I8F-MC-GPGF Statistical Analysis Plan Version 2

A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo in Patients with Type 2 Diabetes.

NCT03311724

Approval Date: 01-May-2018

1. Statistical Analysis Plan: I8F-MC-GPGF: A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo in Patients with Type 2 Diabetes

Confidential Information

LY3298176 Type 2 Diabetes Mellitus

This is a randomized, double blinded, parallel, placebo- and active comparator-controlled Phase 2 multicenter, multi-country study in patients with type 2 diabetes mellitus.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol I8F-MC-GPGF
Phase 2

Statistical Analysis Plan Version 1 was approved on 02-Jan-2018 GMT

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

Approval Date: 01-May-2018 GMT

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3. Revision History

The Statistical Analysis Plan (SAP) Version 1 is approved prior to first production data transfer.

The SAP Version 2 was approved prior to the primary database lock and contains the following changes:

- Changed the modified intent-to-treat (mITT) population to not require 1 postbaseline measurement so it is the same as the safety population
- Analysis datasets were altered to only include full analysis set (FAS) and efficacy analysis set (EAS)
- Removed the per-protocol (PP) population and all associated analyses
- Removed description of calculation of type 2 diabetes mellitus (T2DM) duration as it is in data standard
- Changed thresholds of glycated hemoglobin (HbA1c) targets for categorical analyses
- Corrected classification categories for calcitonin
- Removed all subgroup analyses unless needed post-hoc

4. Study Objectives

4.1. Primary Objectives

The primary objective of this study is to demonstrate that at least one LY3298176 titration scheme is superior to placebo in HbA1c reduction at 3 months in patients with T2DM inadequately controlled with diet and exercise alone, or treated with a stable dose of metformin.

4.2. Secondary Objectives

The secondary objectives are to compare each titration scheme to placebo at 3 months for the following secondary efficacy parameters:

- proportion of patients achieving HbA1c target of <7.0%
- the change in fasting blood glucose (FBG) (central laboratory) from baseline
- the change in body weight from baseline
- the change in waist circumference from baseline
- incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- incidence of nausea, vomiting, and diarrhea
- discontinuation of study drug due to adverse events (AEs)
- incidence and rate of hypoglycemia (severe, total, documented symptomatic, and nocturnal)
- incidence of anti-LY3298176 antibodies

4.3. Exploratory Objectives

- To compare each titration scheme to placebo at 3 months for effect on self-monitoring blood glucose (SMBG) profile.

5. Study Design

5.1. Study Design and Treatment

Study I8F-MC-GPGF (GPGF) is a randomized, double-blind, parallel, placebo-controlled, Phase 2, multicenter, study designed to examine the efficacy and safety of once-weekly LY3298176, compared with placebo in patients with T2DM.

The design for Study GPGF is illustrated in Figure 5.1.

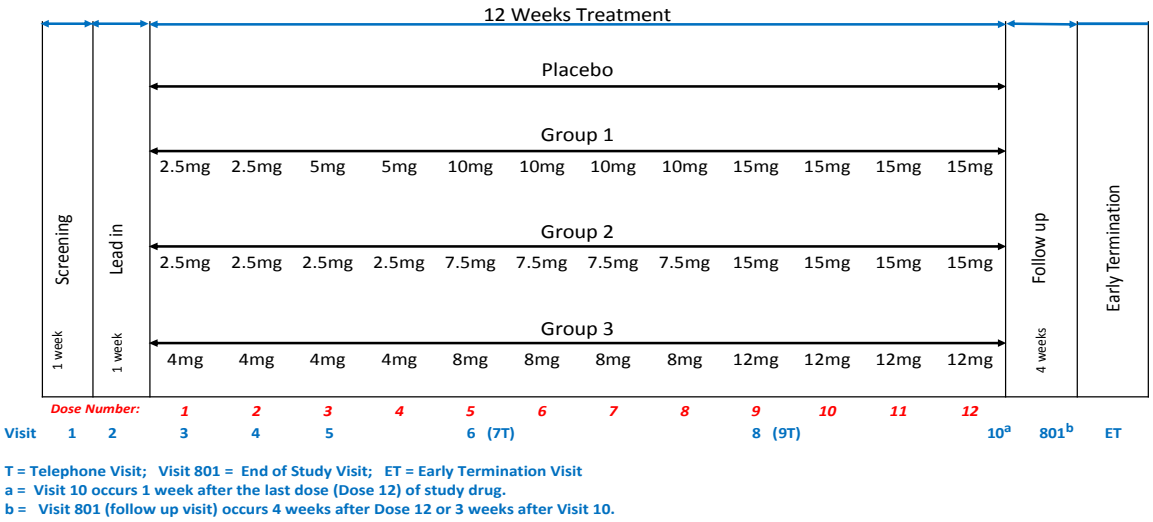

Figure 5.1. Study design for I8F-MC-GPGF.

Study procedures and timing for the lead-in, blinded treatment, and follow-up phases are outlined in the schedule of events (Appendix 1). Eligibility for this study will be determined at the screening visit (Visit 1).

5.2. Treatment Assignment

A unique 4-digit patient number will be assigned to each patient when the patient signs the informed consent form (ICF).

Patients will be assigned to placebo, or one of three LY3298176 dose groups. Patients who meet all criteria for enrollment will be randomized at Visit 3 and assigned to their respective treatment arms via interactive web response system (IWRS) using the following stratification variables: baseline HbA1c (<8.5%, ≥8.5%), metformin use (Yes, No), and body mass index (BMI) (<30, ≥30). There will be equal randomization to the treatment arms (1:1:1:1). However, placebo patients will be randomized such that a portion will be randomized to each cohort to receive the same dose volume as that cohort in order to maintain the study blind.

The randomization scheme will be performed using IWRS to ensure balance between treatment arms.

5.3. Determination of Sample Size

Approximately 92 patients will be randomized to placebo or to one of three LY3298176 titrations arms, assuming a 13% dropout rate, resulting in approximately 20 completers per arm.

Assuming a standard deviation of 1.1, 20 patients per arm will provide at least 90% power to detect a statistically significant difference between LY3298176 titration schemes to placebo with a dose response assumption as shown in Table 5.1.

Table 5.1. Dose-Response Assumption Used in Sample Size Determination

	Placebo	LY 12 mg	LY 15 mg-1	LY 15 mg-2
CFBL HbA1c (%)	-0.2%	−1.4%	−1.5%	−1.5%

Abbreviations: CFBL = change from baseline; HbA1c = glycated hemoglobin; LY = LY3298176.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the statistical methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the statistical analyses and the justification for the change will be described in the SAP and/or clinical study report (CSR). Additional exploratory analyses of data may be conducted, as deemed appropriate, without further changes made to the protocol or SAP even after the database lock (DBL).

No adjustments for multiplicity will be performed.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and/or 2-sided 95% confidence interval (CI) unless otherwise stated. This is different from what is stated in the protocol.

The baseline visit will be Visit 3. For all variables, if baseline data are not available or are missing, the last nonmissing measurement taken prior to Visit 3 will be used for the baseline measurement.

All efficacy and safety data will be summarized by each treatment group at each scheduled visit unless otherwise indicated. Imputed data may be applied in model-based data analysis, but will not be used in data listing.

6.1.1. Analysis of Repeated Measures

The mixed model for repeated measures (MMRM) using restricted maximum likelihood (REML) will be used to fit change from baseline values at all scheduled visits. The model will include the treatment group, strata (that is, baseline HbA1c category, baseline BMI category, and metformin use [yes, no]), visit, and treatment-by-visit interaction as fixed effects, baseline value of the dependent variable as a covariate, and patient as a random effect. If the analysis is on the primary endpoint, baseline HbA1c category will not be included in the model in addition to the continuous covariate of baseline HbA1c. To model the covariance structure within patients, the unstructured covariance matrix will be selected initially. If the unstructured covariance structure leads to nonconvergence, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- autoregressive with heterogeneity
- compound symmetry with heterogeneous variances
- Toeplitz
- autoregressive
- compound symmetry without heterogeneous variances
- compound symmetry

The first covariance structure that converges will be used.

Kenward-Roger method will be used to estimate the denominator degrees of freedom and the restricted maximum likelihood approach will be used to determine the model estimates.

The MMRM model will present least squares (LS) mean estimates for each scheduled week by treatment group and 2-sided 95% CIs for mean changes from baseline within and (when warranted) between treatments. T-statistics corresponding to the Type III sums of squares for the differences in the LS means will be used to obtain p-values for treatment group comparisons.

6.1.2. Analysis of Covariance Model for Change from Baseline Endpoints

The analysis of covariance (ANCOVA) models of change from baseline to Week 12 efficacy endpoints will include treatment group, strata (that is, baseline HbA1c category, baseline BMI category, and metformin use [yes, no]) as fixed effects and baseline measurement as a covariate. If the analysis is for the primary endpoint, baseline HbA1c category will not be included in the model in addition to the continuous covariate of baseline HbA1c.

The ANCOVA will present LS mean estimates and 2-sided 95% CIs for mean changes from baseline within and (when warranted) between treatments. T-statistics corresponding to the Type III sums of squares for the differences in the LS means will be used to obtain p-values for treatment group comparisons.

6.2. Patient Disposition

All patients who discontinue the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment. The percentage of patients discontinuing from each treatment will be compared using the Fisher's exact test.

Patient statuses at the end of the 12-week treatment period will be summarized, displaying the numbers of patients:

- entered
- screen failed, along with the primary reason for screen failure
- randomized
- randomized and not treated
- permanently discontinued from treatment, along with the primary reason for treatment discontinuation
- discontinued from study, along with the primary reason for study discontinuation
- completed 12 weeks blinded treatment
- completed study

The summary of status at the end of the 12-week treatment period will count patients by randomized treatment group and overall, except that "Entered" and "Screen failures" only apply to the overall entered population. Entered is defined as signing an informed consent form (ICF). The percentage of patients discontinuing from each treatment will be compared using the Fisher's exact test.

6.3. Analysis Populations and Datasets

Three patient populations are defined for the analyses in this study with detailed information listed in Table 6.1. Analyses datasets specifying data exclusion are listed in Table 6.2.

Unless otherwise specified, listings will include FAS for all randomized patients; safety analyses, except for hypoglycemia events, will be conducted in the mITT population with the FAS; and efficacy analyses including primary and key secondary efficacy analyses will be conducted in the mITT population with the EAS.

Table 6.1. Analysis Populations

Population	Definition
All Entered	All patients who signed informed consent forms (ICFs)
All randomized (Intent-to-Treat [ITT])	All patients who were randomized to a treatment arm
Safety Population (Modified Intent-to-Treat [mITT])	All randomized patients who have taken at least 1 dose of the study medication. This is different from what is stated in the protocol. Analyses using the mITT population will be presented by the planned treatment group.

Table 6.2. Analyses Datasets

Analysis Dataset Name	Description
Full Analysis Set	All data available
Efficacy Analysis Set	Only include data on study medication without using rescue medication, i.e., excluding data after rescue medication initiation or after study treatment discontinuation (last dose date +7).

6.4. Patient Characteristics and Medical History

Demographic and baseline characteristics will be summarized by treatment group and overall using the mITT population and the FAS. Categorical variables will be summarized by frequencies and percentages. For categorical variables, comparisons between treatment groups will be assessed using a Pearson Chi-Square test. Continuous variables will be summarized by means and standard deviations (SDs). For continuous variables, comparisons between the treatment groups will be performed using a 1-way analysis of variance with treatment as the fixed effect.

Demographic and baseline diabetes characteristics will be presented in listings for each patient.

All summaries of continuous characteristics will be based on nonmissing observations. For categorical characteristics, percentages will be calculated out of the total number of patients in the data set, overall and by treatment group (that is, each denominator includes the number of patients with missing/unknown values for the characteristic).

The numbers and percent of patients with general medical history findings will be provided using the randomized (that is, ITT) population using the FAS. A listing will be provided by patient.

6.5. Treatment Compliance

Treatment compliance will be listed using all randomized patients and summarized using the mITT population using the FAS for the listings and summaries. For a given patient, overall compliance for treatment period is defined as not missing 2 or more doses of the assigned treatment in the study. Patients who miss 2 or more doses at any point during the study will be considered significantly noncompliant.

The number and percent of patients compliant during the 12-week treatment period will be summarized at Week 12 using the safety population by the actual treatment group.

6.6. Exposure of Study Treatment

Exposure to each therapy during the treatment period of the study will be calculated for each patient and summarized by treatment group.

The extent of exposure to study medication (LY3298176, placebo) during the 12-week treatment period is defined as: date of last dose of study medication +7 days - date of first dose of study medication.

The extent of exposure to study medication will be summarized at 12 weeks using the safety population and categorized by the actual treatment group. The number and percent of patients with an extent of exposure within pre-specified day ranges will be presented for the 12-week treatment period by treatment group.

The mean, SD, median, minimum, and maximum days of exposure will also be presented.

In addition, the exposure in terms of total patient-years will be calculated by treatment group using the sum of the exposure to study medication of all patients (in years) in a treatment group.

A patient listing of study medication taken will also be generated.

6.7. Concomitant Drugs

Listings and summary of concomitant therapies will be provided by treatment group.

Previous and concomitant medications will be summarized using the randomized (that is, ITT) population by drug class with generic drug name and planned treatment group, as defined by the World Health Organization (WHO) drug dictionary most current at the time of DBL. A summary will be produced for all concomitant medications during the:

- 12-week treatment period

- treatment period + follow-up period

All previous and concomitant medication use will be listed on a single listing.

Previous medication is defined as medication with a recorded stop date before the date of the first dose of study treatment.

Concomitant medication during the 12-week treatment period is defined as medication with either a recorded medication start date falling:

- within the 12-week treatment period, or
- prior to the first day of study medication but continuing or stopping after at least 1 day on study medication

This means that concomitant medications for the 12-week treatment period will be any medication taken for at least 1 day during the 12-week treatment period.

Similarly, concomitant medications for the follow-up period will be any medication taken for at least 1 day during the follow-up period.

Anti-hyperglycemic medication taken for any reason as well as taken as rescue for severe, persistent hyperglycemia will be summarized for mITT and will also be listed. Metformin dose at baseline will be summarized, as will proportion of patients who adjusted their metformin dose during the trial.

6.8. Protocol Deviations

Important protocol deviations will be listed for all randomized patients and summarized by treatment group. A list of important protocol deviation criteria for patients from the trial issues management plan is given in Appendix 2. Patients meeting criteria for important protocol deviations will be identified either by statistical programming or based off study monitoring that is maintained by the study clinical trial manager (CTM). The final list of important protocol deviations will be reviewed and documented in the Important Protocol Deviations document by the study team prior to the primary outcome DBL.

6.9. Efficacy Analyses

All statistical models will include all treatment groups, including LY3298176 and placebo.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and/or 2-sided 95% CI. No adjustments for multiplicity will be performed.

6.9.1. Primary Outcome and Methodology

The primary outcome is the difference in HbA1c change from baseline between treatment groups at the end of the treatment period of 12 weeks. The primary analysis model will be a MMRM for HbA1c change from baseline to 12 weeks described in Section 6.1.1. The treatment p-value will be used as evidence of difference between active drug and placebo, whereas the comparison of LS means versus placebo (unadjusted for multiple comparisons) will provide magnitude and significance of this difference.

6.9.1.1. Supporting Analyses of Primary Outcome

An MMRM analysis on the FAS will be performed for the primary parameter.

An ANCOVA model will be used on the last observation carried forward (LOCF) endpoint of HbA1c with fixed effects of metformin use, baseline BMI category, treatment, and baseline HbA1c as a covariate. Within the framework of this ANCOVA model, point estimates and 95% CIs for the mean change from baseline within each treatment group as well as for the difference in mean change from baseline between each investigative treatment group and placebo will be calculated. This analysis will be performed on FAS in addition to the EAS.

Table 6.3 describes the analyses to meet the primary objective, all performed on the HbA1c change from baseline values, including the above sensitivity analyses. The descriptive statistics will also be performed on the HbA1c measurements at each visit.

Table 6.3. Summary of Analyses for Primary Endpoint

Analysis Type	LOCF or Observed Values	Analysis Dataset[a]
MMRM [b]	Observed	EAS
MMRM	Observed	FAS
ANCOVA	LOCF	EAS
ANCOVA	LOCF	FAS

Abbreviations: ANCOVA = analysis of covariance; EAS = efficacy analysis set; FAS = full analysis set; LOCF = last observation carried forward; MMRM = mixed model repeated measures.

[a] Refer to Table 6.2.

[b] Primary analysis.

6.9.2. Efficacy - Secondary Outcomes

The following secondary efficacy endpoints are going to be analyzed:

- body weight change from baseline to 12 weeks
- percentage of patient with ≥5% body weight loss at 12 weeks
- percentage of patients reaching the HbA1c target of ≤7.0%
- change from baseline of FBG at 12 weeks
- change from baseline of waist circumference at 12 weeks

6.9.2.1. Continuous Variable Analyses

For each continuous endpoint (body weight, FBG, and waist circumference), the observed absolute values and changes from baseline will be summarized using descriptive statistics by scheduled visit. The change from baseline in body weight at 12 weeks, change from baseline in FPG at 12 weeks, and change from baseline in waist circumference at 12 weeks will all be analyzed using a MMRM-based model described in Section 6.1.1.

Body mass index (kg/m^2) will be calculated at each visit at which weight is measured, using height as measured during screening. Change from baseline in BMI will be listed and summarized.

6.9.2.2. Analyses on Variables with Percent of Patients Reaching a Target

The proportion of patients who have ≥5% body weight loss at 12 weeks will be analyzed using a logistic regression model with treatment, strata (baseline HbA1c category, and baseline BMI category) and metformin use (yes, no), as fixed effects, and baseline body weight as a covariate. Descriptive statistics will also be presented, including sample size, frequency, and percent.

Additional logistic regression analyses will be performed at 12 weeks for the proportion of patients who have achieved an HbA1c level of <7% and HbA1C level of ≤6.5%. Treatment, baseline BMI category, and metformin use (yes, no) will be fixed effects and continuous baseline HbA1c level will be a covariate. Descriptive statistics will also be presented, including sample size, frequency, and percent.

The proportion of patients who initiated rescue therapy will be summarize by descriptive statistics including sample size, frequency, and percent.

6.9.2.3. Exploratory Analyses

For HbA1C and body weight, a longitudinal dose-response model with titration may be performed. Other exploratory analyses taking account of patients with titration not as planned may also be performed.

6.10. Safety Analyses

Safety analyses will be classified by the actual titration treatment group. Safety descriptive statistic summaries may also include all LY3298176 doses combined, if appropriate. Unless specified otherwise, safety listings will display values/events during all study periods; AEs summaries will be presented for all postbaseline data. For some key summary tables, data will be presented both for the treatment period only and for the treatment period and follow-up period combined, if applicable.

For each patient, treatment period is defined as the date of first treatment dose to last treatment dose date +7 day.

Safety measures will include extent of exposure, vital signs, physical characteristics, TEAEs (including SAEs), adverse events of special interest (AESIs; that is, injection site reactions, hypersensitivity reactions, hypoglycemia episodes, gastrointestinal [GI] events [nausea, vomiting, and diarrhea], acute pancreatitis, and major adverse cardiovascular [CV] events), laboratory measures (including hematology, chemistry, urinalysis, and samples collected for testing for anti-LY3298176 and antibodies), and electrocardiograms (ECGs).

The summary statistics for continuous variables will be sample size, mean, SD, median, minimum, and maximum. If applicable (for example, in the case of MMRM analyses) these descriptive statistics may also include LS means, LS means standard error (SE), and 95% CI for each treatment group, as well as for LY3298176 difference from placebo.

The summary statistics for categorical variables will be sample size, frequency, and percentage.

Additional analyses, such as concentration-safety laboratory plots, may be performed, if warranted, upon review of the data.

6.10.1. Vital Signs

Vital sign measurements (that is, systolic blood pressure [SBP] and diastolic blood pressure [DBP] in mmHg and pulse rate [PR] in beats/minute]) will be collected according to the Study Schedule of Events (Appendix 1). The average 3 measurements for BP and PR will be calculated and analyzed; however, values obtained from fewer than 3 measurements will also be included in summaries and analyses.

Descriptive statistics will be provided by treatment arm for change from baseline at each visit for SBP, DBP, PR. Figures will display LS mean values for change from baseline at each visit for the LY3298176 groups versus placebo.

The above measures will be analyzed using the MMRM-based model described in Section 6.1.1. The dependent variable will be the postbaseline change from baseline value for the applicable measure.

The frequency and percentage of patients showing vital sign results in each of the categories specified in Table 6.4 will also be summarized by treatment and visit.

Table 6.4. Vital Sign Summary Categories

Vital Sign Measure	Unit	Low	High
Systolic Blood Pressure	mmHg	≤90 and decrease ≥20	≥160 and increase ≥20
Diastolic Blood Pressure	mmHg	≤50 and decrease ≥10	≥100 and increase ≥10
Pulse Rate	bpm	<50 and decrease ≥15	>100 and increase ≥15

Abbreviations: bpm = beats per minute.

All vital signs and physical characteristics measurements will be listed.

For pulse rate, a longitudinal dose-response model with titration may be performed, if deemed necessary.

6.10.2. High-Density Lipoprotein Cholesterol, Total Cholesterol, Triglycerides, and Low-Density Lipoprotein Cholesterol

Change from baseline in high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) will be analyzed using the ANCOVA model similar to the model used for the supportive analysis on the primary endpoint. The model will include strata (baseline HbA1c category, baseline BMI category, metformin use [yes, no]), treatment, as fixed effects, the applicable baseline measurement as a covariate. The dependent variable will be the postbaseline change from baseline value for the applicable measure.

Descriptive summaries will also be presented.

6.10.3. Adverse Events

No statistical tests will be performed to compare AE rates between treatment groups.

Treatment-emergent AEs, defined as events that are newly reported after randomization or reported to worsen in severity from baseline, will be determined based on occurrence, on or after the date of first dose of investigational product.

Adverse events will be summarized as TEAEs. Summaries of TEAEs will be presented for the combined treatment and follow-up periods. A few selected tables may be presented for both the treatment period only, and the combined treatment and follow-up period.

Adverse event summary tables will include a "Total LY3298176" column for all LY3298176 treatment groups combined, if appropriate.

In summaries by System Organ Class (SOC) or Preferred Term (PT), SOC will be displayed in alphabetical order and PT will be displayed by decreasing frequency of the "Total LY3298176" patient incidence within each SOC. In summaries by PT, PT will be displayed by decreasing frequency of the "Total LY3298176" patient incidence. Ordering by frequency should be based on percentages and not on frequency counts.

All AEs (not only TEAEs) will be presented in listings by patient, actual term, PT, severity, and relationship to treatment (yes, no). Listings will also include treatment group, start date, and stop date (or ongoing), assessment of seriousness, relationship to nonstudy drug treatment (study disease, study procedure, none), relationship to study device (yes, no), action taken with study medication, and outcome of AE.

Listings will report data as recorded (for example, unknown severity or relationship and partial or unknown dates). Where necessary, such as for determination of TEAEs, partial or unknown dates will be imputed.

6.10.3.1. All Treatment-Emergent Adverse Events

The incidence of patients with at least 1 TEAE and the patient incidence of TEAEs will be summarized, showing frequency and percentage of patients, by SOC, PT, and treatment group. The total number of TEAEs and the number of TEAEs for each SOC and PT will also be reported for each treatment group.

The patient incidence of TEAEs will also be summarized by SOC, PT, maximum severity, and treatment group.

6.10.3.2. Related Adverse Events

The incidence of patients with at least 1 TEAE assessed as related (including possibly related or unknown) and the patient incidence of related TEAEs will be summarized by SOC, PT, and treatment group. In addition, the total number of related TEAEs and the number of related TEAEs for each SOC and PT will be reported for each treatment group.

6.10.3.3. Serious Adverse Events

A listing of all SAEs by patient will be produced. If a sufficient number of SAEs are reported (that is, >1 SAE overall per treatment group or >3 SAEs in any 1 treatment group) summary tables will be produced showing the incidence of patients with at least 1 SAE and the patient incidence of SAEs by SOC, PT, and treatment group. In addition, if a sufficient number of SAEs

are reported, the total number of SAEs and the number of SAEs for each SOC and PT will be reported for each treatment group.

6.10.3.4. Adverse Events Leading to Discontinuation

Treatment-emergent AEs reported with an action taken of "drug withdrawn" will be summarized, using patient incidence, by SOC, PT, and treatment group. In addition, a listing of AEs leading to discontinuation of study treatment (that is, with action taken as "drug withdrawn") will be presented.

Treatment-emergent AEs reported as reason for study discontinuation (that is, discontinuation of study procedures as well as study treatment) will be summarized, using patient incidence, by SOC, PT, and treatment group. In addition, a listing of AEs leading to discontinuation of study will be presented.

6.10.3.5. Most Common Adverse Events

The most common TEAEs, determined as TEAEs occurring in ≥5% in any LY3298176 arm, will be summarized by SOC, PT, and treatment group. This summary will also include the number of such events by SOC, PT, and treatment group.

6.10.3.6. Deaths

All deaths recorded on the status page, the AE page, or the SAE page (with a death date, cause of death, outcome, or SAE categorization present) of the case report forms (CRFs) will be considered a death for summary purposes. All deaths (CV or non-CV) that occur during the treatment period or follow-up period will be adjudicated by an independent central adjudication committee in compliance with a study-specific adjudication charter. Results of the adjudication will be entered in the death adjudication electronic case report page (eCRF) page.

A listing of adjudicated results will include the adjudicator assessment of death type, whether or not the adjudicator's assessment of the event date agrees with the investigator's assessment of the event date, and the date of the event, showing the adjudicator's assessment in the case of non-agreement. If adjudicated results show >1 death per treatment group or >3 deaths within any 1 treatment group, a summary table will present patient incidence of deaths by SOC, PT, and treatment group.

6.10.4. Adverse Events of Special Interest

Adverse events of special interest to be identified and described during this study are injection site reactions, hypersensitivity reactions, hypoglycemia, acute pancreatitis, major adverse CV events, and selected GI events (nausea, vomiting, and diarrhea).

Descriptive statistics for AESIs will be presented by treatment group and visit. Continuous responses will be summarized using sample size, mean, SD, median, minimum and maximum, while categorical responses will be summarized using sample size, frequency, and percentage.

In addition, for AESIs with information collected on the AE eCRF page (that is, hypersensitivity reactions, acute pancreatitis, and major adverse CV events) summary tables will be presented only if >3% of patients have the AESI. The incidence of patients with at least 1 AESI and the

patient incidence of AESIs will be summarized, showing frequency and percentage of patients, by SOC (if applicable), PT, and treatment group. The total number of AESIs and the number of AESIs for each SOC (if applicable) and PT will also be reported for each treatment group.

Listings by patient will be provided for AESIs. Listings will also present adjudication information by patient for adjudicated events.

6.10.4.1. Hypersensitivity Reactions

A listing of potential hypersensitivity reactions will be provided. For the purpose of this listing, any event satisfying any one of the Anaphylaxis reaction standard Medical Dictionary for Regulatory Activity (MedDRA) queries (SMQs), Hypersensitivity SMQs, or Angioedema SMQs will be included. Summary tables will be presented only if the number or nature of the events warrants such a comparison.

6.10.4.2. Injection Site Reactions

Injection site reactions are collected in a questionnaire. The following items or other available categories may be collected and summarized for each injection site reaction:

- pain
- itching
- rash
- reaction timing
- swelling
- redness
- erythema
- bruising
- hematoma

Injection site reactions which meet SAE criteria will also be collected as AEs. If >3% patients have such an event occur, then these injection site reactions may be summarized by PT using the version of MedDRA current at the time of programming.

6.10.4.3. Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea event information will be collected on a designated separate eCRF page. Summaries and analyses for incidence will be provided for each randomized treatment group and by visit.

The prevalence and incidence of nausea, vomiting, and diarrhea will be summarized by the treatment and the time interval of interest. In addition, similar tables will also be generated by actual dose and time interval. The duration of each event will also be computed in days as event stop date minus event start date. For computation purposes, events that are ongoing will be considered censored (that is, ended) at the date of last study contact.

The maximum severity and duration from baseline to Week 12 of nausea, vomiting, and diarrhea will be summarized by treatments.

Plots with the percentage number of subjects with the events versus initiation time course will also be generated. The y-axis is the percentage of subjects with the specified AE and the x-axis is the time since the first dose.

A listing with GI TEAEs of interest will be provided.

6.10.4.4. Hypoglycemic Episodes and Total Hypoglycemia

Hypoglycemic episodes will be defined as follows: documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia. Total or overall hypoglycemia is defined as any event meeting the criteria for documented symptomatic hypoglycemia, asymptomatic hypoglycemia, or probable symptomatic hypoglycemia:

- **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 ≤3.9 mmol/L (≤70 mg/dL).
- **Asymptomatic Hypoglycemia:** An event not accompanied by typical symptoms of hypoglycemia, but with ≤3.9 mmol/L (≤70 mg/dL) plasma glucose.
- **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.
- **Nocturnal Hypoglycemia:** Any hypoglycemic event that occurs between bedtime and waking.
- **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 ≤3.9 mmol/L [≤70 mg/dL]).
- **Total or Overall Hypoglycemia:** Any event meeting the criteria for documented symptomatic hypoglycemia, asymptomatic hypoglycemia, or probable symptomatic hypoglycemia.

Information will be collected on the eCRFs to allow for classification of hypoglycemic episodes into these categories. Note that there is possible overlap among the categories, meaning that it is possible for a single event to have >1 classification.

A monthly rate of episodes per patient will be computed by visit, with 1 month defined as a 30-day period. At each applicable visit, the total number of episodes since the previous visit and the number of days since the previous visit will be determined. The monthly rate of episodes will be calculated as the total number of episodes divided by the number of days since the

previous visit and multiplied by 30 days. An overall monthly rate will be determined as the total number of episodes over all visits divided by the total number of days between all visits and multiplied by 30 days.

The monthly rate of episodes per patient by visit and overall will be computed for episodes of total hypoglycemia and episodes of nocturnal hypoglycemia. These rates will be summarized by treatment for each visit and overall.

The incidence of hypoglycemic episodes during a time period is defined as the number of patients experiencing at least 1 hypoglycemic episode within that time period. The incidences of total hypoglycemic, nocturnal hypoglycemic episodes and severe hypoglycemic episodes will be determined at each visit (that is, for the time period since the previous visit), and overall (that is, for the time period from first dose of study treatment to last study visit while on study treatment). The incidences for total and nocturnal hypoglycemic episodes will be summarized by treatment for each visit and overall using descriptive statistics (that is, sample size, frequency, and percentage); if a sufficient number of severe hypoglycemic episodes are reported, then incidence of these episodes will also be summarized.

Listings of hypoglycemic episodes of all types will be presented by visit for each patient.

Hypoglycemic episodes occurring after a patient discontinues treatment will be counted in the determinations of rate or incidence of episodes.

6.10.4.5. 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 >3% patients have pancreatic event(s). Determination of investigator-reported events will be through the "Acute pancreatitis" 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 12, and the maximum post-dose value will be summarized by each randomized treatment in a shift table using >1× the upper limit of normal (ULN), and ≥3× ULN separately for the mITT population, mITT population with normal baseline, mITT population with baseline value >ULN.

6.10.4.6. C-cell Hyperplasia and C-cell Neoplasms

Listings of AEs of interest using a LSC will be provided by High-Level Terms (HLTs) thyroid neoplasms, thyroid neoplasms malignant, and thyroid disorders. The summary report for these AESIs by each randomized treatment will be reported if there are >3% patients with these AESIs.

Calcitonin data will be summarized using an ANCOVA model similar to the supportive analyses.

Calcitonin values will be listed for those patients with a post-first-dose serum calcitonin increase from baseline ≥50% and the absolute value ≥20 pg/mL. These patients will be classified by their absolute calcitonin values into the following categories: ≥20 and <35 pg/mL; ≥35and <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%.

6.10.5. Laboratory Measurements

Laboratory measurements will be summarized by treatment group using descriptive statistics at each scheduled time of assessment during the treatment and follow-up periods and including any off-treatment safety follow-up visits that occur after discontinuation of study treatment. Descriptive statistics for laboratory analyses with continuous results will include sample size, mean, SD, median, minimum, and maximum for both actual values and change from baseline. Laboratory analyses with categorical responses will be summarized by visit and treatment group using sample size, frequency, and percentage.

A listing of laboratory measurements for individual patients will be presented by visit. An additional listing will be presented for all laboratory measurements that are outside the normal range. All laboratory measures that meet the criteria for a listing will be reported, including unscheduled and repeat or multiple measurements.

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/minimum postbaseline value to Week 12 for selected analytes using clinically meaningful thresholds will be summarized. A shift table for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and direct bilirubin will be generated using cutoff ≤1 × ULN, (>1 × ULN and <3 × ULN), (≥3 × ULN and <5 × ULN), (≥5 × ULN and <8 × ULN), ≥8 × ULN.

A listing of ALT, AST, and total bilirubin values at all visits will be presented for all patients who meet any of the following criteria:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- total bilirubin ≥2 × ULN
- ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN.

6.10.6. Electrocardiograms

For ECG parameters that collected in triplicates, the arithmetic mean from the 3 measures for the same parameter at the same visit will be calculated and use for all subsequent analyses. This will include ECG heart rate (HR) in beats per minutes (bpm), QRS complex (milliseconds [msec]), and PR interval (msec), as well as the time elapsed between the onset of ventricular depolarization and the end of ventricular repolarization (QT) and QT corrected by heart rate (HR) values using Fridericia's formula (QTcF). Fridericia's correct QT formula will be reported in (msec). Descriptive statistics for the absolute values and changes from baseline for the ECG

parameters (HR, PR interval, QRS, QT, QTcF) will be presented by treatment arm. Additional summary statistics will be provided for abnormal values (categorized as Low or High as shown in Table 6.5). An MMRM-based model similar to the analysis of the primary outcome will also be used for the change from baseline in HR, PR, and QTcF.

Table 6.5. Electrocardiogram Abnormal Categories

Measure	Low	High
PR Interval	<120 msec	≥220 msec
QRS Interval	<60 msec	≥120 msec
HR	<50 and decrease of ≥15 bpm	>100 and increase ≥15 bpm
QT	NA	>500 msec
QTcF	NA	>450, >480, and >500 msec

Abbreviations: bpm = beats per minute; HR = heart rate; msec = milliseconds; NA = not applicable; QTcF = QT corrected values using Fridericia's formula.

In addition, LY3298176 concentration-response analysis of QTcF and RR results may be performed, using figures that display change from baseline in QTcF on the vertical axis versus LY3298176 concentration (from pharmacokinetics/pharmacodynamics [PK/PD]) on the horizontal axis, time-matched with the QTcF measurements. The figures will also include a regression line and corresponding regression analysis.

Summaries of categories for absolute observations and change from baseline for QTcF intervals will be provided as well, with absolute categories as >450, >480, and >500 msec and change from baseline categories as >30 msec and >60 msec.

6.11. Exploratory Analyses

Baseline will be the measurements prior to treatment for SMBG.

Immunogenicity will be analyzed and summarized.

6.11.1. 7-Point SMBG

The 7-point SMBG profile consists of pre-meal and 2-hour postprandial blood glucose (BG) measurements for morning, midday, and evening meals, as well as a bedtime BG measurement. Analyses will apply to the changes from baseline in the following variables for 7-point glucose profiles:

1. pre-morning meal-fasting BG (mg/dL)
2. morning meal 2-hour (hr) BG (mg/dL)
3. pre-midday meal BG (mg/dL)
4. midday meal 2-hour BG (mg/dL)
5. pre-evening meal BG (mg/dL)
6. evening meal 2-hour BG (mg/dL)

7. bedtime BG (mg/dL)
8. morning meal 2-hour excursion (mg/dL)
9. midday meal 2-hour excursion (mg/dL)
10. evening meal 2-hour excursion (mg/dL)
11. mean of all meals 2-hour excursion (mg/dL)
12. mean of all 7-point BG (mg/dL)
13. mean of all pre-meals BG (mg/dL)
14. mean of all 2-hour postprandial BG (mg/dL).

The morning, midday, and evening meal 2-hour excursions (that is, variable 8 through variable 10) will be calculated for each meal as the 2-hour postprandial BG minus the pre-meal BG.

The change from baseline of 7-point SMBG profiles will be calculated using a similar ANCOVA model to the one used for the supporting analysis for the primary endpoint described in Section 6.9.1.1. The corresponding baseline will be used in the model instead of the baseline HbA1c levels. The ANCOVA model will include a term for the HbA1c stratification group.

6.11.2. Evaluation of Immunogenicity

6.11.2.1. Definitions of Sample Anti-drug Antibody Status

At a high level, an individual sample is potentially examined multiple times, in a hierarchical procedure to produce a sample anti-drug antibodies (ADA) assay result and potentially multiple cross-reactive antibodies assay results and multiple neutralizing antibodies (NAb) assay results. The cut points used, the drug tolerance of each assay, and the possible values of titers are operating characteristics of the assay.

It can be the case that the presence of high concentrations of LY will affect immunoassays, and conversely high levels of antibodies may affect the measurement of LY concentration. Thus, an LY drug concentration, assessed from a sample drawn at the same time as the ADA sample, plays a key role in clinical interpretation of a sample when the laboratory result is Not Detected (Table 6.6).

Table 6.6. Sample Anti-Drug Antibodies (ADA) Assay Results

Sample Laboratory Result	Explanation
Detected	ADA are detected and confirmed.
Not Detected	The raw result as reported from the laboratory indicates not detected. The clinical interpretation of such results depends other factors (see below).
NO TEST, QNS, etc.	Sample exists but was unevaluable by the assay

Abbreviations: QNS = quantity not sufficient.

Table 6.7. Sample Clinical Anti-Drug Antibodies (ADA) Interpretation Results

Sample Clinical Interpretation	Explanation
ADA Present	ADA assay result is Detected
ADA Not Present	ADA assay result is Not Detected and simultaneous drug concentration is at a level that has been demonstrated to not interfere in the ADA detection method (that is, drug concentration is below the assay's drug tolerance level). For patients receiving placebo, drug concentration is not assessed and is assumed to be below the assay's drug tolerance level. If drug concentration was planned but is not available for a treatment-period sample, a Not Detected sample will be declared ADA Inconclusive.
ADA Inconclusive	ADA assay result is Not Detected but drug concentration in the sample is at a level that can cause interference in the ADA detection method.
ADA Missing	ADA sample not drawn, QNS, not tested, etc., causing there to be no laboratory result reported or the result is reported as "no test."

Abbreviations: QNS = quantity not sufficient.

Parallel terminology applies for each type of cross-reactive and NAb. Importantly, each of these are distinct assays and, in general, have different assay operating characteristics.

6.11.2.2. Definitions of Immunogenicity Assessment Periods

Immunogenicity Baseline Observations: Baseline period for immunogenicity assessment for each patient includes all observations on or prior to first administration of study drug. In instances where multiple baseline observations are collected, to determine patient ADA status the last nonmissing immunogenicity assessment prior to first administration of study drug is used to determine treatment-emergent status (see below). In this context, "missing" includes explicit "ADA Missing" results, as defined in Table 6.7.

Immunogenicity Postbaseline Period Observations: Postbaseline period observations for each patient include all observations after the first administration of study drug.

6.11.2.3. Definitions of Patient ADA Status

Patient evaluable for treatment-emergent ADA (TE-ADA): A patient is evaluable for TE-ADA if the patient has a nonmissing baseline ADA result, and at least 1 nonmissing postbaseline ADA result.

Treatment-emergent ADA positive (TE-ADA+) patient: A patient who is evaluable for TE-ADA is TE-ADA+ if either of the following holds:

- The patient has baseline status of ADA Not Present and at least 1 postbaseline status of ADA Present with titer ≥2*MRD, where the MRD is the minimum required dilution of the ADA assay.
- The patient has baseline and postbaseline status of ADA Present, with the postbaseline titer being 2 dilutions (4-fold) greater than the baseline titer. That is, the patient has baseline status of ADA Present, with titer 1:B, and at least 1 postbaseline status of ADA Present, with titer 1:P, with P/B ≥4.

Treatment-emergent ADA Inconclusive patient: A patient who is evaluable for TE-ADA is TE-ADA Inconclusive if ≥20% of the patient's postbaseline samples, drawn pre-dose, are ADA Inconclusive and all remaining postbaseline samples are ADA Not Present.

Treatment-emergent ADA negative (TE-ADA-) patient**:** A patient who is evaluable for TE-ADA is TE-ADA- when the patient is not TE-ADA+ and the patient is not TE-ADA Inconclusive.

6.11.2.4. Analyses to be Performed

The number and proportion of patients who are TE-ADA+ will be tabulated by treatment group, where proportions are relative to the number of patients who are TE-ADA evaluable, as defined above. The tabulation will include the number and proportion of patients with ADA Present at baseline, and also the number and proportion of TE-ADA+ patients exhibiting each type of cross-reactive antibodies and NAb. This analysis will be performed for: (a) the active treatment period; and also for (b) the entire postbaseline period including follow-up.

A listing will be provided of all immunogenicity assessments for those patients who at any time had ADA Present. This includes the LY concentration from a simultaneous PK sample, and the clinical interpretation result (ADA Present, ADA Not Present, ADA Inconclusive, Missing). In the case of ADA Present, a titer will be included, and TE-ADA+ observations will be flagged. Also included, for each cross-reactive antibodies and NAb assay that was performed, will be the clinical interpretation result.

A summary will be provided of the number and percentage of LY-treated patients experiencing specific TEAE (see Table 6.8) by patient TE-ADA status (TE-ADA+, TE-ADA-, TE-ADA Inconclusive). The PT will be ordered by decreasing incidence in TE-ADA+ status group.

A listing will be provided of all TEAEs alongside ADA data for any patient who had ADA Present at any time (including baseline) or had any specific TEAE (see Table 6.8). This listing includes a time course of ADA (clinical interpretation result plus flags for samples meeting TE-ADA+ criteria and for samples with cross-reactive antibodies and NAb present) along with the TEAE.

Table 6.8. Adverse Events for Analysis with Immunogenicity Results

Events satisfying Anaphylaxis standardized MedDRA query (SMQ) (narrow or broad)
Events satisfying Hypersensitivity SMQ (narrow or broad)
Events satisfying Angioedema SMQ (narrow or broad)
Events mapping to High-Level Term (HLT) of Injection site reaction
Events mapping to HLT of Infusion site reaction

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

The primary efficacy measure of change in HbA1c from baseline to 12 weeks may be examined in relation to ADA. The initial examination will be boxplots of change in HbA1c at 12 weeks, compared to maximum observed titer (1 category for each titer value) during the active treatment period, for patients who were TE-ADA+ during that period. An additional category will be provided for patients who were not TE-ADA+ during the active treatment period.

Additional immunogenicity analyses as determined later may be presented. The relationship between antibody titers, the PK parameters, and PD response to LY3298176 may also be assessed.

6.12. Pharmacokinetic and Pharmacodynamic Analyses

LY3298176 trough PK samples collected over the course of this study will be used to assess that exposures in the study are consistent with known LY3298176 PK.

Additionally, PK/PD data from this study may be used as a validation dataset to enable evaluation of PK/PD models built based on data from the core Phase 2 study, Study I8F-MC-GPGB (GPGB). These analyses may be conducted using nonlinear mixed-effects modeling implemented with the NONMEM software.

If antidrug antibody titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3298176 PK or any relevant PD parameters may also be examined.

6.13. Subgroup Analyses

No subgroup analyses are planned for this study.

6.14. Interim Analyses

No interim analyses are planned for this study.

The study team will perform periodic, blinded safety reviews during the study.

A database lock may be performed when all patients have completed the treatment part of the study (prior to completion of the follow-up phase for all patients), if deemed necessary. It will include all safety, efficacy, and PK data available through the 12-week treatment.

6.15. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. For CTR analyses, an AE will be considered "Serious" whether or not it is a TEAE. An AE will be considered to be in the "Other" category if it is both a TEAE and not serious.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both Serious AEs and "Other" AEs will be summarized by treatment group and by MedDRA PT.
- For each Serious AE and "Other" AE, for each PT and treatment group, the number of each of the following will be provided:
    - participants at risk of an event
    - participants who experienced each event PT
    - events experienced

Consistent with ClinicalTrials.gov (National Institutes of Health [NIH] [WWW]) requirements, a threshold (at a maximum of 5%) for frequency of "Other" AEs can be implemented rather than

presenting all “Other” AEs. The determination of a threshold will be based on the overall number of “Other” AEs.

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 CSR reports, data reviews, dose selection (interim efficacy/safety only), and developing/refining exposure analyses.

There is no interim analysis planned for this study.

The access to subject treatment assignments will not be provided to the investigator and site personnel until DBL is authorized for the planned final analysis at the completion of the blinded study.

Until the data lock is authorized for the final analysis at the completion of the study, access to subject treatment assignments will not be provided to the following personnel:

- Lilly personnel with direct site contact
- Lilly personnel responsible for data entry and data validation
- Lilly study team

After DBL, the study team will be unblinded to the study data to prepare for the analyses for the 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 after final DBL.

7.1. Operational Procedures

The randomization code (treatment assignment) will be stored in the Lilly 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 DBL.

More specifically, the data movement group will load CRF data, clinical laboratory results, ECG, and IWRS data into the designed blinded and unblinded locations. The data movement group is not blinded, but is not involved in study-level activities.

Periodically throughout the trial until the DBL, blinded data will be transferred by 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, trial-level safety review (TLSR) reports table, figure, listing (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 AEs 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 TLSR summaries and listings will be produced by the blinded Lilly statistics group and delivered to the blinded Lilly study teams. These summaries will be blinded until after DBL. They will contain neither randomization assignments nor 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 organizations (TPOs) performing the labs. The complete list of TLSR variables include overall AEs, SAEs, TEAEs, AESIs, laboratory data, vital signs, discontinuations, and concomitant medications.

7.4. 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 may be obtained later after the final DBL in a separate transfer without overwriting the already locked database.

8. References

[NIH] National Institutes of Health. ClinicalTrials.gov. Available at: https://www.clinicaltrials.gov/. Accessed September 28, 2015.

9. Appendices

Appendix 1. Schedule of Events

Study Phase	Screen	Lead-In	Randomize	Treatment							Follow-Up	Early Term.
Visit	1	2	3	4	5	6	7T[a]	8	9T[a]	10[b]	801[d]	ET
Week of Treatment	–2	–1	0	1	2	4	4	8	8	12	(15)	
Study Day/(dose number)			0/(1)	7/(2)	14/(3)	28/(5)	31-34	56/(9)	59-62	84	105	
Visit Window (days)		+7	0	0	±2	±3		±3		±3	±3	
Administrative												
Informed consent	X											
Diabetes medical history/therapy	X											
Inclusion/exclusion	X	X	X									
Preexisting conditions	X											
Randomization			X									
IWRS	X	X	X	X	X	X		X		X	X	X
BG meter/supplies, if needed		X										
BG meter, instructions		X										
Diet, exercise, BG counseling		X										
Study diary, dispense		X	X	X	X	X		X		X		
Review patient diaries for BG values, AEs, hypoglycemic or hyperglycemic events		X	X	X	X	X		X		X	X	X
Subcutaneous injection training		X	X	X	X	X		X				
Study drug and injection supplies, dispense			X	X	X	X		X				
Health habits (alcohol use, tobacco use current/past)	X											
Patient returns study drug vials						X		X		X		
Study drug, assess compliance			X	X	X	X		X		X		
Patient Demographics												
Age	X											
Gender	X											
Race/ethnicity	X											

Study Phase	Screen	Lead-In	Randomize	Treatment							Follow-Up	Early Term.
Visit	1	2	3	4	5	6	7T[a]	8	9T[a]	10[b]	801[d]	ET
Week of Treatment	–2	–1	0	1	2	4	4	8	8	12	(15)	
Study Day/(dose number)			0/(1)	7/(2)	14/(3)	28/(5)	31-34	56/(9)	59-62	84	105	
Visit Window (days)		+7	0	0	±2	±3		±3		±3	±3	
Clinical Variables												
Physical examination[c]	X											
Height	X											
Weight	X		X			X		X		X	X	X
Waist circumference	X		X			X		X		X	X	X
Vital signs (BP and PR)	X	X	X	X	X	X		X		X	X	X
Antidiabetic medication	X	X	X	X	X	X		X		X	X	X
Concomitant medication	X	X	X	X	X	X		X		X	X	X
Other												
ECG[e]	X[e]		X			X		X		X	X	X[e]
Evaluation of injection site reactions			X	X	X	X		X		X	X	X
Collect AEs	X	X	X	X	X	X		X		X	X	X
Diagnostics (Safety)												
Screening laboratory tests[f]	X											
Pregnancy test[g]	X		X[g]									
FSH[h]	X											
Chemistry panel	X		X							X	X	X
Lipid panel	X		X							X	X	X
Lipase and amylase	X		X			X		X		X	X	X
eGFR	X											
Hematology	X		X							X	X	X
Urinalysis	X		X							X	X	X

Study Phase	Screen	Lead-In	Randomize	Treatment							Follow-Up	Early Term.
Visit	1	2	3	4	5	6	7T[a]	8	9T[a]	10[b]	801[d]	ET
Week of Treatment	–2	–1	0	1	2	4	4	8	8	12	(15)	
Study Day/(dose number)			0/(1)	7/(2)	14/(3)	28/(5)	31-34	56/(9)	59-62	84	105	
Visit Window (days)		+7	0	0	±2	±3		±3		±3	±3	
Diagnostics (Efficacy)												
Calcitonin	X									X		X
HbA1c	X		X			X		X		X	X	X
Fasting glucose	X		X			X		X		X	X	X
Total and active GLP-1/GIP			X			X		X		X	X	
7-point SMBG			X[i]							X[j]		
PK[k]						X		X		X	X	X
Immunogenicity			X			X		X		X	X[l]	X
Nonpharmacogenetic stored samples			X							X		

Abbreviations: AE = adverse event; BG = blood glucose; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = Early Termination; FSH = follicle-stimulating hormone; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; IWRS = interactive web response system; PK = pharmacokinetics; PR = pulse rate; SMBG = self-monitoring of blood glucose; T = telephone visit; TE-ADA = treatment emergent anti-drug antibodies; Term. = termination.

a Telephone visits occur during the week following a dose escalation and should be done 3 to 6 days after a site visit for dose escalation and administration. At telephone visits, the sites should call the patient, ask how the patient is, and ask whether the patient would like to come to the site for assistance with the next study drug dilution and administration. Sites should also remind patients to write down any AEs in their diaries at the telephone visits (as well as at all site visits).

b Visit should occur approximately 1 week after the last dose (Dose 12).

c Additional physical examinations may be performed throughout the study if determined necessary due to patient symptoms.

d Visit should occur 4 weeks after the last dose of study drug or 3 weeks after Visit 10.

e ECGs should be collected prior to all blood draws and study drug administrations. Local ECGs will be collected for screening (Visit 1) and Early Termination. Centralized ECGs, collected in supine position and in triplicate, should be collected for all other designated visits.

f Screening laboratory tests include serum hepatitis B surface antigen (Ag), hepatitis C antibody (Ab), and human immunodeficiency virus (HIV) Ab tests for all patients (see Appendix 2).

g Serum pregnancy test will be performed by central laboratory at Visit 1 for women of child-bearing potential. For the remainder of the study, a urine pregnancy test may be performed at the investigator's discretion if pregnancy is suspected during the study (local laboratory). A urine pregnancy test (local) should be given to all women of child-bearing potential at Visit 3 prior to administration of first dose of study drug to confirm lack of pregnancy.

h Collect serum FSH in women whose menopausal status needs to be determined.

[i] The patients should collect the SMBG during the lead-in period between Visits 2 and 3 and return the results within their diaries at Visit 3.
[j] The patients should collect the SMBG during the week after Dose 12 and return the results within their diaries at Visit 10.
[k] PK samples are to be collected pre-dose.
[l] Patients who have clinically significant TE-ADA should be followed with ADA testing every 3 months for approximately 1 year or until the ADA titers have returned to baseline ADA titer (defined as ADA titer within 2-fold of baseline). Patients who have clinical sequelae that are considered potentially related to the presence of TE-ADA may also be asked to return for additional follow-up testing.

Appendix 2. Important Protocol Deviations

	Important Protocol Deviation			Source of Information	Function Accountable for Identifying Deviation	Programmable/ Nonprogrammable	Immediate Notification (Y/N)
	Category	Sub-category	Trial-specific Term				
1	Investigational Product	Other	Not fit for use	Monitoring	Site Monitor	Nonprogrammable	Y
2	Eligibility	Inclusion/ Exclusion	Age out of range	Monitoring	Site Monitor	Nonprogrammable	N
3	Eligibility	Inclusion/ Exclusion	Non-compliant to T2DM criteria.	Monitoring	Site Monitor	Nonprogrammable	Y
4	Eligibility	Inclusion/ Exclusion	HbA1c not in compliance with the entry criteria	CLUWE/CLO	CLO	Programmable	Y
5	Eligibility	Inclusion/ Exclusion	Abnormal thyroid-stimulating hormone (TSH) levels.	Monitoring/ CLO	Site Monitor	Monitoring (nonprogrammable)/ CLO (programmable)	Y
6	Eligibility	Inclusion/ Exclusion	Not on stable dose of cholesterol lowering drugs.	Monitoring	Site Monitor	Nonprogrammable	Y
7	Eligibility	Inclusion/ Exclusion	BMI out of range.	Monitoring	Site Monitor	Nonprogrammable	Y
8	Eligibility	Inclusion/ Exclusion	Non-compliance to weight loss medication criteria.	Monitoring/ CLUWE	Site Monitor/ CLUWE	Monitoring (nonprogrammable)/ CLUWE (programmable)	N
9	Safety	Other	Failure to report product complaint within 24 hrs.	Monitoring	Site Monitor	Nonprogrammable	Y
10	Safety	Other	Positive urine and/or serum pregnancy test.	Monitoring/ CLO	Site Monitor/ CLO	Monitoring (nonprogrammable)/ CLO (programmable)	Y
11	Informed Consent	Informed Consent Not	NA	Monitoring/ InForm	Site Monitor	Monitoring (nonprogrammable)/	Y

	Important Protocol Deviation			Source of Information	Function Accountable for Identifying Deviation	Programmable/ Nonprogrammable	Immediate Notification (Y/N)
	Category	Sub-category	Trial-specific Term				
		Obtained				InForm (programmable)	
12	Study Procedures	Violation of Discontinuation Criteria	NA	Mixed (monitoring and CLO/CLUWE)	Site Monitor/CLO/ CLUWE	Monitoring (nonprogrammable)/ CLO, CLUWE (programmable)	Y
13	Study Procedures	Excluded Conmeds	OAMs besides met for more than 7 cumulative days.	Monitoring/ InForm/ CLUWE	Stats/Site Monitor	Monitoring (nonprogrammable)/ CLUWE, InForm (programmable)	N
14	Study Procedures	Excluded Conmeds	Wt. loss meds taken 7 days or more during tx phase	Monitoring/ CLUWE	Stats/Site Monitor	Monitoring (nonprogrammable)/ CLUWE (programmable)	N
15	Study Procedures	Lab Criteria	Missing HbA1c at designated visits per SoA.	Monitoring/ CLUWE/ CLO	Stats/Site Monitor/CLO	Monitoring (nonprogrammable)/ CLO and CLUWE (programmable)	Y
16	Study Procedures	Other	Missing safety data for all 3:BP, Pulse, or ECGs.	Monitoring/ InForm	Site Monitor/InForm	Monitoring (nonprogrammable)/ InForm (programmable)	N
17	Study Procedures	Other	Missing lab of lipase, amylase, LFTs, or FBG.	CLUWE	CLO	Programmable	N
18	Study Procedures	Other	Missing body wt. and/or waist circ. per SoA.	Monitoring/ InForm	Site Monitor/InForm	Monitoring (nonprogrammable)/I nForm (programmable)	N
19	Investigational product	Other	IP lost or stolen	Monitoring	Site Monitor	Nonprogrammable	Y
20	Investigational	Dosing	NA	Monitoring/	Site Monitor/InForm	Monitoring	N

	Important Protocol Deviation			Source of Information	Function Accountable for Identifying Deviation	Programmable/ Nonprogrammable	Immediate Notification (Y/N)
	Category	Sub-category	Trial-specific Term				
	product	Error		InForm		(nonprogrammable)/ InForm (programmable)	
21	Investigational product	Compliance	Missing 2 or more doses.	Monitoring/ InForm/ CLUWE	Site Monitor/InForm/ CLUWE	Monitoring (nonprogrammable)/ InForm and CLUWE (programmable)	Y

Abbreviations: BMI = body mass index; BP = blood pressure; circ. = circumference; CLO = Clinical Laboratory Operations; CLUWE = Clinical Users Working Environment; conmeds = concomitant medications; ECGs = electrocardiograms; FBG = fasting blood glucose; HbA1c = glycated hemoglobin; hrs. = hours; IP = investigational product; lab = laboratory; LFTs = liver function tests; N = no; NA = not applicable; OAMs = oral antihyperglycemic medications; SoA = Schedule of Events; T2DM = type 2 diabetes mellitus; tx = treatment; wt. = weight; Y = yes.