Statistical Analysis Plan I8F-MC-GPGB (3)

I8F-MC-GPGB: A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus
NCT03131687

Approval Date: 26-Mar-2018

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

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.

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Protocol I8F-MC-GPGB
Phase 2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 27 July 2017
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

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3. Revision History

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

The second version is approved before the first interim analysis. The following changes are made for the second version:

1. The second interim analysis time is changed from 100% patients finishing 16 weeks of treatment to 90% patients finishing 12 weeks of treatment.
2. A titrated dose integrated two-component prediction (ITP) model is added for the dose response analyses.

The third version is approved before the primary database lock. The following changes are made for the third version:

1. Clarify analyses datasets. Analysis dataset for modified intent-to-treat (mITT) population, excluding data after study drug discontinuation or rescue drug initiation, is added for the efficacy analyses to better reflect the study treatment effect.
2. Add a missing data imputation analysis for HbA1c and body weight.
3. Delete country from the statistical analyses that was accidently included as a strata factor. Delete visit window.

4. Study Objectives

4.1. Primary Objectives

The primary objective of this study is to demonstrate a dose-response relationship of once-weekly subcutaneous (SC) injections of LY3298176 on hemoglobin A1c (HbA1c) change from baseline relative to placebo, in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.

4.2. Secondary Objectives

To determine the effect of LY3298176 versus dulaglutide and placebo on:

- mean body weight change from baseline to 12 and 26 weeks
- change from baseline of HbA1c at 12 weeks
- percentage of patients with ≥5% body weight loss at 26 weeks
- percentage of patients with ≥10% body weight loss at 26 weeks
- percentage of patients reaching the HbA1c target of ≤6.5% and of ≤7.0%
- change from baseline of fasting plasma glucose (FPG) at 12 and 26 weeks
- change from baseline to 26 weeks in high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C)
- waist circumference
- safety and tolerability, including gastrointestinal (GI) tolerability, incidence and rate of hypoglycemia, hypersensitivity reactions and pancreatic safety.

In addition, it is intended to assess

- the development of treatment-emergent anti-drug antibodies (TE ADA) to LY3298176
- the pharmacokinetics (PK) of LY3298176 and potential patient factors that may influence its PK and pharmacodynamics (PD).
- the relationship between LY3298176 dose and/or exposure and key efficacy, and safety measures, where applicable.

4.3. Exploratory Objectives

Evaluate the effect of LY3298176 compared with placebo and dulaglutide on:

- Change from baseline of 7-point self-monitoring of blood glucose (SMBG) profiles at 4, 12, 26, and 30 weeks
- Biomarkers
- Evaluate patient-reported outcomes (PROs) questionnaires: the Ability to Perform Physical Activities of Daily Living Questionnaire (APPADL), and the Impact of Weight on Self-Perception (IW-SP).

4.4. Pharmacogenomics Objectives

- To evaluate genetic variants in genes in the glucagon signaling pathway and glucose-dependent insulinotropic peptide/glucagon-like peptide-1 (GIP/GLP-1)

associated genes for association with efficacy responses to LY3298176 such as change from baseline in HbA1c, fasting glucose, body weight, and body mass index (BMI).

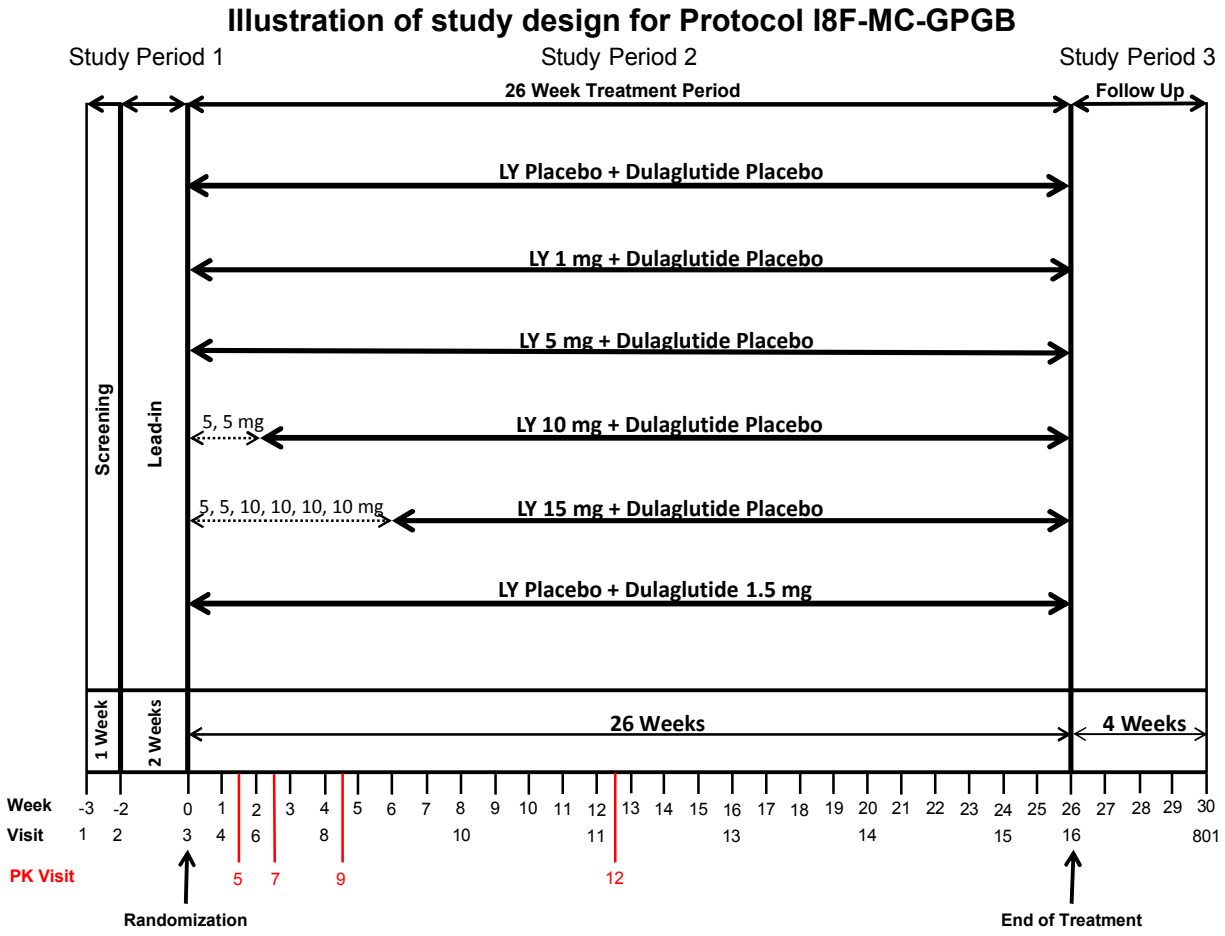
- To evaluate the association of genetic variants in the glucagon signaling pathway and GIP/GLP-1 associated genes with other PD and clinical endpoints of interest (including circulating glucagon levels, blood pressure (BP), serum amylase and lipase, GI tolerance, lipid metabolism, bone metabolism, etc).
- To investigate the genetic variants associated with dulaglutide treatment response (identified from dulaglutide clinical trials) on the efficacy and safety endpoints in response to LY3298176.

5. Study Design

5.1. Study Design and Treatment

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

The design for Study GPGB is illustrated in Figure 5.1.



Abbreviations: LY = study drug LY3298176; PK = pharmacokinetics.

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

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 a screening visit (Visit 1). Screening procedures will be performed on approximately Day –21 according to the Schedule of Activities. Patients will receive training on the routine BG monitoring and paper diary completion required during the study. Patients should follow the investigator's instructions related to frequency of SMBG but should test their glucose a

minimum of 3 times per week and as specified for determination of 7-point glucose profiles. Eligible patients will return to the site for some baseline procedures during the lead-in phase and again for randomization to treatment and to receive their first dose of study drug at Visit 3.

After randomization and the first dose (Visit 3), patients will return to the site for PK collection just prior to the second dose (Visit 4). Patients will also have a predose PK collection prior to Week 8 (Visit 10), Week 12 dose (Visit 11), and Week 26 (Visit 16) dose. There will be postdose PK collections after the second dose (PK-specific Visit 5), third dose (PK-specific Visit 7), fifth dose (PK-specific Visit 9, and 12-week dose (PK-specific Visit 12). A safety follow-up visit will occur approximately 4 weeks following the last dose of the study drug. Patients randomized to LY3298176 who develop treatment-emergent anti-LY3298176 antibodies will be monitored after the last visit.

Throughout the study, patients treated with metformin will remain on the same dose they were receiving at Visit 1 unless changes need to be made for safety reasons. All patients will be encouraged to maintain their prestudy diet and exercise levels through the course of the study.

In the treatment phase, a double-dummy dose administration scheme will be employed to ensure patients and investigators (as well as sponsor study team and monitors) remain blind to the LY3298176, dulaglutide 1.5 mg, and placebo treatment assignments within each treatment group. At each dosing occasion, the study drug will be administered as 1 to 3 SC injections of LY3298176 or matched placebo and 1 SC injection of dulaglutide 1.5 mg or its placebo. Therefore, each patient will self-administer 2 to 4 injections per week.

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 dulaglutide 1.5 mg, placebo, or 1 of 4 LY3298176 dose levels. 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 BMI (<30, ≥30). There will be equal randomization to the treatment arms (1:1:1:1:1:1). However, LY3298176 placebo patients will be randomized such that a portion will be randomized to each cohort in order to receive the same dose volume as that cohort in order to maintain the study blind. For the active dulaglutide 1.5 mg group, LY3298176 placebo patients will be distributed through the treatment groups in order to maintain the blind.

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

5.3. Determination of Sample Size

Approximately 300 patients will be randomized to placebo, dulaglutide, or 1 of the 4 LY3298176 treatment arms assuming a 10% dropout rate resulting in approximately 45 completers per arm.

The Bayesian approach using a dose-response model with respect to an HbA1c change from baseline to 26 weeks will provide approximately 98% probability to show with 90% confidence that at least 1 LY3298176 dose has superior glycemic control over placebo with a superiority bound of -0.8%. The sample size also provides >95% probability to show with 80% confidence that at least 1 LY3298176 dose has non-inferior glycemic control compared with dulaglutide from baseline to 26 weeks with a 0.3% non-inferiority bound. This assumes a profile for the change in HbA1c from baseline to 26 weeks shown in Table 5.1, and a standard deviation (SD) of 1.0%.

In addition, this sample size also provides approximately 89% probability to show with 60% confidence that at least 1 LY3298176 dose has superior weight loss compared with dulaglutide from baseline to 26 weeks with a superiority bound of -2 kg. This assumes a profile for the change in body weight from baseline to 26 weeks shown in Table 5.1, and an SD of 6 kg.

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

	Placebo	LY 1	LY 5	LY 10	LY 15	Dulaglutide
CFBL HbA1c (%)	0%	-0.74%	-1.17%	-1.29%	-1.44%	-1.28%
CFBL Body Weight (kg)	0	-2.0	-3.0	-5.0	-6.0	-2.5

Abbreviations: CFBL = change from baseline; HbA1c = hemoglobin A1c; LY = study drug 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 documented in the clinical study report. 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).

Tests of treatment effects will be conducted at a one-sided alpha level of 0.1 and/or one-sided 90% credible interval (CI) for the Bayesian dose response analysis, and at a two-sided alpha level of 0.05 for other analyses, unless otherwise stated. No adjustments for multiplicity will be performed.

The baseline visit will be Visit 3. The baseline values used for the analyses will be the last scheduled baseline value obtained for each patient prior to first dosing. For all variables, if baseline data are not available or if they are missing, then the last non-missing measurement taken prior to first treatment 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. A scheduled visit is based on the actual visit number reported by the site. 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 26 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

The primary reasons for discontinuation by treatment will be listed and summarized. Using the Fisher's exact test, the percentage of patients discontinuing from each treatment will be compared.

Patient statuses at the end of the 26-week treatment period displaying the numbers of patients will be summarized:

- entered
- screen failed, along with the primary reason for screen failure
- randomized
- randomized and not treated
- permanently discontinued from treatment
- discontinued from study, along with the primary reason for study discontinuation
- completed 26 weeks blinded treatment
- completed study.

The summary of status at the end of the 26-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 ICF. The percentage of patients discontinuing from each treatment using the Fisher's exact test will be provided.

6.3. Analysis Populations

Five patient populations for the analyses with detailed information are defined in Table 6.1. Unless otherwise specified, listings will include all randomized patients.

Table 6.1. Analysis Populations

Population	Definition
All Entered	All patients who signed informed consent forms (ICFs)
Intend-to-Treat (ITT)	All patients who were randomized to a treatment arm
Safety Population	All patients who took at least 1 dose of double-blind treatment. The taking of at least 1 dose will be established using the "Study Treatment" electronic case report form (eCRF) pages. In all safety analyses, patients by the actual treatment group will be presented.
Modified Intent-to-Treat (mITT)	All randomized patients who have taken at least 1 dose of the study medication and have at least 1 post baseline measurement. Analyses, by planned treatment group, using the mITT population will be presented.
Per-Protocol (PP)	All patients in mITT who complete the study and also meet the following criteria: • Have been appropriately randomized • Have not discontinued from the study for any of the early discontinuation criteria • Have not missed 4 or more doses during the treatment period • Have not been rescued or taken a concomitant antihyperglycemic medication besides metformin for >7 cumulative days during the treatment period • No important protocol deviations. The deviations to be used for excluding patients from the PP population will be specified prior to study unblinding.

6.4. Patient Characteristics and Medical History

Demographic and baseline characteristics, by treatment and overall, will be summarized using the mITT population and PP population. Categorical variables will be summarized using frequencies and percentages, and compared between treatments using a Pearson Chi-Square test. Continuous variables will be summarized using means and SDs, and compared between treatments using a 1-way analysis of variance.

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

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

6.5. Treatment Compliance

Treatment compliance will be listed using all randomized patients and summarized using the mITT population. For a given patient, overall compliance for treatment period is defined as not missing 2 or more consecutive doses of the assigned treatment or missing 4 or more doses at any point through the entire study. Patients who miss 4 or more doses at any point during the study will be considered significantly noncompliant, will not be included in the PP analysis.

Safety population during the 26-week treatment period by treatment group will be used to summarize the number and percent of patients compliant at 26-week.

6.6. Exposure of Study Treatment

For the safety population, exposure for each patient during the treatment period of the study, will be calculated and will be summarized by treatment group.

The extent of exposure to study medication (LY3298176, placebo, or dulaglutide) during the 26-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 26 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 for the 26-week treatment period will be summarized 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 by treatment group will be provided.

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:

- 26-week treatment period
- follow up period

All previous and concomitant medication use will be listed.

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 26-week treatment period is defined as medication with either a recorded medication start date falling:

- within the 26-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 26-week treatment period will be any medication taken for at least 1 day during the 26-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 and 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 3. Patients who deviate from the protocol in ways that would possibly affect efficacy results are going to be excluded from the per protocol analyses. That information can be found in Appendix 3. Patients meeting criteria for important protocol deviations will be identified either by statistical programming or based off of study monitoring that 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

The primary efficacy analysis, which is the Bayesian dose-response analysis on the change in HbA1c, will be performed on mITT population without rescue (i.e., data after use of rescue medication will not be included). Unless specified, all other efficacy analyses will be performed on mITT population on treatment without rescue (i.e., data after rescue medication or data after study treatment discontinuation will not be included). Some key efficacy measures, such as HbA1C and body weight, will also be analyzed on mITT population with all available data and on a PP dataset.

With the exception of the dose-response analyses on the HbA1c and body weight endpoints, all statistical models will include all treatment groups, including LY3298176, placebo, and dulaglutide.

6.9.1. Primary Outcome and Methodology

The primary efficacy outcome is HbA1c change from baseline to the 26-week endpoint.

6.9.1.1. Primary Analyses

The primary objective is to examine the probability each LY3298176 dose has demonstrated superiority relative to placebo using a superiority margin of –0.8%. Analyses will also consist of the 90% one-sided credible interval for the difference in mean response for each LY3298176 dose versus placebo at 26 weeks.

The primary analyses will be performed on the mITT without rescue analysis set using a Bayesian dose-response model and will include data from the blinded 26-week treatment period. The model will include LY3298176 doses, dulaglutide, and placebo.

The Hierarchical Logistic Model will be used to model the dose response in HbA1c change from baseline to the 26-week endpoint, . . The placebo group (d=0) will be modeled with the LY3298176 doses (d=1,…,D-1) using the Hierarchical Logistic model. Dulaglutide(d=D) is modeled independently. Each dose arm follows a prior structure as specified below:

$$\begin{cases} \theta_{dT} \sim a_1 + \dfrac{a_2 x_{dT}}{x_{dT} + a_3} + \varsigma_{dT}, & d = 0, \ldots, D-1 \\ y_T | a_1, a_2, a_3, \varsigma_{dT}, x_{dT} \sim N(\theta_{dT}, \sigma^2), & \\ \theta_{dT} \sim N(\mu_{dT}, v_{dT}^2) = N(0, 30\ ), & d = D \end{cases}$$

where

$$\begin{cases} \varsigma_{dT} \sim N(0, \alpha_4^2), \ \sum \varsigma_{dT} = 0 \\ \alpha_4^2 \sim IG\left(\dfrac{\Lambda_n}{2}, \dfrac{\Lambda_\mu^2 \Lambda_n}{2}\right), \\ a_i \sim N(\Lambda_i, \lambda_i\ ), \text{for } i = 1,2 \\ a_i \sim N^+(\Lambda_i, \lambda_i\ ), \text{for } i = 3 \\ \sigma^2 \sim IG\left(\dfrac{\sigma_n}{2}, \dfrac{\sigma_\mu^2 \sigma_n}{2}\right), \end{cases}$$

and $\Lambda_1 = 0,\ \Lambda_2 = 0,\ \Lambda_3 = 20,\ \Lambda_\mu = 3,\ \Lambda_n = 1,\ \sigma_\mu = 3.3,\ \sigma_n = 1,$ and $\lambda_i = 30,$ where $i = 1,2,3.$ T denotes the final time point at 26 weeks. The parameters $a_1,\ a_2,$ and a_3 represent, respectively, the basal effect when the dose level is zero, the maximum effect that can be achieved by any dose level, and the dose level that produces half of the maximum improvement (ED_{50}). So $a_2 - a_1$ gives the maximum improvement attributable to the drug. The parameter ς_{dT} is equivalent to a dose-specific random effect term but the sum of ς_d is constrained at zero to make sure it is identifiable from the error term, σ^2.

For placebo (d=0) and LY3298176 (d = 1,…,D-1), each successive θ_{dT} is modeled using all other estimated dose level means.

Additional definitions are as follows:

- d is the dose arm index, with d = 0,…,D (d=0 as placebo, and d=D as dulaglutide)
- D is the number of non-placebo dose arms, including dulaglutide. D is also the dose arm index for dulaglutide.
- x_{dT} is the dose strength, with d = 0, 1, …, D-1 in ascending order. Dulaglutide is not included in the Hierarchical Logistic model, and therefore does not require a dose strength.
- Λ_i and λ_i are, respectively, the prior means and variances of $a_i, i = 1,2,3.$
- θ_{dT} is the modeled dose arm effect at dose d at the final time point T of the 26-week of the study.
- $E\left(\frac{1}{a_4^2}\right) = \frac{1}{\Lambda_\mu}$ and Λ_n represents the weight of the prior information carried in Λ_μ.
- $E\left(\frac{1}{\sigma^2}\right) = \frac{1}{\sigma_\mu^2}$ and σ_n represents the weight of prior information carried in σ_μ^2.

The dose strength, x_{dT}, used in the model will reflect the actual selected doses for the study. The planned values for x_{dT} are shown in Table 6.2. Dulaglutide is modeled separately. The magnitude of the parameters x_{dT} impact the estimation in the dose-response model.

Table 6.2. Dose Strength Parameters and Corresponding Dose Strengths

Dose Strength Parameter	Dose Strength (mg)
x_0	0*
x_1	1
x_2	5
x_3	10
x_4	15
x_5	NA

Abbreviation: NA = not applicable.

* Different FACTS files are used when comparing to placebo and dulaglutide. When comparing to dulaglutide, $x_0 = 1$ because of limitations in FACTS.

Any missing responses for the primary outcome will be imputed using the longitudinal integrated two-component prediction (ITP) model. This is a slight deviation from the protocol, which is specified to use the Simple Linear Regression (SLR) model. The model is as follows:

$$Y_{djt} = (\omega_d + S_{dj} + \varepsilon_{djt}) \times (\frac{1 - e^{k_d t}}{1 - e^{k_d \times 26}}) = f(d,t) + (S_{dj} + \varepsilon_{djt}) \times (\frac{1 - e^{k_d t}}{1 - e^{k_d \times 26}})$$

Where Y_{djt} represents the response for dose d, subject j at time t. where time is t = 1, 2, …, 9 (1, 2, 4, 8, 12, 16, 20, 24, 26 weeks), T is the 26 week time point, patient is i = 1, …, N_d, where N_d is the number of patients for dose d, and d = 0, …, D. f(d,t) represents the mean response.

The prior distributions for time t and d = 0, …, D dose levels are as follows:

$$\begin{cases} \omega_d \sim N(\omega_\mu, \omega_\sigma^2) = N(0,3^2), \\ S_{dj} \sim N(0, \tau^2), \\ \varepsilon_{djt} \sim N(0, \lambda^2), \\ \lambda^2 \sim IG\left(\frac{\lambda_n}{2}, \frac{\lambda_\mu^2 \lambda_n}{2}\right), \\ \tau^2 \sim IG\left(\frac{\tau_n}{2}, \frac{\tau_\mu^2 \tau_n}{2}\right), \\ k \sim N(\mu_k, {\sigma_k}^2), \end{cases}$$

where $\lambda_\mu = 1$ and $\lambda_n = 1$, $\tau_\mu = 1$ and $\tau_n = 1$ and $IG(x|\alpha,\beta)$ is an inverse gamma distribution $\frac{\beta^\alpha e^{-\beta/x}}{x^{\alpha+1}\Gamma(\alpha)}$, μ_k=-0.1, and σ_k=1.

Since there are two treatment arms have titration doses, we will implement a titration ITP model for those two arms if data permits. Specifically, the mean response will be modeled as

$$f_{\boldsymbol{d},\boldsymbol{t_c}}(t) = f(t; d_1) + \sum_{i=1}^{m-1} \big(f(t - t_{ci}; d_{i+1}) - f(t - t_{ci}; d_i)\big) I(t > t_{ci}),$$

where $\boldsymbol{d} = (d_1, d_2, \dots, d_m)$ are the doses a subject takes, and $\boldsymbol{t_c} = (t_{c1}, t_{c2}, \dots, t_{c,m-1})$ are the times of the dose change.

The longitudinal ITP and Hierarchical Logistic dose-response models will be analyzed using Markov Chain Monte Carlo (MCMC). To obtain final results, at least 60 000 total MCMC iterations will be run, with at least 10 000 initial MCMC iterations being discarded as burn-in and at least 50 000 iterations used in calculations. Each iteration of the MCMC chain progresses as follows: Missing observations for the 26-week time point T are imputed for each subject at each dose level "d" using the longitudinal ITP model. These data are then used in the Hierarchical Logistic dose-response model to update θ_{dT}. Therefore, at each MCMC iteration, parameters from both the ITP model as well as the Hierarchical Logistic model will be updated. The 2 models are linked together through the missing data by imputing the missing response at the 26-week endpoint. If there was no missing data, the longitudinal model would not affect the fit of the Hierarchical Logistic model.

Primary analysis will consist of the posterior mean and 90% one-sided credible interval for the difference in mean response for each LY3298176 dose versus placebo (posterior mean and 90% credible intervals for $\theta_{dT} - \theta_{0T}$ for d = 1, ..., D-1 at the 26-week T time point). The primary objective will be met if at least 1 of the 90% credible intervals excludes -0.8% HbA1c at 26 weeks in favor of LY3298176. No adjustment for multiplicity will be performed.

Probabilities based on posterior distributions of each dose group's mean response exceeding the placebo group's mean response by clinical thresholds of interest (by -0.3%, -0.6%, and -1.2%) will be provided.

6.9.1.2. Secondary Analysis of the Primary Efficacy Outcome

This secondary analysis is to evaluate the non-inferiority of LY3298176 to dulaglutide for the change in HbA1c from baseline to 26 weeks, using the primary analysis model. This secondary objective will be met if the upper limit for the 90% credible interval for the difference between LY3298176 and dulaglutide less than 0.3% (non-inferiority margin) for at least one LY3298176 dose arm.

6.9.1.3. Supporting Analyses of Primary Outcome

The following supportive analyses will be performed for the primary outcome:

- An analysis using the same statistical model as the primary analysis will also be performed using mITT population on treatment without rescue dataset.
- The change in HbA1c from baseline will be analyzed using MMRM with restricted maximum likelihood estimation described in section 6.1.1. Comparisons between each LY3298176 dose arm with dulaglutide and placebo will be made. This analysis will be performed on three analyses sets: mITT population on treatment without rescue data, mITT population with all data, and PP dataset.
- An ANCOVA model will be used on the last observation carried forward (LOCF) endpoint of HbA1c as described in section 6.1.2. using MITT on treatment without rescue, and mITT population.

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.

Table 6.3. Summary of Analyses for Primary Outcome

Analysis Type	LOCF or Observed Values	Analysis Set
Hierarchical Logistic[a]	Observed	mITT without rescue
Hierarchical Logistic	Observed	mITT on treatment without rescue
MMRM	Observed	mITT
MMRM	Observed	PP
MMRM	Observed	mITT on treatment without rescue
MMRM, subgroup analyses	Observed	mITT on treatment without rescue
ANCOVA	LOCF	mITT on treatment without rescue, mITT

Abbreviations: ANCOVA = analysis of covariance; HbA1c = hemoglobin A1c; LOCF = last observation carried forward; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; PP = per protocol.

[a] primary analysis

6.9.2. Efficacy - Secondary Outcomes

6.9.2.1. Dose Response Analyses on HbA1c and Body Weight

Change from baseline in HbA1c at 12 weeks will be accessed using a superiority margin of -0.8% to placebo as well as a non-inferiority margin of 0.3% to dulaglutide, based on the primary analysis model.

The body weight change from baseline at both 12 and 26 weeks will compare to a superiority margin of -2 kg to placebo. Similar Bayesian dose-response analysis as for HbA1c will also be performed for the change in body weight, except with an exponential dose-response model:

$$\theta_{dT} \sim a + b * d^{\gamma} + \varsigma_{dT}, \qquad d = 0, \ldots, D-1$$
$$y_T \sim N(\theta_{dT}, \sigma^2),$$

γ is a sigmoidicity parameter indicating shape or steepness of dose response. The priors for each parameters are: α~N(0, 50), b~N(1, 10), γ~N(1, 5). Other dose-response models may be explored if the exponential dose-response model does not fit the data well. The analysis will be performed in two datasets: mITT without rescue, and mITT on treatment without rescue.

6.9.2.2. Continuous Variable Analyses

The MMRM model described in Section 6.1.1 will be performed on the following variables to obtain inference for the corresponding secondary objectives:

- Body weight change from baseline
- Change from baseline of HbA1c

- Change from baseline of FBG
- Change from baseline of waist circumference

BMI (kg/m2) 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.

6.9.2.3. Analyses Based on Multiple Imputations

The MMRM model produces consistent estimator for missing at random (MAR). To understand the key efficacy results with potential missing not at random (MNAR), analyses will be further explored using selected pattern mixture models for missing data in the mITT population for the change in HbA1c and change in body weight. In this case, the missing data will be imputed using the non-missing data in the placebo arm through a multiple imputation procedure. The imputed 26-week HbA1c or body weight response for the missing data along with the non-missing 26-week data will be employed using an ANCOVA model or MMRM model. The parameter estimates and inferences will be calculated by method of Little and Rubin (1987).

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

The proportion of patients who have ≥5% and ≥10% body weight loss will be analyzed using a longitudinal logistic regression model with treatment, strata (baseline HbA1c category, and baseline BMI category) and metformin use (yes, no), visit, and treatment-by-visit interaction as fixed effects, and baseline body weight as a covariate.

The proportion of patients who have achieved an HbA1c level of <=7% and <=6.5% at 26 weeks will be analyzed by a logistic regression with factors treatment, baseline BMI category, and metformin use (yes, no) will be fixed effects and continuous baseline HbA1c level will be a covariate. Other HbA1C categories may be added.

6.10. Safety Analyses

Safety analyses will be performed on the safety population and classified by the actual treatment group unless specified. 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; key adverse events (AEs) summaries will be presented separately for the treatment period and for the treatment period and follow-up period combined if applicable. Any events/values reported after start of rescue therapy but before the start of the follow-up period will be included in safety analyses for the treatment period.

Safety measures will include extent of exposure, vital signs, physical characteristics, treatment-emergent adverse events (TEAEs; including serious adverse events [SAEs]), adverse events of special interest (AESIs; that is, injection site reactions, hypersensitivity reactions, hypoglycemia episodes, 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). In addition, the change from baseline to 26 weeks in HDL-C, total cholesterol, triglycerides, and LDL-C will be analyzed on the mITT population.

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 lab 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; mmHg] and pulse rate [PR; beats/minute]) will be collected according to the Study Schedule of Events (Appendix 1). The average 3 measurements for BP and PR is going to 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 and dulaglutide.

The change from baseline for the above measures will be analyzed using an MMRM-based model as described in Section 6.1.1. on two analysis sets: mITT and mITT population on treatment without rescue.

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

A Bayesian analysis for pulse rate will be performed to assess the probability of the posterior distribution of the change in HR from baseline of 26 weeks for each LY3298176 treatment dose arm compared to placebo

$$\Pr(\Delta LY - \Delta Placebo \leq 10 \text{ bpm} | Data)$$

The mixed effect linear model will be used to fit the response for treatment i, subject j and time k:

$$Y_{ijk} = \mu_{ik} + s_{ij} + e_{ijk},$$

where μ_{ik} is the mean response for treatment i at time point k, and $s_{ij} \sim N(0, \sigma_s^2)$ and $e_{ij} \sim n(0, \sigma^2)$ are independent. The analysis will be performed on mITT population on treatment without rescue medication.

All vital signs and physical characteristics measurements will be listed, for all randomized patients.

6.10.2. HDL-C, Total Cholesterol, Triglycerides, and LDL-C

Change from baseline in HDL-C, total cholesterol, triglycerides, and LDL-C will be analyzed using the MMRM model described in Section 6.1.1.

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. Since the eCRF does not collect dosing time, it is acknowledged that there is a possibility that a small number of TEAEs could actually have onset prior to the time of first dose.

Adverse events will be summarized as TEAEs. Summaries of TEAEs will be presented for the combined treatment and follow-up periods, and the treatment period only.

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 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. Chi-square test will be performed for overall comparison between treatments if deemed appropriate.

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 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 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.

If data warrant, continuous elements of AESIs (such as the duration of hypoglycemaic events) will be analyzed using an MMRM-based model described in Section 6.1.1.

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 has 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 SMQ, Hypersensitivity SMQ, or Angioedema SMQ 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 event occur, then these injection site reactions may be summarized by PT using the version of Medical Dictionary for Regulatory Activities (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.

The incidence of nausea, vomiting, and diarrhea will be summarized by the treatment and the time interval of interest. The duration of each event will also be computed in days as event stop date minus event start date. For computation purposes, the end date for ongoing events is the date of last study contact.

The maximum severity and duration from baseline to Week 26 of nausea, vomiting, and diarrhea will be summarized by treatments.

Plot with the % number of subjects with the events vs initiation time course by day and week will also be generated. The y-axis is the % subjects with the specified AE and the x-axis is the time in day or week 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.

In addition, statistical analyses will be performed for the overall total hypoglycemia (occurred versus did not occur) using a logistic regression analysis with treatment, metformin use (yes, no), and HbA1c strata (<8.5%, ≥8.5%) as fixed effects.

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" **S**tandardized **M**edDRA **Q**ueries (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 26, and the maximum post-dose value will be summarized by each randomized treatment in a shift table using >1x upper limit of normal (ULN), and ≥3x 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 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 MMRM 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 <25 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 by treatment group 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, will be summarized using descriptive statistics. 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 by visit and treatment group will be summarized using sample size, frequency, and percentage.

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

A summary report and analysis for treatment-emergent abnormal laboratory values (outside the reference ranges as appropriate) for each continuous analyte by treatment will be provided. Shift tables of the change from baseline value to the maximum/minimum postbaseline value to Week 26 for selected analytes using clinically meaningful thresholds will be summarized. A shift table for ALT, 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 for all patients who meet any of the following criteria will be presented:

- Alanine aminotransferase (ALT) ≥3 × ULN
- Aspartate aminotransferase (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 bpm, QRS complex (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 HR values using Fridericia's formula (QTcF). QTcF in milliseconds (msec) will be reported. 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 for abnormal values (categorized as Low or High as shown in Table 6.5) will be provided. An MMRM-based model similar to the supportive 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; 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 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.

6.10.7. Renal Safety

To assess renal safety, a summary and analyses use similar MMRM model as the supportive analysis for primary parameter will be performed for renal functional laboratory measures: estimated glomerular filtration rate (eGFR), creatinine, urine albumin/creatinine ratio (uACR). A log transformation for the analysis of uACR may be performed.

The minimum eGFR value and the maximum creatinine, urine ACR will be used for baseline and postbaseline calculation to generate the shift table. The shift table will use eGFR cutoff (<30,

30-<60, 60-<90, and ≥90 mL/min/1.73m^2), creatinine (≤1 ULN, >1 and ≤2 ULN, >2 and ≤4 ULN, and >4 ULN), 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 26 will be summarized.

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.

6.11. Exploratory Analyses

Baseline will be the mean value of the 2 measurements prior to treatment for SMBG. The change from baseline of 7-point SMBG profiles, and PROs will be summarized and analyzed.

Immunogenicity will besummarized and analyzed .

Genetic markers will be evaluated for their contribution to the variability of LY3298176 pharmacology and will also be included as covariates in PK/PD model-based analyses if applicable.

6.11.1. 7-Point SMBG

The 7-point SMBG profile consists of pre-meal and 2-hour postprandial 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 MMRM-based model described in section 6.1.1. The corresponding baseline will be used in the

model instead of the baseline HbA1c levels. The MMRM model will include a term for the HbA1c stratification group.

6.11.2. Health Outcome/Quality of Life Measures

Health-related quality of life will be assessed using 2 self-rated questionnaires that provide standardized measures of patients' perceived current health status: the Ability to Perform Physical Activities of Daily Living (APPADL) and the Impact of Weight on Self-Perception (IW-SP) questionnaires. Patients will complete the questionnaires at specified clinic visits prior to any other visit procedures or after the patient has sufficiently recovered from the preceding visit procedures (for example, in the case of fasting).

For each questionnaire change from baseline at Week 12 and Week 26 in the transformed overall scores will be analyzed using MMRM model as described in section 6.1.1 An analysis for LOCF endpoint will also be performed.

Additional exploratory analyses may also be done to explore relationships in weight loss (such as BMI lowered by >5%) with better HbA1c, APPADL, and IW-SP.

6.11.2.1. Ability to Perform Physical Activities of Daily Living

The APPADL questionnaire is useful in evaluating weight loss interventions in individuals with T2DM. The APPADL contains 7 items that assess how difficult it is for patients to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs. Items are scored on a 5-point numeric rating scale where 5 = "not at all difficult" and 1 = "unable to do."

A raw total APPADL score is calculated by summing the scores of the 7 items and dividing by the number of items (7). The raw APPADL total score ranges from 1 to 5. A transformed overall score is obtained by linearly transforming the raw overall score to a 0-100 scale, using the following transformation formula:

$$[(\text{actual raw score} - \text{lowest possible raw score}) / (\text{highest possible raw score} - \text{lowest possible raw score})] \times 100$$

For example, using the transformation formula, a raw APPADL total score of "3.0" becomes a transformed total score of "50.0" on a scale of 0 to 100:

$$[(3.0-1.0)/(5-1)]*100 = 2/4*100 = 50.0$$

Higher raw APPADL raw total scores and higher transformed APPADL total scores indicate better self-reported ability to perform physical activities of daily living.

6.11.2.2. Impact of Weight on Self-Perception

The IW-SP questionnaire contains 3 items that assess how often the patient's body weight affects how happy they are with their appearance and how often they feel self-conscious when out in public. Items are scored on a 5-point numeric rating scale where 5 = "never" and 1 = "always."

A raw total IW-SP score is calculated by summing the scores of the 3 items and dividing by the number of items (3). The raw IW-SP total score ranges from 1 to 5. To transform the IW-SP total score to a scale ranging from 0 to 100, the same transformation formula as for the APPADL scores is used. For example, using the formula, a raw IW-SP total score of "2.0" becomes a transformed total score of "25.0" on a scale of 0 to 100:

$$[(2.0-1.0)/(5-1)]*100 = 1/4*100 = 25.0$$

Higher raw IW-SP total scores and higher transformed IW-SP total scores indicate better self-perception.

6.11.2.3. Missing Data Imputation for Ability to Perform Physical Activities of Daily Living and Impact of Weight on Self-Perception

For both the APPADL and the IW-SP questionnaires, the following rule will be applied in the case of missing item scores. If >50% of item scores are available, then missing item scores will be imputed using the mean of the available item scores. For the APPADL, this means there must be ≥4 item scores completed and for the IW-SP there must be ≥2 item scores completed. If the data for any respondent does not meet this missing data rule (>50% of item scores completed), then the questionnaire total score for that respondent will be considered missing. For analyses, missing scores will be imputed using LOCF.

6.11.3. Pharmacodynamic or Biomarker Analyses

Change from baseline to 12 and 26 weeks in fasting fibroblast growth factor-21 (FGF-21), adiponectin, β-hydroxy butyrate, glucagon, insulin levels, and other biomarkers will be analyzed and summarized using the mITT population on treatment without rescue dataset.

The change from baseline of fasting FGF-21, adiponectin, β-hydroxy butyrate, glucagon, insulin levels, and the bone biomarkers (CTX-1, PINP, Osteocalcin) will be analyzed using a similar MMRM-based model as described in section 6.1.1. A data transformation may be applied if the normality assumption is violated. If data warrant, a subgroup analysis with age >50 years women for the bone biomarkers will be performed.

Additional exploratory analyses may be performed if deemed necessary.

Additional LY3298176 concentration-response analyses of exploratory biomarkers may be performed and will be detailed in the PK modeling plan.

6.11.4. Evaluation of Immunogenicity

6.11.4.1. Definitions of Sample ADA 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

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 (ie, 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."

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.

6.11.4.2. 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 non-missing 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 includes all observations after the first administration of study drug.

6.11.4.3. 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 non-missing baseline ADA result, and at least 1 non-missing 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:

a. 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.
b. 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.

6.11.4.4. 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 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 TEAE 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

The primary efficacy measure of change in HbA1c from baseline to 26 weeks will be examined in relation to ADA. The initial examination will be boxplots of change in HbA1c at 26 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

This section provides a high level description of the population pharmacokinetic/ pharmacodynamic (PK/PD) analysis. Initially, a PK model will be developed as described in subsequent sections. PK/PD models for HR, BP, body weight, glucose and HbA1c will subsequently be developed incorporating the structural model and parameter estimates from the developed PK model. Detailed descriptions are provided in the Population PK/PD Analysis Plan.

Drug concentration data will be combined with dosing information, covariate data (eg, age, sex, weight, BMI, ethnic origin, concomitant medications, and baseline of PD variables), and the corresponding time-of-event data to produce the NONMEM dataset for population PK/PD analysis. The PD or clinical endpoints that will be analyzed may include weight, fasting glucose, HbA1c, DBP and SBP and heart-rate. If ADA titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3298176 PK or any relevant PD parameters may also be examined.

Univariate and bivariate descriptive statistics, along with plots of independent and dependent variables, will be assessed to verify appropriate data distributions and to identify potential data errors, missing data, and outliers, as described in detail in the Population PK/PD Analysis Plan.

The population PK and PK/PD dataset will be analyzed using the nonlinear mixed effects modeling program NONMEM with PREDPP. The data will be fit to provide estimates of the population PK and/or PD parameters and error terms. NONMEM uses the extended-least-squares fitting routine, which continues iteratively until a minimal value of the objective function (MOF) is reached.

Inter-subject variability will be assessed separately on each of the PK or PD parameters using an exponential error structure (ie, log-normal distribution of individual parameter values). Once inter-subject variability terms are selected, covariance between the terms may be assessed by application of the omega block. Proportional, additive, and combined proportional and additive error structures may be evaluated for the residual error. The criteria used in selecting the most

appropriate base model will be based on overall goodness of fit, MOF, and robustness of parameter estimates.

Once a structural and statistical model has been established, the effect of potential patient factors will be assessed. Potentially significant patient factors (age, weight, gender, and renal function among others) based on graphical assessment will first be tested individually for their effect on each of the relevant PK (eg, Ka, CL, V) or PD (eg, baseline, Emax, EC50) parameters. For the continuous covariates, a variety of linear and nonlinear models will be tested.

A full model will be developed by testing, in combination, those covariates individually identified as significant in the covariate selection step. Once the full model has been established, the process will be reversed. The significance of potential covariates will be confirmed by removing each covariate individually from the full model. The criterion for retention of a covariate in the final model is an increase of ≥10.828 point drop in MOF ($p<0.001$) when the covariate is omitted from the full model. In the case of physiologically related and highly correlated factors (eg, weight and BMI), only 1 of the alternative factors may be selected for inclusion.

The validity of the final model will be tested by multiple approaches. This may include but is not limited to objective function mapping, leverage analysis, and posterior predictive check.

6.13. Subgroup Analyses

The primary efficacy endpoint of HbA1c change from baseline at Week 26 will be summarized for the subgroups as defined for each of the grouping variables as follows:

- age (<65 years, ≥65 years)
- race (White, Non-White)
- ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- gender (Female, Male)
- duration (years) of T2DM, from "Date Diagnosed" to informed consent date (< study median, ≥ study median)
- baseline HbA1c (<8/5%, ≥8.5%)
- metformin use at baseline (Yes, No)
- baseline BMI (<30 kg/m^2, ≥30 kg/m^2
- country (US/Puerto Rico, Poland, Slovakia, Mexico).

If the value of a grouping variable cannot be determined for a patient, the patient will be excluded from the corresponding subgroup analysis.

The subgroup by treatment interaction will be assessed for the HbA1c endpoint with the following parameters in the ANCOVA model: baseline HbA1c (continuous), metformin use (yes, no), baseline BMI category, subgroup factor, treatment group, and subgroup-by-treatment group interaction. For subgroup analyses by baseline HbA1c, the HbA1c category (<8.5%, ≥8.5%) will be used to replace the continuous HbA1c measurement in the model. For all other subgroup variables, the categories as given above will be used to assess the subgroup-by-treatment interaction.

The adjusted mean changes from baseline, SEs, 95% CIs within each treatment group as well as the difference in mean change from baseline and corresponding 95% CIs between each investigative treatment group and the placebo for each subgroup will be calculated. In addition, the corresponding subgroup-by-treatment interaction p-value from the model will be calculated. The nominal p-values for the subgroup-by-treatment interactions will not be adjusted for multiplicity.

Change from baseline in body weight will also be analyzed for the subgroup of BMI baseline category, and HbA1C baseline category.

6.14. Interim Analyses

6.14.1. Overview

There will be up to 3 interim analyses for this study. This study will not be stopped for either positive efficacy or futility at any interim analysis.

The first interim analysis will occur after 30% patients finishing 12 weeks of treatment. It will only include key safety data (demographics, discontinuations, exposure, TEAE, AESIs, SAE, vital sign, and some lab parameters) review. The second interim analysis will occur after approximately 90% patients finish 12 weeks of treatment. It will include some key efficacy and safety parameters to monitor the compound safety and to support preliminary Phase 3 dose selection. These 2 interims will be for internal business decisions. The third interim analysis will occur when all patients have completed the treatment part of the study (prior to completion of the follow-up phase for all patients) and will include all safety, efficacy, and PK data available through the 26-week treatment for all patients to determine Phase 3 doses. We will refer this as the primary DBL.

An Assessment Committee (AC) will be formed to review the first and second interim analyses. Any change on the study design based on an interim analysis will be determined by the AC. A number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or primary outcome DBL in order to initiate population PK/PD model development processes for interim and final analyses, as well as plan and prepare for Phase 3 studies. Statistical Analysis Center (SAC) will be authorized to evaluate unblinded interim analyses and prepare the reports for the AC to review. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

All study team members will be unblinded after the primary DBL.

The study team will perform periodic, blinded safety reviews during the study and if safety signals or concerns arise from these reviews, the AC may be called upon to review unblinded safety data in an unplanned interim analysis.

6.14.2. Description of Analyses

For the first interim analyses, only some key safety parameters described in the prior section will be examined and summarized.

The second interim analysis will include the MMRM analyses for HbA1c change from baseline, and body weight change from baseline. In addition to the safety parameters summarized for the first interim, ECG data will also be analyzed.

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 Preferred Term (PT).
- For each Serious AE and 'Other' AE, for each PT and treatment group, the following will be provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event PT
    - the number of 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 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 interim analyses in support of the AC meetings.

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.

The access to subject treatment assignments will not be provided to the following personnel until the primary data lock is authorized for the third interim analysis at the completion of the treatment period:

- 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 DBL, 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 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. 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 or Lilly designated third party organization (TPO) 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 data movement group in order to generate unblinded tables, figures, and listings (TFLs) for the AC. Membership is listed in Table 7.1 for each of the groups mentioned above.

Table 7.1. Study I8F-MC-GPGB 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, CTM, data sciences and solutions, GPS 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)
SAC (unblinded)	Lilly statisticians and statistical analyst(s) or TPO statistical analysts
Unblinded PK/PD team scientists (part of the SAC)	Lilly study team PK/PD scientists and analyst(s), etc.
Assessment Committee	Lilly physicians, statisticians, and GPS personnel
Unblinded data movement group	Unblinded data movement representative
The program senior management	Lilly GIP/GLP senior medical director or above

Abbreviations: CTM = clinical trial manager; GIP/GLP = glucose-dependent insulinotropic peptide/glucagon-like peptide; GPS = global patient safety; PK/PD = pharmacokinetics/ pharmacodynamics; SAC = Statistical Analysis Center; SAE = serious adverse event; TPO = third party organization.

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 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 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, AC reports, trial-level safety review (TLSR) 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 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 the DBL. They will contain neither randomization assignments nor postrandomization 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 TPO performing the labs.

The complete list of TLSR variables include overall AEs, SAEs, TEAEs, AESIs, laboratory data, vital signs, discontinuations, concomitant medications.

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 IWRS representative, 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.

7.4.1. Interim Reports

The first interim will be safety only reviews. The second interim will include key efficacy and safety. Due to data availability, PK/PD analyses will be performed at a later time.

7.4.1.1. First Interim

The following personnel will be unblinded to the first interim data, in order to perform the data analysis, prepare the AC reports, and review/discuss the results:

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

7.4.1.2. Second Interim

For the second interim or PK/PD analyses, the following personnel will be unblinded to the PK-related data in order to develop the PK/PD modeling and/or TFLs:

- ☑ The AC (determined in AC Charter)
- ☑ SAC (Lilly or TPO study personnel)
  - ☑ Computational Statisticians
- ☑ Internal Pharmacokinetic Analysis Group (Lilly study personnel, part of the SAC)
  - ☑ Pharmacokineticist and Pharmacokinetics Analysts

7.4.1.3. Reports Delivery

The following personnel will be unblinded to the efficacy, safety, and PK data, in order to perform data analysis, prepare the interim reports, review the results, and discuss business related matters:

- ☑ AC (determined in AC Charter)
- ☑ 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: Others who don't have direct site contact may be granted access to the results with approval of program team leader.

If PK reports needs more time to be generated, this interim reviews 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.

7.4.2. Primary Lock (Third Interim)

The third interim analyses will be performed at week 26, the end of treatment period including both safety and efficacy reviews. The data will be cleaned and locked. Results will be unblinded for the study team. Lilly PK/PD scientists may obtain unblinding information before the DBL in order to perform PK/PD model-based analysis if deemed necessary.

7.5. 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

Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.

Lilly] Eli Lilly and Company, Cardiovascular Safety Advisory Committee. August 2013. Selected reference limits for pulse/heart rate, arterial blood pressure (including orthostasis), and electrocardiogram numerical parameters for use in analyses of Phase 2-4 clinical trials. Version 1.2.

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

9. Appendices

Appendix 1. Protocol GPGB Study Schedule (Schedule of Events)

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	−3	−2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study Day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		98/(15)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Administrative																		
Informed consent	X																	
Diabetes/medical history/therapy	X																	
Inclusion/Exclusion	X		X															
Preexisting conditions	X		X															
Randomization			X															
IWRS			X	X		X		X		X	X		X	X	X	X	X	X
Drug accountability				X		X		X		X	X		X	X	X	X		X
BG meter/supplies, if needed		X						X		X	X		X	X	X	X		
BG meter, instructions		X	X															
Diet, exercise, BG counseling		X																
Study diary, dispense		X	X	X		X		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	X	X	X	X
Subcutaneous injection training		X	X															

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		98/(15)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Study drug and injection supplies, dispense			X	X		X		X		X	X		X	X	X	X		
Health habits (alcohol use yes/no, tobacco use current/past)	X																	
Patient returns unused study drug supplies								X		X	X		X	X	X	X		X
Study drug, assess compliance								X		X	X		X	X	X	X		X
Patient Demographics																		
Age	X																	
Gender	X																	
Race/Ethnicity	X																	
Clinical Variables																		
Physical examination	X															X		X
Symptom-driven physical exam			X					X		X	X		X	X	X	X	X	X
Height	X																	
Weight	X		X	X		X		X		X	X		X	X		X	X	X
Waist circumference	X		X					X		X	X		X	X		X	X	X
Vital signs (BP and PR)	X		X	X		X		X		X	X		X	X		X	X	X
Antidiabetic medication	X	X	X	X		X		X		X	X		X	X	X	X	X	X
Concomitant medication	X	X	X	X		X		X		X	X		X	X	X	X	X	X

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		98/(15)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Other																		
ECGs[b]	X		X							X[c]	X[c]	X[c]				X[c]	X	X
Evaluation of Injection Site Reactions			X	X		X		X		X	X		X	X	X	X		X
APPADL and IW-SP questionnaires		X									X					X		X
Diagnostics (Safety)																		
Screening Laboratory Tests[d]	X																	
Pregnancy test[e]	X		X															
Estradiol, FSH, LH[f]	X																	
Chemistry panel	X		X					X			X					X	X	X
Lipase and amylase	X		X	X		X		X		X	X		X	X	X	X	X	X
Lipid panel	X		X					X			X					X		X
eGFR	X		X					X			X					X	X	X
Hematology	X							X			X					X	X	X
Urinalysis	X										X					X	X	X
Urine albumin, creatinine, UACR	X										X					X	X	X

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	−3	−2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		98/(15)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Diagnostics (Efficacy)																		
Calcitonin	X		X								X					X		X
HbA1c	X		X	X		X		X		X	X		X	X	X	X	X	X
Fasting glucose	X		X			X		X			X					X	X	X
Fasting insulin and c-peptide			X					X			X					X		X
Fasting glucagon			X					X			X					X		X
Total and active GLP-1/GIP			X					X			X					X	X	X
Remind Patients about 7-point SMBG		X				X				X					X	X		
7-point SMBG		X[g]						X			X					X	X	
Osteopontin, FGF-21 (active), Adiponectin, β-hydroxy butyrate, glycerol, free fatty acids, MCP-1, CTX-1, P1NP, osteocalcin			X								X					X		X

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		98/(15)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Pharmacogenetic stored samples			X															
Nonpharmacogenetic stored samples			X			X		X			X					X		
Immunogenicity testing			X	X		X		X			X					X	X	X
PK sample for Immunogenicity[h]						X[h]		X[h]									X[h]	
Pharmacokinetics (see PK schedule)[a]				X[a*]	X[a]		X[a]		X[a]	X[a*]	X[a*]	X[ac]				X[a*]		X[a]

Abbreviations: AE = adverse event; APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; d = day; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; FGF-21 = fibroblast growth factor-21; FSH = follicle-stimulating hormone; GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic peptide; HbA1c = hemoglobin A1c; IWRS = Interactive Web Response System; IW-SP = Impact of Weight on Self-Perception; LH = luteinizing hormone; PK = pharmacokinetics; PR = pulse rate; SMBG = self-monitoring of blood glucose; UACR = urine albumin-to-creatinine ratio.

* Indicates PK samples to be collected predose.

a See Pharmacokinetics Schedule of Events (Appendix 2)

b ECGs should be collected centrally at Visits 3, 10, 11, 12, 16, and 801, and locally at screening and early termination.

c ECG should be collected immediately prior to PK sample collection.

d Screening laboratory tests include serum hepatitis B surface Ag, hepatitis C antibody (Ab), and human immunodeficiency virus Ab tests for all patients.

e Serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing 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).

f Collect serum estradiol, FSH, and LH in women whose menopausal status needs to be determined.

g Two baseline collections during the lead-in period.

h PK samples specifically for immunogenicity.

Appendix 2. Protocol GPGB Illustration of PK Sampling Schedule

Study Phase	Screen	Lead-in	Randomize	Treatment Phase													Follow-up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Month of treatment		0	0	0	0	0	0	1	1	2	3	3	4	5	6	6	(7)	
Week of treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)		±7d	0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		98/(15)	140/(21)	168/(25)	182/(27)		
PK-specific visit					X		X		X			X						
PK blood draw				X*	X		X		X	X*	X*	X				X*		X

[I] Predose PK samples will be collected at Visit 4 (Week 1), Visit 10 (Week 8), Visit 11 (Week 12), and Visit 16 (Week 26). X* = Predose sample.

[II] Postdose PK samples will be collected per the assigned schedule after dosing at Visit 5 (Week 1), Visit 7 (Week 2), Visit 9 (Week 4), and Visit 12 (Week 12), and at early termination from all patients. An early termination PK sample may be taken at any time during the visit.

1. At Visit 5 (Week 1), 1 predose PK sample should be collected prior to administering study drug from all patients. Later in the week (Visit 5), an additional PK sample should be taken within 1 to 48 hours (i.e., within 2 days of administrating study drug).
2. At Visit 7 (Week 2), 1 PK sample should be collected after administration of the study drug within 1 to 48 hours (i.e., within 2 days of administrating study drug).
3. At Visit 9 (Week 4), 1 PK sample should be collected after administration of the study drug within 48 to 72 hours (i.e., 2 to 3 days after the administration of study drug) .
4. At Visit 12 (Week 12), 1 predose PK sample should be collected prior to administering the study drug from all patients. Later in the week (Visit 12), an additional PK sample should be taken within 96 to 168 hours (i.e., any time between 4 days after study drug administration up to just prior to the next dose of study drug administration)

Appendix 3. Important Protocol Deviations

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

	Important Protocol Deviation			Source of Information	Function Accountable for Identifying Deviation	Programmable/ Nonprogrammable	Excluded Per Protocol Set (Y/N/NA)	Immediate Notification (Y/N)
	Category	Sub-category	Trial-specific Term					
11	Study Procedures	Excluded Conmeds	Conmed antihyperglycemic besides metformin for more than 7 cumulative days	Mixed (monitoring and clinical database)	Stats/Site Monitor	Programmable	Y	Y
12	Study Procedures	Excluded Conmeds	Receive weight loss medication for more than 7 days during treatment phase	Mixed (monitoring and clinical database)	Stats/Site Monitor	Programmable	Y	Y
13	Study Procedures	Lab Criteria	Missing HbA1c at baseline or wk 26	Mixed (monitoring and clinical database)	Stats/Site Monitor	Programmable	Y	Y
14	Study Procedures	Lab Criteria	Missing HbA1c at wk 12	Mixed (monitoring and clinical database)	Stats/Site Monitor	Programmable	N	Y
15	Study Procedures	Other	Missing safety data for all 3:BP, Pulse, ECG's	Mixed (monitoring and clinical database)	Site Monitor	Non programmable	N	Y
16	Study Procedures	Other	Missing lab of lipase, amylase, LFTs or FBG.	Programmable (CLUWE)	CLO	Programmable	N	Y
17	Study Procedures	Other	Missing body weight or waist circumference.	Mixed (monitoring and clinical database)	Site Monitor	Non programmable	N	N
18	Investigational product	Other	IP lost or stolen	Mixed (monitoring and clinical database)	Site Monitor	Non programmable	N	Y
19	Investigational product	Dosing Error	NA	Mixed (monitoring and clinical database)	Site Monitor	Non programmable	Y	Y
20	Eligibility	Inclusion/ Exclusion	Age out of range	InForm	Site Monitor	Programmable	N	Y
21	Investigational product	Compliance	Missing greater than or equal to 4 doses	Mixed (monitoring and clinical database)	Site Monitor	Programmable	Y	Y

	Important Protocol Deviation			Source of Information	Function Accountable for Identifying Deviation	Programmable/ Nonprogrammable	Excluded Per Protocol Set (Y/N/NA)	Immediate Notification (Y/N)
	Category	Sub-category	Trial-specific Term					
22	Investigational product	Compliance	Missing greater than 2 consecutive doses and total missing less than 4 .	Mixed (monitoring and clinical database)	Site Monitor	Programmable	N	Y
22	Study Procedures	Violation of Discontinuation Criteria	Patient met criteria for permanent discontinuation of study drug & stayed on study drug	Mixed (monitoring and clinical database)	Site Monitor	Non Programmable	Y	Y

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