned analysis related to site will be conducted. This will be only performed upon request after datalock.

6.5. Multiple Comparisons/Multiplicity

This is an exploratory Phase 2 study; thus, multiplicity adjustment will not be performed.

6.6. Patient Population

Five patient populations are defined for the analyses in this study with detailed information listed in [Table GBGJ.2](#). Unless otherwise specified, listings will include all randomized patients. Efficacy and safety analyses will be conducted in the intent-to-treat (ITT) population. The primary efficacy measure (change from baseline in HbA1c) will also be evaluated in the per protocol (PP) population and Completer set (CS) population.

In all efficacy and hypoglycemia analyses, all data after rescue therapy will be censored unless otherwise stated.

Analyses of safety parameters, except for hypoglycemia events, will be conducted in the ITT population including the post-rescue therapy data.

Table GBGJ.2. Populations for Analyses

Population	Description
Entered	All participants who sign informed consent
Intent-to-treat	All participants who are randomized and take at least 1 dose of study medication for an assigned treatment arm
All randomized population	All patients who are randomized
Per protocol	All ITT patients who meet all of the following criteria: <ul style="list-style-type: none"> • Have no important protocol deviation that could impact the assessment of the primary endpoint; the list of specific criteria is provided in Section 6.15 • At least 75% compliant with study drug administration • Complete the treatment period (18 weeks) • Have a value of the primary efficacy measure at 18 weeks Note: the final criteria will be documented in electronic Trial Master File (eTMF).
Completer set	All ITT patients who complete 18 weeks of study drug treatment without rescue therapy

Abbreviation: HbA1c = hemoglobin A1c; ITT = intent to treat.

6.7. Patient Disposition

The reasons for patient discontinuations from study medication and from the study will be summarized for all randomized subjects by each randomized treatment, by visit, and overall. An additional report will be provide to provide combined disposition report for early discontinuation of study drug and early discontinuation of study, by visit, cumulative and overall. The latter report is need to account for patients who permanently discontinue study drug but continued in the trial, as allowed by the study protocol.

The p-value to test the overall treatment effect among all randomized treatments and the p-value will be presented using Fisher's exact test or Chi-square test detailed in Section 6.1.

Kaplan-Meier curves by treatment for time to study discontinuation due to any reason will be presented. 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 all randomized population.

6.8. Patient Characteristics

Demographic and baseline clinical characteristics will be summarized by treatment for ITT population detailed in Section 6.1. For continuous measures, summary statistics will include sample size, mean, median, maximum, minimum, and SD along with the ANOVA p-value to test for difference among all randomized treatment groups. For categorical measures, summary statistics will include sample size, the number and percentage of patients for each category with Fisher's or Chi-square p-value. In the summary report, each algorithm arm will be included.

Similar summary reports will be generated separately for PP ad CS population.

The patient characteristics will be listed for all randomized population.

6.9. Treatment Compliance

Treatment compliance in GBGJ is defined as taking at least 75% of the required injections for the prespecified time intervals: titration phase from the first dose to the sixth dose, and every 4 weeks thereafter: from the seventh dose to the 10th dose, from the 11th dose to the 14th dose, from the 15th dose to the 18th dose. Overall compliance is defined as being at least 75% compliant with investigational product across the treatment period. Compliance source data is from the site reported case report form (CRF) data.

Compliance will be summarized using ITT population by each randomized treatment and time interval, and overall. Listings will also be produced from all randomized population.

6.10. Concomitant Therapy

The prespecified concomitant medications of interest will be summarized (detailed in Section 6.1) by all randomized treatments groups for baseline and after randomization, for the ITT population. In addition, antihyperglycemia medications will be also summarized at screening and for the last 3 months prior to study enrollment by each randomized treatment group. The concomitant therapies will be mapped using the World Health Organization (WHO) DRUG dictionary in the clinical trial database and will be further classified using Anatomic-Therapeutic-Chemical (ATC) codes for reporting purposes.

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

- antihyperglycemia agents
 - background metformin therapy
 - agents used for short term therapy for acute condition
 - rescue therapy (only applicable for after randomization)
 - agents used for other reasons
- weight loss medications
- systemic glucocorticoids
- antihypertensive agents
- lipid lowering agents
- anticoagulant agents
- anti-inflammatory agents
- cardiac therapy

Concomitant therapy will be listed for the all-randomized population.

6.11. Efficacy Analyses

6.11.1. Primary Outcome and Methodology

The primary analysis for the primary outcome, change from baseline in HbA1c at Week 18 (Visit 12), will employ MMRM described in Section 6.1 in ITT population by censoring all post rescue data.

The report from this analysis includes LS means and corresponding 95% CIs for each randomized treatment at each scheduled visit, and the difference in LS means, corresponding 95% CI along with p-value compared to placebo and to dulaglutide 1.5 mg at the same visit.

6.11.2. Additional Analyses of the Primary Outcome

6.11.2.1. MMRM in different populations

Different populations including ITT regardless of rescue therapy or adherence to study drug, PP, CS population 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.

The output will be generated as that listed in Section 6.11.1.

6.11.2.2. Missing data imputation

If the conclusions differ among the four populations listed in Section 6.11.1 and Section 6.11.2.1, additional analyses may be further explored using selected pattern mixture models for missing data (Kenward and Rosenkranz 2011) in the ITT population regardless of rescue therapy or compliance to the study treatment. In this case, imputed 18-week HbA1c response for the missing data along with the non-missing 18-week data will be employed using an ANCOVA model by removing all visit related terms. The missing data will be imputed from the non-missing subjects who took rescue therapy or continued on the study but discontinued study medication. Depending on the missing data status, the non-missing data used for imputation may be altered from what is described in this section.

The tipping-point approach is like a progressive stress-test to assess how severe departures from missing at random (MAR) need to be in order to overturn conclusions from the primary analysis. In the dulaglutide arms, the imputed values will be replaced by the imputed value plus a shift parameter beginning from 0 with the increment of 0.05. Each value of the shift parameter will be tested sequentially until the value is reached at which the conclusion from the MMRM analysis is reversed. That value is the tipping point indicating that the conclusion under MAR is questionable if this shift parameter value is plausible. If implausible departures from MAR are required to change the results from statistically significant ($p \leq 0.05$) to not statistically significant ($p > 0.05$), the results will be said to be robust to the departure from MAR assumption and provide more confidence in the results obtained based on statistical methods with the MAR assumptions.

6.11.2.3. Bayesian Analyses For Exploratory Objectives

A Bayesian integrated 2-component prediction (ITP) model (Fu and Manner 2010) will be fitted for the primary endpoint separately in ITT population by censoring all post rescue therapy data,

and in ITT population including all available data regardless of rescue medication or adherence to the study drug. Non-informative priors will be used in this model. In addition, the informative priors from the posterior for placebo and posterior for dulaglutide 1.5 mg obtained from Study H9X-MC-GBCF (GBCF) and Study H9X-MC-GBDE (GBDE) will be evaluated in this model to check the robustness of the analysis.

$$Y_{ijt} = (\theta_i + S_{ij} + \alpha \times (B_{ij} - \bar{B}) + \varepsilon_{ijt}) \times \left(\frac{1 - e^{k_i \times t}}{1 - e^{k_i \times 18}} \right)$$

Prior information: $\Theta_i, \alpha \sim N(0, 3)$; $S_{ij}, \varepsilon_{ijk}, \sim \text{uniform}(0.01, 3)$; $k_i \sim \text{uniform}(-1, 1)$ where Y_{ijt} represents HbA1c change from baseline from dose i , subject j at time t . Parameter Θ_i is the predicted drug effect of dose i at 18-week therapy. The parameter S_{ij} is a random between-subject SD, and ε_{ijt} is the within subject SD. The B_{ij} is baseline HbA1c for subject j at dose i and \bar{B} is the overall arithmetic mean baseline HbA1c from all subjects. k_i is the parameter to represent how fast to reach the effect for dose i at Week 18.

Probabilities based on posterior distributions of the parameter of interest: change from baseline to Week 18, and Week 26 will be generated from this model using 10000 MCMC samples with thin=10 and burn-in=10000:

$$\text{pr}(\Delta_i - \Delta_{\text{dula}1.5\text{mg}} < \text{threshold})$$

i stands for dulaglutide 3.0 mg or 4.5 mg.

The threshold of -.15, -.2, and -.3% will be used, separately.

If this model fails to converge, an alternative Bayesian model will be fitted:

$$y_{ijt} \sim \text{MVN}(\mu[i, t], \Omega)$$

$$u[i, t] = \alpha \times (B[i, j] - \bar{B}_0) + \beta[i, t] \times T[i, t]$$

Where $\beta[i, t]$ is the effect for dose i at time t . Ω is the variance-covariance matrix.

The priors for each parameters are: $\alpha \sim N(0, 3)$, $\beta[i, t] \sim N(0, 3)$, $\Omega \sim \text{wishart}(t, t\text{-dimension Identity matrix})$.

The probability for Week 26 will be assumed to be the same as Week 18 from this model.

6.11.3. Secondary Efficacy Analyses

6.11.3.1. The Primary Analyses for Secondary Efficacy Endpoints

The ITT population by censoring the post-rescue data is the analysis population for secondary efficacy endpoints. Data for secondary endpoints will be summarized as described in Section 6.1. The MMRM described in Section 6.1 will be used to analyze each secondary

continuous efficacy endpoint: change from baseline in FSG and body weight. The result will be reported as detailed in Section 6.11.1.

The proportion of patients achieving HbA1c target <7.0% will be analyzed using repeated measures logistic regression mixed model described in Section 6.1 as the primary analysis. Pooled country, treatment, visit, treatment-by-visit interaction will be fitted as fixed effects, baseline HbA1c as a covariate. This model will be fitted to leverage all available data without imputation.

6.11.3.2. Supporting Analyses For Secondary Efficacy Endpoints

As a sensitivity analysis for proportion of patients on HbA1c targets, a logistic regression model will be fitted with pooled country and treatment as fixed effect, baseline HbA1c as a covariate to analyze the endpoint data. Prior to this analysis, the missing data or the patients rescued up to Week 18 will be imputed as not achieving HbA1c target.

The analyses listed in Section 6.11.3.1 will be repeated for the ITT population without censoring the post rescue data as a sensitivity analysis to FSG and body weight change from baseline.

6.11.3.3. Bayesian Analyses For Exploratory Objectives

A similar Bayesian ITP model listed in Section 6.11.2.3 will be fitted to analyze body weight change from baseline as a supportive analysis by only changing the prior information with Θ_i , $\alpha \sim N(0, 100)$.

Probabilities based on posterior distributions of the parameter of interest: change from baseline in body weight at Week 18, and Week 26 will be generated from this model using 10000 MCMC samples with thin=10 and burn-in=10000:

$$\text{pr}(\Delta_i - \Delta_{\text{dula}1.5\text{mg}} < \text{threshold})$$

i stands for dulaglutide 3.0 mg or 4.5 mg.

The threshold for this analysis will be -1 kg and -2 kg.

If this model doesn't converge, the similar alternative Bayesian model in Section 6.11.2.3 will be adopted with the priors: $\alpha, \beta[i,t] \sim N(0, 100)$.

The probability for Week 26 will be assumed to be the same as Week 18 from this model.

The imputed data along with non-missing 18-week data will be analyzed using an ANCOVA model following the same method listed in Section 6.11.2.2.

6.12. Pharmacokinetic/Pharmacodynamic (PK/PD) Methods

All PK/PD analyses will be performed by Lilly and details will be documented in a separate analysis plan.

6.13. Safety Analyses

The safety analyses will include adverse events (AEs), serious adverse events (SAEs), AEs of special interest (AESIs), and treatment emergent adverse events (TEAEs), safety laboratory

analytes, vital signs, ECG. Adverse events of special interest include hypoglycemic and hyperglycemic episodes, pancreatitis, thyroid C-cell hyperplasia and C-cell neoplasms, allergic/hypersensitivity reactions, supraventricular arrhythmias and cardiac conduction disorders.

An AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as postbaseline events that are new events or preexisting conditions that worsened in severity after randomization using MedDRA low level term (LLT). The maximum severity level for baseline and post baseline for each same LLT term 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 post baseline event.

Unless otherwise specified, the ITT population will be used for analyses of safety measures, and all randomized population for data listing.

6.13.1. Extent of Exposure

Treatment exposure is defined as the time from when the patient took his/her first dose until the last dosing date. If that 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 or completed the treatment period, whichever is earlier.

Exposure will be calculated for each patient. It will be summarized for ITT population by treatment with mean, SD, minimum, maximum, the first quartile and the third quartile. The mean exposure duration in days among treatment groups will be compared with ANOVA model using treatment as a fixed effect. The p-value to compare the overall randomized treatment effect will be presented. The total patient-years of study drug exposure will be added at the end of the summary. Duration of exposure was categorized into the following groups: ≤ 28 days, >28 to ≤ 42 days, >42 to ≤ 56 days, >56 to ≤ 70 days, >70 to ≤ 98 days, >98 and 126 days, >126 days. These categories were summarized as frequency by treatment.

Similar summary reports will be generated separately for PP and CS population. Each subject's detailed dose information at each post dose week (first dosing week will be coded as week 1) will be calculated based on the CRF sourced from the study drug administration log. For the maintenance phase, the dose information will use the package information for the missed injection(s). For the titration phase, the package information is not needed. For the first four weeks, missed injection means the entire dose is missed. For each of the last 2 titration week doses, missed 0, 1, and 2 injections means full dose, half dose, or no dose injected, respectively. This dose information along with the actual dosing date/time will be used for patient narratives, and PK analysis. The actual dosing information calculated in this section will be summarized by randomized treatment group. The exposure data will be listed for ITT population.

6.13.2. Adverse Events

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), in addition to the SOC and PT, for consistency with other dulaglutide studies. Treatment-

emergent AEs are defined as events that are newly reported after the first dosing or reported to worsen in severity from the first dosing.

Summary statistics will be provided for the following data: medical history and/or pre-existing condition AEs, TEAEs, SAEs, TEAESIs, and study discontinuations due to death or AEs. For TEAEs, SAE and TEAESIs will be reported separately from baseline to the end of the treatment period, and to the end of the study including safety follow-up. The number and proportions of patients experiencing each corresponding AEs will be reported for each randomized treatment group. Chi-square or Fisher's exact tests will be used to compare the randomized treatment groups detailed in Section 6.1.

The incidence of patients with at least one TEAE will be reported, and the proportion of patients experiencing each reported TEAE will be presented by PT (descending order) and by randomized treatment group, and also by the SOC (alphabetical order) and by descending PT order within the SOC. The proportion of patients experiencing each reported TEAE that are assessed as related to the study disease, study drug device, or procedures will be summarized. Note, drug device is coded as concomitant device. Additionally, a summary of TEAEs by maximum severity will be presented descriptively by randomized treatment group.

Separate summary reports will be provided for the number and percentage of patients who discontinued from the study and for patients who discontinue study treatment due to AE or death by descending frequency PT and within SOC by the randomized treatments. If deemed necessary, a Bayesian model may be fitted to evaluate if the probability of the incidence of discontinuation due to AEs for any investigational dose being $\leq 10\%$, $\leq 15\%$.

Listings will be provided for SAEs, TEAEs, and discontinuations due to AE or death.

Additional analyses will be performed for the purpose of fulfilling the clinical trial registry (CTR) requirements (Section 6.19).

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

All SAEs will be summarized by treatment by PT term using descending frequency order, and by SOC and PT (descending frequency order within SOC). Death will be listed including both adjudicated and investigator reported. Patient listings for the patient narratives will be generated for further processing. The criteria for patient narratives will be provided by the trial medical team and will be documented in eTMF.

6.13.4. Adverse Events of Special Interest

6.13.4.1. Hypoglycemic Episodes

Summary reports will include both incidence and rates of hypoglycemia in the ITT population by censoring the post rescue data. Hypoglycemia will be analyzed as documented symptomatic, asymptomatic, probable, severe, total, and nocturnal hypoglycemia with the definition (American Diabetes Association 2005) below:

- **Documented symptomatic hypoglycemia:** any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of ≤ 70 mg/dL (≤ 3.9 mmol/L).
- **Asymptomatic hypoglycemia:** any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤ 70 mg/dL (≤ 3.9 mmol/L).
- **Probable symptomatic hypoglycemia:** an event during which symptoms of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by a PG concentration ≤ 70 mg/dL [≤ 3.9 mmol/L]).
- **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 PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- **Total hypoglycemia:** any event of documented symptomatic, asymptomatic, probable, unspecified, severe hypoglycemia. Unspecified hypoglycemia is defined as an event during which PG ≤ 70 mg/dl (3.9 mmol/l) but no information relative to symptoms of hypoglycemia was recorded.
- **Nocturnal hypoglycemia:** any total hypoglycemic event that occurs between bedtime and waking.

A different glucose threshold of <54 mg/dL (<3 mmol/l) may also be included in these analyses when deemed appropriate.

For each category of the aforementioned hypoglycemia categories, the incidence will be analyzed using the methods for analyses of categorical data described in Section 6.1, by visit and 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, treatment, visit, and treatment-by-visit interaction as fixed effects and baseline HbA1c and baseline rate as covariates. The logarithm of days between visits will be adjusted as an offset to account for possible unequal duration between visits and 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 and by 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. For rare hypoglycemic episodes such as severe hypoglycemia, stratified Wilcoxon rank sum test will be used to test 1-year corresponding hypoglycemia rate between each dulaglutide dose and placebo, and between each 2 higher dose and dulaglutide 1.5 mg.

A listing of individual hypoglycemic episodes by patient will be presented.

6.13.4.2. Severe, Persistent Hyperglycemia

Summaries (if appropriate) will be provided for events of severe, persistent hyperglycemia (Protocol Section 7.4.1.3) resulting in initiation of rescue therapy by each randomized treatment. The time to the first rescue therapy use will be analyzed using PROC LIFETEST to generate Kaplan-Meier (KM) curves for each treatment. The summary reports will be only generated if more than 3% patients receive rescue intervention.

The patients who experienced severe, persistent hyperglycemia will be listed.

6.13.4.3. Pancreatitis

Summaries of adjudicated and investigator-reported pancreatic events will be provided by each randomized treatment. However, the summary report will only be generated if more than 3% patients have pancreatic event(s). Determination of investigator-reported events will be through the “Acute pancreatitis” Standardized MedDRA Queries (SMQ) and a “Chronic pancreatitis” Lilly Search Categories (LSC) of the AE database, while adjudication-confirmed pancreatitis will be found from adjudication CRF.

The patients developing pancreatitis will be listed separately for the investigator-reported and the adjudicated events.

Each pancreatic enzyme at Week 6 and Week 18, and the maximum post-dose value will be summarized by each randomized treatment, dulaglutide 3.0 mg/algorithm 1, dulaglutide 3.0 mg/algorithm 2, dulaglutide 4.5 mg/algorithm 1, dulaglutide 4.5 mg/algorithm 2, algorithm 1, and algorithm 2 in a shift table using >1 upper limit normal (ULN), and ≥ 3 ULN separately for the ITT population, ITT population with normal baseline, ITT population with baseline value $>$ ULN.

A MMRM with pooled country, baseline HbA1c strata, treatment, visit, and treatment-by-visit interaction as fixed effects will be fitted to analyze each pancreatic enzyme (p-amylase and lipase). In this model, the log transformed ratio (post first dose measure/baseline measure) will be the response variable and log transformed baseline measure instead of baseline measure will be a covariate. The variance-covariance structure selection is detailed in Section 6.1. The treatment in the model will include placebo, dulaglutide 1.5 mg, dulaglutide 3.0 mg/algorithm 1, dulaglutide 3.0 mg/algorithm 2, dulaglutide 4.5 mg/algorithm 1, dulaglutide 4.5 mg/algorithm 2. The report from this analysis will include:

- 1) Geometric LS means and corresponding 95% CIs for each randomized treatment at each scheduled visit, and the ratio in geometric LS means, corresponding 95% CI along with p-value compared relative to placebo and to dulaglutide 1.5 mg at the same visit.
- 2) Geometric LS means and corresponding 95% CIs of pancreatic enzyme for algorithm 1, algorithm 2 after adjusting for baseline, and the ratio between algorithm 2 and algorithm 1 (using algorithm 1 as reference) at Week 6 (Visit 6). These results won't be acquired directly from the MMRM model. Rather, they will be obtained from the same model by forming appropriate estimate statements with the same algorithm across dulaglutide 3.0 mg and dulaglutide 4.5 mg.

- 3) Geometric LS means and corresponding 95% CIs of pancreatic enzyme for dulaglutide 3.0, dulaglutide 4.5 after adjusting for baseline, and the ratio between each combined treatment across algorithms and placebo, and the difference between each combined treatment to Dulaglutide 1.5 at the same Week (Visit): Week 6 (Visit 6), Week 18 (Visit 12). These results will be obtained through the same model by forming appropriate estimate statements for the same dose across different algorithms.
- 4) The ratio of geometric LS means and the corresponding 95% CIs along with the p-value between each maintenance visit (Week 18/Visit 12) and the end of titration (Week 6/Visit 6) within the same treatment including the dulaglutide 3.0 mg, and 4.5 mg, and within the same algorithm will be presented. Any result related to combined treatment across algorithms and each algorithm at Visit 6 (Week 6) will be formed by constructing an appropriate estimate statement.

6.13.4.4. C-cell hyperplasia and C-cell Neoplasms

Listings of AEs of interest using a LSC will be provided by high level terms thyroid neoplasms, thyroid neoplasms malignant and thyroid disorders, as well as a listing of biopsy reports. The summary report for these AESIs by each randomized treatment will be reported if there are more than 3% patients with these AESIs.

Calcitonin data will be summarized using an ANCOVA model with treatment as a fixed effect by using LOCF. The response variable will be the rank on the change from baseline.

Calcitonin values will be listed for those patients with a post first dose serum calcitonin increase from (mean of the screening and baseline measures) $\geq 50\%$ and the absolute value ≥ 20 pg/ml. These patients will be classified by their absolute calcitonin values into the following categories: ≥ 20 and < 25 pg/ml; ≥ 35 and < 50 pg/ml; and ≥ 50 pg/ml. A shift table using these categories will be generated if the proportion of patients with these changes is 3% or more.

6.13.4.5. Allergic/Hypersensitivity Reactions

Listings of allergic/hypersensitivity AEs will be generated. If the number of patients with these events is 3% or more, then, a summary report will also be generated by each randomized treatment group.

A similar summary and listing will be generated for patients with injection site reactions.

6.13.4.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Summaries of these AESIs will be produced by PT with decreased frequency and by each randomized treatment using SMQ. The data listing will be generated. The qualitative ECG data including conduction and arrhythmia will be summarized by each randomized treatment and listed by treatment and patient.

6.13.5. Gastrointestinal Safety

Because certain 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, dulaglutide 3.0 mg/algorithm 1, dulaglutide 3.0

mg/algorithm 2, dulaglutide 4.5 mg/algorithm 1, dulaglutide 4.5 mg/algorithm 2, algorithm 1, algorithm 2 during the 18-week treatment period and during the first 6 weeks (titration phase), overall, and by visit, to compare the effects of the 4 different dose escalations (2 algorithms for each of the 2 investigational doses) and effects of the 2 titration algorithms on GI tolerability, as well as the overall effects of randomized treatments.

The prevalence of GIs, as well as the incidence of the first occurrence of nausea and/or vomiting will be summarized separately by the treatment and the time interval of interest mentioned in the first paragraph.

The maximum severity and duration from baseline to Week 18 of nausea and/or vomiting TEAEs will be summarized by the aforementioned treatments.

The time course plot on the initiation of nausea regardless of severity (prevalence) will be generated for each treatment. The y-axis is the % subjects with nausea and the x-axis is the time since the first dose.

If data warrant, a negative binomial model similar to the rate of hypoglycemia analysis may be implemented for each of the aforementioned parameters.

A listing with treatment-emergent GI AEs of interest will be provided.

6.13.6. Treatment of Overdose

A study drug overdose (more than the specified number of injections, whether for placebo or dulaglutide treatment) will be reported as an AE. This AE will be summarized only if it occurs with more than 3% of patients. Otherwise, only a data listing will be generated including the actual dose data (Section 6.13.1) along with treatment overdose AE reported date.

6.13.7. Cardiovascular Safety

6.13.7.1. Cardiovascular Events

Listings and summaries of adjudicated and investigator-reported CV events will be provided. The summary report for adjudicated and investigator-reported CV events will only be generated if more than 3% patients have the events. The test statistics are detailed in Section 6.1.

6.13.7.2. Electrocardiograms

Heart rate (HR), PR interval (PR), and QT corrected for heart rate using QTcF are collected in triplicates. Prior to any analysis, the arithmetic mean from the three measures for the same parameter at the same visit will be calculated and use for all subsequent analysis. MMRM model detailed in Section 6.1. for continuous variable analysis will be used to analyze each parameter in change from baseline. The treatment in the model will be placebo, dulaglutide 1.5 mg, dulaglutide 3.0 mg/algorithm 1, dulaglutide 3.0 mg/algorithm 2, dulaglutide 4.5 mg/algorithm 1, dulaglutide 4.5 mg/algorithm 2.

The reports for these analyses will include:

- LS means and corresponding 95% CIs for each randomized treatment at each scheduled visit, and the difference in LS means, corresponding 95% CI along with p-value compared to placebo and to dulaglutide 1.5 mg at the same visit.
- LS means and corresponding 95% CIs of each parameter's effect for algorithm 1, algorithm 2, and the difference between algorithm 2 and algorithm 1 (using algorithm 1 as reference) at Week 6 (Visit 6). These results will not be acquired directly from the MMRM model. Rather, they will be obtained from the same model by forming appropriate estimate statements with the same algorithm across dulaglutide 3.0 mg and dulaglutide 4.5 mg.
- LS means and corresponding 95% CIs of each parameter's effect for dulaglutide 3.0, dulaglutide 4.5, and the difference between each combined treatment across algorithms and Placebo, and the difference between each combined treatment to Dula 1.5 at the same Week (Visit): Week 8 (Visit 8), Week 10 (Visit 10) and Week 18 (Visit 12). These results will be obtained through the same model by forming appropriate estimate statements for the same dose across different algorithms.
- The difference in LS means and the corresponding 95% CIs along with the p-value between each maintenance visit (Week 8/Visit 8, Week 10/Visit 10, Week 18/Visit 12) and the end of titration (Week 6/Visit 6) within the same treatment including the combined dulaglutide 3.0 mg and 4.5 mg, and within the same algorithm will be presented. Any result related to combined treatment across algorithms and each algorithm at Visit 6 (Week 6) will be formed by constructing an appropriate estimate statement.

The threshold analysis will only include HR, PR by visit and by randomized treatment, dulaglutide 3.0, and dulaglutide 4.5 mg. The threshold is defined in [Table GBGJ.3](#).

Table GBGJ.3. Heart Rate, PR-Interval, and QTcF Abnormal Data

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

Abbreviations: QTcF = Fridericia's corrected QT interval.

Note: CFB means change from baseline; and %CFB is the percentage change from baseline.

The qualitative summary related to the treatment-emergent cardiac conduction and rhythm abnormalities will be reported by treatment. The abnormal ECG outcomes will be listed by treatment and patient.

A non-ITP Bayesian model will be fitted detailed in Section 6.11.2.3 with the priors: $\alpha, \beta[i, t] \sim N(0, 100)$ using 10000 MCMC samples with thin=10 and burn-in=10000. The probability of the posterior distribution of the parameter of interest on heart rate increase from baseline of each investigational dulaglutide dose compared to Dula 1.5 mg at Week 18.

$$\text{pr}(\Delta_i - \Delta_{\text{dula1.5mg}} < \text{threshold})$$

i stands for dulaglutide 3.0 mg/algorithm 1, dulaglutide 3.0 mg/algorithm 2, dulaglutide 4.5 mg/algorithm 1, and dulaglutide 4.5 mg/algorithm 2.

The threshold for this analysis will be 3bpm, 5 bpm, 7 bpm, 10 bpm.

The probability for Week 26 will be assumed to be the same as Week 18 from this model. The algorithm comparison at Week 6 will be evaluated.

6.13.7.3. Vital Signs

Vital signs will be listed for all randomized patients. Prior to any analysis, the arithmetic mean from the triplicates for the same parameter at the same visit will be calculated and used for all subsequent analysis. The change from baseline in pulse rate, systolic blood pressure, diastolic blood pressure (SBP, DBP) will be analyzed using a similar MMRM-based model as that described in Section 6.13.7.2. The result will be reported in the same manner as that for heart rate listed in Section 6.13.7.2. The threshold analyses will be summarized with the threshold definition is listed in Table GBGJ.4.

Table GBGJ.4. Abnormality Data for Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure

Parameter (unit)	Visit	Threshold definition
Pulse rate (bpm)	Baseline (Visit 1)	>100, ≥130
	Post baseline	>100 and CFB > 15
SBP (mmHg)	Baseline (Visit 1)	≥160, ≤90
	Post baseline	≥160 and CFB ≥20
		≤90 and CFB ≤-20
DBP (mmHg)	Baseline (Visit 1)	≥100, ≤50
	Post baseline	≥100 and CFB ≥10
		≤50 and CFB ≤-10

Abbreviations: bpm = beats per minute; CFB = change from baseline; DBP = diastolic blood pressure; SBP = systolic blood pressure

A non-ITP Bayesian model will be fitted detailed in Section 6.11.2.3 with the priors: $\alpha, \beta[i, t] \sim N(0, 100)$ using 10000 MCMC samples with thin=10 and burn-in=10000. The probability of the posterior distribution of the parameter of interest on heart rate increase from baseline of each investigational dulaglutide dose compared to dulaglutide 1.5 mg at Week 18.

$$\text{pr}(\Delta_i - \Delta_{\text{dula}1.5\text{mg}} < \text{threshold})$$

i stands for dulaglutide 3.0 mg/algorithm 1, dulaglutide 3.0 mg/algorithm 2, dulaglutide 4.5 mg/algorithm 1, and dulaglutide 4.5 mg/algorithm 2.

The threshold for this analysis will be 3 bpm, 5 bpm, 7 bpm, 10 bpm.

The probability at Week 26 will be assumed to be the same as Week 18 from this model. The algorithm comparison at Week 6 will be evaluated.

6.13.8. Renal Safety

To assess renal safety, a summary and analyses using LOCF will be provided for renal functional laboratory measures: estimated glomerular filtration rate (eGFR), Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI), creatinine, urine albumin/creatinine ratio (ACR), by treatment. The ANOVA model will be fitted with treatment as a fixed effect on the ranked LOCF change from baseline data.

An ANCOVA model will be fitted with treatment as a fixed effect. The change from baseline in rank for each parameter will be the response variable.

The minimum eGFR value and the maximum creatinine, urine ACR will be used for baseline and post baseline calculation to generate the shift table. Within treatment comparison will be tested using generalized McNemar's test. The shift table will use eGFR cutoff (<30, 30-<60, 60-<90, and ≥90 mL/min/1.73m²), creatinine (≤1ULN, >1 and ≤2 ULN, >2 and ≤4ULN, and >4ULN), and UACR (<30, (≥30 and ≤300), and >300 mg/g). The overall randomized treatment comparison will be tested using a likelihood-ratio Chi-square test. The shift table for minimum eGFR for both baseline and post-first dose at Week 18 will be classified using the

To examine AE indicating decrease in renal function, the SMQ for acute renal failure and a LSC for chronic renal failure events will be used to search the clinical trial data base for events of interest. A listing will be provided with all detected TEAE from these categories.

6.13.9. Immunogenicity

Summaries dulaglutide anti-drug-antibodies (ADA) will be generated separately for treatment-emergent ADA, for detected ADA by each dulaglutide treatment if more than 3% patients developed an ADA.

The patient treatment-emergent ADA data will be listed.

6.13.10. Clinical Laboratory Evaluation

Amylase, lipase, calcitonin, eGFR, creatinine, urine ACR are included in Section 6.13.4.3, Section 6.13.4.4, and Section 6.13.8. For other laboratory safety measurements summaries will be provided in this Section. For continuous (numeric) laboratory analytes, the rank on the change from baseline to endpoint (Week 18) will be analyzed as detailed in Section 6.1. For qualitative laboratory analytes, the number and percentages of patients with normal and abnormal values will be analyzed using Chi-square tests or Fisher's exact test.

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 post baseline value to Week 18 for selected analytes using clinically meaningful thresholds will be summarized separately using generalized McNemar's test for within-treatment comparison and using likelihood ratio test for between-treatment (randomized) comparisons. A shift table for ALT, AST, ALP, GGT, total bilirubin, and direct bilirubin will be generated using cutoff $\leq 1\text{ULN}$, ($> 1\text{ULN}$ and $<3\text{ULN}$), ($\geq 3\text{ULN}$ and $<5\text{ULN}$), ($\geq 5\text{ULN}$ and $<8\text{ULN}$), $\geq 8\text{ULN}$.

Laboratory measurements will be listed by patient. Additional listings will be presented for laboratory measurements that are outside the normal range and for measurements outside certain prespecified clinically relevant thresholds if deemed appropriate. A listing of patients with either AST or ALT $\geq 3\text{xULN}$, and total bilirubin $\geq 2\text{X ULN}$ will also be provided.

6.14. Subgroup Analyses

Subgroup analyses of the treatment interaction for important factors, including age group, race, gender, country, duration of diabetes ($<$ median, \geq median), baseline HbA1c ($<8\%$, $\geq 8\%$), and BMI ($<$ median, \geq median), may be conducted for the primary endpoint of HbA1c. Country will use the pooled country.

These 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 analysis of covariance (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.

TEAE exceeding 5% will be summarized descriptively for the patients with the top quartile of the body weight reduction from baseline by treatment group.

Other exploratory subgroup analyses may be performed as deemed appropriate.

6.15. Important Protocol Deviations

Important protocol deviations will be listed for all randomized patients and summarized by treatment group. All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient managements or patient assessment will be described. The important rotocol deviations will be prospectively defined in the study-specific monitoring requirements. Some of the protocol deviations that may not be prospectively identified may later be considered important by the Lilly study team, in which case will be also reported. The important protocol deviations will be captured from the clinical trial database as well as an excel file managed by the study clinical trial manager (CTM). The excel file generated by the CTM will be converted in a domain of the study data tabulation model (SDTM) as a source in addition to other necessary SDTM domains to define the PP population. 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 measures. The decision and rationale for not reporting certain protocol deviations as important ones will be documented in the eTMF. The following protocol conditions will result in exclusion from the PP population:

- informed consent was never obtained
- patients were randomized but the informed consent date is missing.
- age <18 years old at randomization
- patients have known type 1 diabetes
- patients who had any hematologic condition that may have interfered with HbA1c measurement (eg, hemolytic anemias, sickle-cell disease)
- excluded medicine use prior to safety follow-up
 - weight loss agents,
 - prohibited glucose-lowering agents (>14 days of use during the treatment period or any time during the screening/lead-in period of sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, SGLT2 inhibitors, meglitinides, other GLP receptor agonists or DPP4 inhibitors, etc.)
 - >14 days use of systemic glucocorticoid
- patients have an HbA1c <7% or >10% at Visit 1.
- patients have a missing HbA1c at baseline (both Visit 1 and Visit 3) or at 18 weeks (Visit 12).
- patients do not have an overall compliance with study drug of at least 75% up to 18 weeks.

A complete list and summary report of important protocol deviations will be generated.

6.16. Interim Analyses and Assessment Committee

At least three safety interim analyses and one efficacy/safety interim analysis will be conducted according to the specifications included in the protocol. The purpose of the safety analyses will be to monitor the safety and tolerability of the 2 investigational dulaglutide doses. The interim efficacy/safety analysis will be conducted for internal clinical development planning purposes to enable preliminary dose-selection for Phase 3 planning. The study will not be stopped based on the efficacy results at this interim analysis.

6.16.1. Assessment Committee

The interim analyses will be conducted under the auspices of an Assessment Committee (AC). The AC is authorized to review unblinded interim analyses. Before any interim analysis is performed, an AC will be established to control the dissemination of the findings. Lilly representatives having direct contact with the investigative sites will not be part of the AC unless they stop contact with the sites from the time of their inclusion into the study AC. Statistical Analysis Center (SAC) will be authorized to evaluate unblinded interim analyses and prepare the reports for the AC to review. 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 AC proceedings will be described in an AC charter. Any change to the proceedings will be included in the AC charter and will not require a protocol or SAP amendment. The AC Charter describes the precise plan of the unblinded safety monitoring and interim statistical analyses.

6.16.2. Interim Analyses

6.16.2.1. Timing of the Interim Analysis

The first safety only interim analysis will occur after approximately 15 patients have completed 8 weeks of treatment. The AC will continue to evaluate patient safety and tolerability when approximately 30 patients and 60 patients complete 8 weeks of treatment.

The efficacy/safety interim analysis will be conducted after approximately 120 patients have completed the 18-week treatment period.

6.16.2.2. Evaluation Criteria

For safety only interim analyses, the totality of the safety data on AEs, SAEs, TEAEs, and AESIs, disposition, discontinuation due to AEs, ECG, vital signs, ADA, GI AEs, cardiovascular events, and safety laboratory analytes will be evaluated. The analysis for each mentioned parameter will be analyzed in the same way as defined in this SAP.

For efficacy/safety analysis, the AC will base their decision on the following criteria in addition to the safety parameters listed in the preceding paragraph:

HbA1c Criterion:

At least 80% probability that at least one dose of dulaglutide 3.0 or dulaglutide 4.5 mg reduces HbA1c by at least 0.2% compared to dulaglutide 1.5 mg at Week 18, that is,

$\Pr(\Delta_{\text{dula}3.0 \text{ or dula}4.5} - \Delta_{\text{dula}1.5} < -0.2\%) \geq 80\%$]. The other thresholds of -0.15% and -0.3% will be also be evaluated. The probability will be at least 55% at the end of the study.

Other efficacy endpoint at week 18: change from baseline in body weight, will also be assessed relative to 1.5 mg as, $\Pr(\Delta_{\text{dula}3.0 \text{ or dula}4.5} - \Delta_{\text{dula}1.5} < \text{threshold of -1 and -2 kg}$.

Safety Parameters:

Heart rate from ECG, pulse rate from vital signs using change from baseline to be assessed relative to placebo as , $\Pr(\Delta_{\text{dula}3.0 \text{ or dula}4.5} - \Delta_{\text{placebo}} < \text{threshold of 3, 5, 7, 10 bpm}$.

MMRM analysis results will be reported for change from baseline in HbA1c, body weight, selected ECG, vital signs, and pancreatic enzymes , too.

PK/PD exposure-response results will be generated based on a separate PK/PD analysis plan by PK/PD group.

6.17. Planned Exploratory Analyses

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

The analysis of patients reaching HbA1c target $\leq 6.5\%$ will use the same model as that for HbA1c target $< 7.0\%$ described in Section 6.11.3.

Longitudinal continuous variables such as fasting glucagon will be analyzed using MMRM described in Section 6.1. If the normality assumption is violated, appropriate data transformation is needed prior to analysis.

Non-longitudinal continuous variables such as 6-point SMPG, c-peptide, fasting insulin, HOMA2-IR, and HOMA2-%B will be analyzed using LOCF by fitting a linear model with pooled country, treatment, 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 main meals within the same day. Each of the time point of the 6-point SMPG will be analyzed separated.

6.18. Annual Report Analyses

The following reports are needed for the Development Safety Update Report (DSUR): **(1)** Estimated cumulative subject exposure, **(2)** Cumulative exposure to investigational drug, by demographic characteristics for ongoing unblinded clinical trials and completed clinical trials, **(3)** Exposure information for ongoing clinical trials and clinical trials that completed during the reporting period, **(4)** Listing of subjects who died during the DSUR period, **(5)** Discontinuations from the study due to adverse event, **(6)** Discontinuations from the study treatment due to adverse event during the DSUR Period.

6.19. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both SAE and 'Other' AE are summarized: by treatment group, by MedDRA preferred term.

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

7. Unblinding Plan

The purpose of the unblinding plan is to detail the procedures that are in place to minimize bias while preparing for or conducting any summary or analysis of the data for AC reports, data reviews, dose selection (interim efficacy/safety only), and developing/refining exposure analyses. Additionally, this plan identifies personnel who will be unblinded during the study, including unblinding for the AC safety only analyses, and safety/efficacy interim analyses in support of the AC meetings.

The access to subject treatment assignments will not be provided to the following personnel until datalock is authorized for the planned final analysis at the completion of the blinded study:

- investigator and site personnel
- Lilly personnel with direct site contact
- Lilly personnel responsible for data entry and data validation
- Lilly study team not in the AC and/or SAC

After datalock, the study team will be unblinded to the study data to prepare for the analyses for CSR. Investigators can be provided treatment assignments for their subjects when unblinding has occurred and the information will not impact scientific integrity or introduce bias.

7.1. Operational Procedures

The randomization code (treatment assignment) will be stored in the Lilly interactive web response system (IWRS) and will not be accessible to the blinded Lilly study team, except for those pre-specified in the unblinding plan to be unblinded, until the final database lock (DBL). Members from the SAC, AC, and the study global patient safety (GPS) scientist may be unblinded to data prior to the DBL. The SAC, composed of Lilly unblinded statistics personnel, PK/PD scientists and the PK/PD analysts (for efficacy/safety interim analysis only) will form a separate team from the Lilly blinded team. The SAC will obtain the randomization code from the unblinded inVentiv data movement group in order to generate unblinded TFLs for the AC. Membership is listed in [Table GBGJ.5](#) for each of the groups mentioned above.

More specifically, the inVentiv data movement group will load CRF data, clinical laboratory results, ECG, and IWRS data into the designed blinded and unblinded locations. The blinded version of the data will then be provided to the blinded Lilly study team. The unblinded data will be provided to the SAC. The inVentiv data movement group is not blinded, but is not involved in study-level activities.

Table GBGJ.5. Study H9X-MC-GBGJ Group Name and Membership

Group Name	Group Members
Blinded Lilly Study Team	Lilly clinical study team personnel who work on the study and have direct site contact including the clinical research physician, clinical trial manager, data sciences and solutions, global patient safety personnel, and study monitors, etc., and non site direct contact regulatory scientist, statistician(s). However, per Lilly procedure, for patient safety, the study GPS scientist will be unblinded to SAE patient level data for patient safety.
Blinded Lilly statistics group	Lilly statisticians and statistical analyst(s)
Statistical Analysis Center (Unblinded)	Lilly statisticians and statistical analyst(s)
Unblinded PK/PD team scientists (part of the SAC)	Lilly study team pharmacokinetic/pharmacodynamics (PK/PD) scientists and analyst(s), etc.
Assessment Committee	Lilly Physicians, Statisticians, and GPS personnel external to the study team
inVentiv data movement group	inVentiv data movement representative
The program senior management	Lilly dulaglutide senior medical director or above

Abbreviations: GPS = global patient safety; PD = pharmacodynamics; PK = pharmacokinetics; SAE = significant adverse events.

Periodically throughout the trial until the DBL, blinded data will be transferred by inVentiv data movement per the data transfer plan to the blinded Lilly study team members including the blinded Lilly statistics group for the purpose of preparing Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) dataset, AC reports, trial level safety review reports, blinded AC reviews, TFL reviews, and CSR preparation. To minimize bias during statistical planning and data review, these transfers will be provided under the guidelines described in the following sections.

By setting up appropriate access privileges, the Lilly system will only allow unblinded personnel (unblinded statistician and/or programmers) to access data that contains unblinding information.

7.2. Site Level Unblinding

The procedure for site personnel to unblind an individual patient's treatment assignment for an emergency is described in the protocol Section 7.3. Emergency unblinding for adverse events may be performed by accessing the IWRS at the site level. When an IWRS Clinical Trial Study Management System (CT-SMS) is used to unblind a patient's treatment assignment, the computer application will maintain the date, reason for unblinding, and the identification of the person unblinding the treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

The site monitor is responsible for verifying compliance with the blinding procedures at the investigative site and verifying that access to the patients' treatment assignments remains restricted from the investigator and site personnel in direct contact with patients.

The investigator and site personnel are instructed to make every attempt to contact Lilly personnel when a patient's treatment assignment is unblinded at the site. The affiliate personnel document the unblinding records and inform the designated study team member, CTM, who documents the overall unblinding records for the entire study. The documentation is filed in the study files. A final Study Unblinding Summary will be prepared at the end of the study (at the study closeout).

7.3. Trial Level Safety Reviews

Periodic Trial Level Safety Review (TLSR) summaries and listings will be produced by the blinded Lilly statistics group and delivered to the blinded Lilly study teams per TLSR plan. These summaries will be blinded until after the DBL. They will contain neither randomization assignments nor post randomization primary endpoint HbA1c, dose information, or PK data with the potential to unblind. Blinding flags will be created in the central laboratory database, based upon the Alert and Blinding Criteria document maintained by the Clinical Laboratory Operations (CLO) group. These flags will blind specific report data to the site and investigators. Data transferred to and exported from the clinical laboratory results will not be blinded to the Lilly team or to the data management of third party organization performing the labs.

The complete list of TLSR variables include overall AEs, serious adverse events (SAEs), TEAEs AEs of special interest, laboratory data, vital signs, ECG, discontinuations, concomitant medications, and historical/pre-existing medical conditions.

7.4. Assessment Committee Reports

The blinded Lilly study team will remain blinded to randomization assignments and potentially unblinding results until after the DBL.

The SAC statistician is responsible for authorizing the access of Lilly personnel to unblinded data. Every attempt should be made to contact the statistician and document the authorization before access is given to unblinded data. A designated Interactive Web Response System (IWRS) representative, inVentiv data movement team or the replacement or their designee, will provide all data transfers to the Lilly statistics group based on the data transfer plan.

The study project statistician will be responsible for keeping a running log of individuals given access to any unblinded study data. This log will include the person's name, title, date of unblinding, level of unblinding (that is, group or patient), and purpose of unblinding. This record will be stored in a secure area and will be stored in eTFM via the study CTM after DBL.

Two types of interim analyses will be performed for this study:

7.4.1. Safety Only Reports

There are at least 3 unblinded safety only reviews. The following personnel will be unblinded to the safety data (efficacy measures will NOT be unblinded), in order to perform the safety data analysis, prepare the AC safety reports, and review/discuss the safety results:

- The AC (determined in AC Charter)
- Internal SAC (Lilly study personnel)
 - Computational Statisticians
- Others: No, but can be added upon AC Chair's request

7.4.2. Efficacy/Safety Interim Report

7.4.2.1. Model Development

For the interim analysis of efficacy, safety and pharmacokinetics, the following personnel will be unblinded to the pharmacokinetics related data about 4 to 6 weeks after approximately 80 subjects complete 18weeks of treatment in order to develop the PK/PD modeling and/or TFLs:

- Internal SAC (Lilly study personnel)
 - Computational Statisticians
- Internal Pharmacokinetic Analysis Group (Lilly study personnel, part of the SAC)
 - Pharmacokineticist and Pharmacokinetics Analysts

7.4.2.2. Reports Delivery

The following personnel will be unblinded to the efficacy, safety, and pharmacokinetics data after approximately 120 subjects complete 18-week treatment, in order to perform data analysis, prepare the interim reports, review the results, and discuss business related matters:

- AC (determined in AC Charter)
- Internal SAC (Lilly personnel) or its delegate
 - Computational Statisticians
- Internal Pharmacokinetic Analysis Group (Lilly personnel, part of SAC) or its delegate
 - Pharmacokineticist and Pharmacokinetics Analysts
- Others: No, but can be added per the request from AC Chair and/or the program senior management

If PK reports needs more time to be generated, this interim review can be proceeded without PK data. A subsequent PK results review can be formed later after the results are available.

In addition, in order to perform the critical business development and the regulatory interactions, some personnel need to be unblinded to the related summary (group) level data, and possibly limited patient-level data after the interim safety/efficacy analysis. This unblinding requires

approval from AC and signature for Confidentiality Responsibilities Agreement. The SAC statistician should be informed by AC Chair for documentation purpose.

7.5. Clinical Study Report

Prior to the final DBL, SDTM/ADaM datasets and draft TFLs will be produced by blinded team members and delivered to the blinded Lilly study team to review as appropriate.

7.5.1. Prelock Unblinding

Lilly PK/PD scientists along with the SAC statistician(s) who generate the data for PK/PD scientists will access randomization codes prior to the final DBL. Lilly PK/PD scientists will obtain unblinding information about 1 to 2 months before the DBL in order to perform PK/PD model-based analysis if deemed necessary.

7.5.2. End of Study Unblinding

After the final DBL, all transfers of SDTM/ADaM files and TFLs to Lilly will be unblinded and will contain unblinded results for all laboratory parameters, PK data, and CRF data.

Immunogenicity data will be obtained about 1 or 2 months after the final DBL in a separate transfer without overwriting the already locked database.

8. References

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- American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care.* 2005;28(5):1245–1249.

9. Appendices

Appendix 1. Analysis Windows for the Selected Parameters

In clinical trials, visits do not always occur as scheduled in the protocol, and a certain visit may actually occur closer to the protocol-specified time of a different scheduled visit. When there is interest in the effect of the drug over time, using the visit number for analysis may not provide the best representation of time. For that reason, analysis windows will be used to define ranges of days relative to the date of first dose in order to associate collected data with scheduled time points of interest. These analysis windows will be implemented in ADaM, and they will not be used to overwrite or change the actual visit number that was reported by the site. Furthermore, these analysis windows are separate from the allowable range of days in the protocol's schedule of events for visits; they are not intended to be provided to sites so that there is no confusion regarding the acceptable timing of patient visits.

There will be cases where a patient has more than 1 measurement in the same analysis window. If multiple measurements fall within the same window but were collected on different days, the measurement closest to the target time will be used. If multiple measurements within the same window are equidistant from the target, the earlier measurement will be used to be conservative with regard to the drug effect. If more than 1 measurement was collected on the same day for a patient, the last measurement on that day will be used for that patient because there may have been an error with the test itself that caused the investigator to repeat it on the same day.

Table APP1.1. Analysis Windows for the Selected Parameters

Visit	Screening and Lead-in		Treatment Period										Safety Follow-up
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V801
Week	-2	-1	0	2	4	6	7	8	9	10	14	18	22
Day	-14	-7	1	15	29	43	50	57	64	71	99	127	155
Vital signs, Height, Weight, BMI	(-∞,-4)	(-10, -4)	(-3,1)	(2,22)	(23, 36)	(37, A)	(A+1, 53)	(54, 60)	(61,67)	(68,85)	(86,113)	(114,B)	(B+1, C)
ECG	(-∞,1)					(2,A)		(A+1, 64)		(65, 99)		(100,B)	(B+1, C)
6-point SMPG, Lipids panel (fasting), c-peptide, fasting insulin			(-∞,1)									(2,B)	
Chemistry panel, urinary analysis, ACR, eGFR, Hematology	(-∞,1)											(2,B)	
HbA1c, fasting glucose	(-∞,-7)		(-6,1)			(2, A)				(A+1,99)		(100,B)	(B+1, C)
(p) amylase, lipase, Serum calcitonin	(-∞,-7)		(-6,1)			(2,A)						(A+1,B)	(B+1,C)
Fasting plasma glucagon			(-∞,1)			(2,A)						(A+1,B)	
Calcitonin	(-∞,-7)		(-6,1)									(2,B)	
Immunogenicity			(-∞,1)			(2, A)						(A+1,B)	(B+1, C)

Abbreviations: ACR = albumin/creatinine ratio; BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; SMPG = self-monitored plasma glucose; V = visit.

Windows represent the range of days, relative to the date of the first dose, associated with a particular time point.

Note: (day1, day2), are inclusive.

A, B, C: actual day on which each patient individually ends the titration phase, maintenance phase, or safety follow-up. If the actual day is missing, the planned day of 46, 141, and 158 will be used to represent the end of the titration phase, maintenance phase, or safety follow-up.

Day 1: The day of the first dosing date or the day of the randomization date if first dosing date is missing

* When creating windows for the baseline, use the last non-missing pre-first dosing value.

The above analysis windows will not be used for analysis of hypoglycemia or compliance over time.

Any other parameters not listed in this table will use the site or investigator reported visit measurement directly without applying the visit window.

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