I8F-MC-GPGF Clinical Protocol

A Phase 2, Double-Blind, Placebo-Controlled, 3-Month Trial of LY3298176 versus Placebo in Patients with Type 2 Diabetes Mellitus.

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Protocol I8F-MC-GPGF

A Phase 2, Double-Blind, Placebo-Controlled, 3-Month Trial of LY3298176 versus Placebo in Patients with Type 2 Diabetes Mellitus

LY3298176

This is a randomized, double-blind, parallel-arm, placebo-controlled, Phase 2, multicenter study in patients with type 2 diabetes mellitus.

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Protocol Electronically Signed and Approved by Lilly on date provided below.

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1. Synopsis

Title of Study:
A Phase 2, Double-Blind, Placebo-Controlled, 3-Month Trial of LY3298176 versus Placebo in Patients with Type 2 Diabetes Mellitus

Rationale:
Study I8F-MC-GPGF is a 3-month Phase 2 study designed to examine the efficacy and tolerability of subcutaneously administered once-weekly (QW) LY3298176 compared with placebo in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control with diet and exercise alone or with a stable dose of metformin. This study will use 3 different titration schemes of LY3298176 to reach the highest planned dose. The primary endpoint will be the change from baseline in hemoglobin A1c (HbA1c) at the end of study drug treatment. Efficacy and tolerability data from this study and from the large Phase 2 study I8F-MC-GPGB (GPGB) will be used to set doses and titration scheme for the Phase 3 studies.

Objectives/Endpoints:

Objectives	Endpoints
Primary • To demonstrate that at least 1 LY3298176 titration scheme is superior to placebo in hemoglobin A1c (HbA1c) reduction at 3 months in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with diet and exercise alone or treated with a stable dose of metformin	• Change in HbA1c from baseline
Secondary <u>Efficacy</u> • To compare each titration scheme to placebo at 3 months for secondary efficacy parameters	• Proportion of patients achieving HbA1c target of <7.0% • The change in fasting blood glucose (FBG; central laboratory) from baseline • The change in body weight from baseline • The change in waist circumference from baseline
<u>Safety</u> • To compare each titration scheme to placebo for selected safety parameters at 3 months	• Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Incidence of nausea, vomiting, and diarrhea • Discontinuation of study drug due to adverse events (AEs) • Incidence and rate of hypoglycemia (severe, total, documented symptomatic, and nocturnal) • Incidence of anti-LY3298176 antibodies
<u>Pharmacokinetics</u> • To evaluate the pharmacokinetics (PK) of LY3298176	• PK trough samples

Summary of Study Design:
LY3298176 is being investigated for its potential use in the treatment of T2DM. LY3298176 is a long-acting, dual incretin receptor co-agonist that binds to both the glucose-dependent insulinotropic polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor. Study GPGF is a Phase 2, multicenter, randomized, double-blind, parallel-arm, placebo-controlled titration study designed to evaluate efficacy, tolerability, and safety of LY3298176 in patients with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy.

Treatment Arms and Duration:
Study GBGF includes 4 treatment arms: 3 titration arms of LY3298176 and matching placebo. Patients will be randomized in a 1:1:1:1 ratio to 1 of the 3 LY3298176 titration groups or placebo. Study participants will be treated for 3 months after randomization in a double-blind manner, followed by a 4-week safety evaluation.

Number of Patients:
A total of approximately 92 patients (23 patients per titration group or placebo) will be randomized, and approximately 80 are expected to complete the treatment period.

Statistical Analysis:
Efficacy: The primary analysis for the endpoint of the primary objective, change from baseline in HbA1c at 3 months, will be mixed model for repeated measures (MMRM) analysis. It will be performed on the modified intent-to-treat (mITT) analysis data set. This model will include baseline body mass index (BMI; <30, ≥30), metformin use, treatment, visit, and treatment-by-visit as fixed effects, and baselineHbA1c value as a covariate.

Additional covariates may be added and will be detailed in the statistical analysis plan (SAP).

The mean weight change from baseline at 3 months will be analyzed using similar MMRM models as the primary analysis with treatment, visit, treatment-by-visit, metformin use, baseline HbA1C category (<8.5%, ≥8.5%) as fixed effects, and baseline body weight as covariate. The change from baseline of fasting blood glucose (FBG) and waist circumference will be analyzed using a similar MMRM-based model. Summaries will include descriptive statistics for continuous measures (sample size, mean, standard deviation [SD], median, minimum, and maximum) and for categorical measures (sample size, frequency, and percentage).

Safety: The summary statistics for continuous variables will be sample size, mean, SD, median, minimum, and maximum. The summary statistics for categorical variables will be sample size, frequency, and percentage. Exposure to each therapy during the treatment period of the study will be calculated for each patient and summarized by treatment group. Additional analyses, such as concentration–safety lab plots, may be performed if warranted upon review of the data.

Pharmacokinetics (PK)/Pharmacodynamics (PD): Trough PK samples collected over the course of this study will be used to assess that LY3298176 exposures in the study are consistent with known LY3298176 PK. Additionally, PK/PD data from this study may be used as a validation dataset to enable evaluation of PK/PD models developed from the core Phase 2 study GPGB

data. These analyses may be conducted using nonlinear mixed-effects modeling implemented with the NONMEM software. If positive antibody titers to LY3298176 are observed, the relationship between antibody titer and LY3298176 PK or any relevant PD parameters will be evaluated.

2. Schedule of Activities

Table GPGF.1. Schedule of Activities

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

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

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

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

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

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

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

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

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

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

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

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

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

3. Introduction

3.1. Study Rationale

Study I8F-MC-GPGF (GPGF) is a 3-month Phase 2 study designed to examine the efficacy, safety, and tolerability of subcutaneously administered once-weekly (QW) LY3298176 administered in 3 different titration schemes compared with placebo in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control with diet and exercise alone or with a stable dose of metformin monotherapy. The primary endpoint will be the change in hemoglobin A1c (HbA1c) at the end of study drug treatment. These data will support selection of doses and a titration scheme to attain the highest dose for Phase 3 trials.

3.2. Background

CCI

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of LY3298176 may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs that are expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate, periodically during the course of the study, and may be found in Section 6 (Effects in Humans) of the IB.

4. Objectives and Endpoints

Table GPGF.2 shows the objectives and endpoints of the study.

Table GPGF.2. Objectives and Endpoints

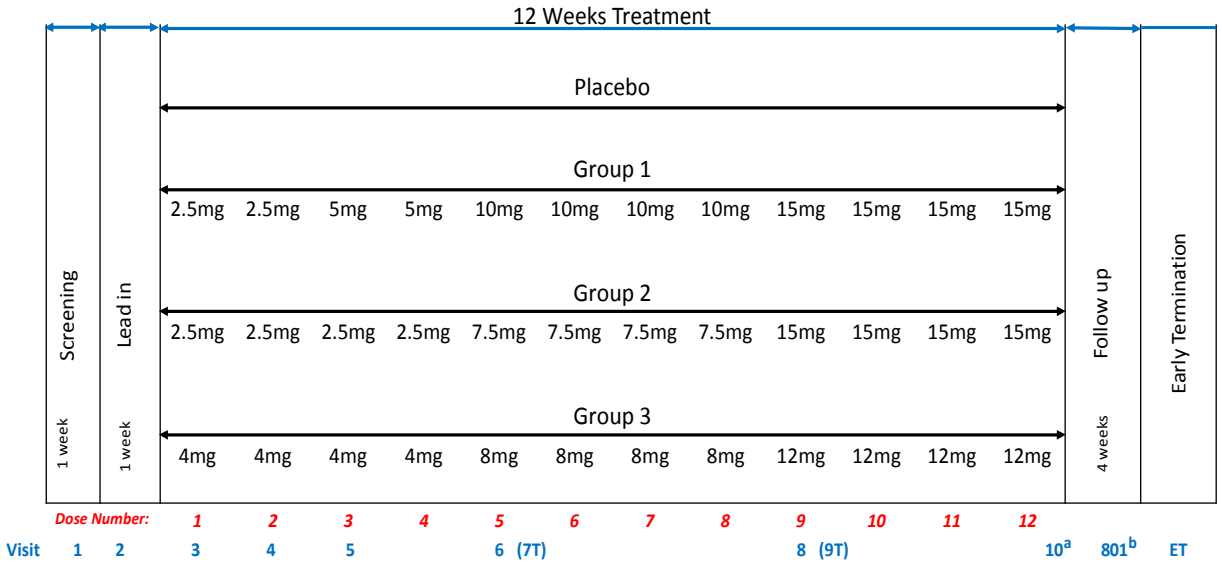
Objectives	Endpoints
Primary • To demonstrate that at least 1 LY3298176 titration scheme is superior to placebo in HbA1c reduction at 3 months in patients with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin	• Change in HbA1c from baseline
Secondary <u>Efficacy</u> • To compare each titration scheme to placebo at 3 months for secondary efficacy parameters <u>Safety</u> • To compare each titration scheme to placebo for selected safety parameters at 3 months <u>Pharmacokinetics</u> • To evaluate the PK of LY3298176	 • Proportion of patients achieving HbA1c target of <7.0% • The change in FBG (central laboratory) from baseline • The change in body weight from baseline • The change in waist circumference from baseline • TEAEs and SAEs • Incidence of nausea, vomiting, and diarrhea • Discontinuation of study drug due to AEs • Incidence and rate of hypoglycemia (severe, total, documented symptomatic, and nocturnal) • Incidence of anti-LY3298176 antibodies • PK trough samples
Exploratory • To compare each titration scheme to placebo at 3 months for effect on SMBG profile.	• SMBG values at baseline and end of treatment.

Abbreviations: AE = adverse event; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; PK = pharmacokinetics; SAE = serious adverse event; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study GPGF is a randomized, multicenter, placebo-controlled, double-blind, parallel arm, Phase 2 titration study in T2DM patients who have inadequate glycemic control with diet and exercise with or without a stable dose of metformin monotherapy. The study is designed to measure the change in HbA1c at the end of study treatment compared with placebo. These data will support dose selection and the optimal titration scheme that minimizes GI-related AEs for Phase 3 trials. The study will consist of 3 treatment periods: approximately 1-week lead-in period, followed by a 3-month treatment period, and a 4-week safety follow-up period (see Figure GPGF.1). 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 and placebo treatment assignments within each titration group.



T = Telephone Visit; Visit 801 = End of Study Visit; ET = Early Termination Visit
a = Visit 10 occurs 1 week after the last dose (Dose 12) of study drug.
b = Visit 801 (follow up visit) occurs 4 weeks after Dose 12 or 3 weeks after Visit 10.

Figure GPGF.1. Illustration of study design for clinical protocol I8F-MC-GPGF.

Study Period I (Screening and Lead-In):

Screening (Visit 1)

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.

The purpose of screening procedures at Visit 1 is to establish initial eligibility (see Section 6) and to obtain blood samples for laboratory assessments needed to confirm eligibility. Patients who meet all applicable inclusion criteria and none of the applicable exclusion criteria at Visit 1 will continue on to Visit 2.

Lead-In (Visit 2 to Visit 3)

During the lead-in period, eligible patients should continue their prestudy therapy, metformin (same formulation and dose), in order to allow reliable assessment of HbA1c at baseline (Visit 3). During the lead-in period, patients will be trained on disease monitoring and disease management procedures, glucometer use, study diaries, and study procedures. Patients will receive training on routine blood glucose monitoring and paper diary completion required during the study. Patients should follow the investigator's instructions related to frequency of blood glucose testing but should test their glucose a minimum of 3 times per week. Patients will also be required to conduct a 7-point self-monitoring glucose test (SMBG) prior to randomization (Visit 3) and return the results in their diary at Visit 3 (see Section 9.1.2.1). Patients will also receive education on how to dilute study drug in the vials, perform SC injections, appropriate injection site locations, injection technique, and the signs and symptoms of local adverse reactions including injection site reactions. Patients will receive instructions on timing of doses (Table GPGF.3 and Section 7.1), and will be instructed to record the date and time of all injections administered throughout the study in their study diaries. Study site staff will observe each patient diluting the study drug vials and self-injecting for training purposes at all site visits beginning with Visit 3.

Visit-specific subject diaries will be dispensed at Visit 2 and at each visit thereafter, until the last study visit (see Schedule of Activities, (Section 2). Patients should be instructed to record all AEs in their diaries.

Study Period II (Treatment Period):

Randomization (Visit 3)

At Visit 3, patients will undergo study procedures that are required prior to randomization.

Patients who continue to be eligible will then be randomized in a 1:1:1:1 ratio to 1 of the titration schemes (Group 1, Group 2, or Group 3) or placebo. Placebo patients will be distributed within each titration group in order to maintain treatment blinding. After randomization, the patient will dilute the study drug vial and inject the first dose of study drug while at the study site. Although patients will be diluting study drug and injecting themselves at home between study site visits, they will be required to dilute the vials and inject themselves under the supervision of site

personnel at every scheduled site visit. However, unscheduled visits to help patients with diluting study drug in the vials and self-injecting are permitted whenever the patient needs or wants additional support.

Following randomization, patients will participate in a 3-month treatment period that consists of dose titrations to reach and maintain the highest scheduled dose level of LY3298176.

Treatment Phase (Visit 3 to Visit 10)

During the treatment phase, the dose of LY3298176 will be escalated within each titration group according to 1 of 3 dose titration schedules as outlined in Figure GPGF.1.

At each dosing time point, the study drug will be self-administered as 1 to 3 SC injections of LY3298176 or matched placebo (number of injections will be determined by where the patient is in the dose titration scheme) (see Section 7.1).

The last treatment visit, Visit 10, will occur approximately 1 week after the last dose of study drug for collection of efficacy and safety parameters.

In addition to the clinic visits, 2 telephone visits will be scheduled during this period and will occur 3 to 6 days after a site visit for dose escalation and will be scheduled to occur prior to the next dose administration. At the telephone visit, the site is to check on the patient and ask if the patient needs to come to the site for an unscheduled visit for help with diluting and self-injecting the study drug. Patients are also to be reminded to write down any AEs in their study diaries. At each of the scheduled site visits, procedures will include assessments of study drug compliance, hypoglycemic events, concomitant medications, and AEs.

General Considerations

At each visit, patients should be reminded to write down any AEs in their study diaries, including any events associated with self-injecting study drug when at the study site visit.

Patients will undergo or perform study procedures listed in the Schedule of Activities (Section 2).

Patients taking a stable dose of metformin at study entry will continue to use concomitant metformin throughout the treatment period. Discontinuation or changes to dose are generally not permitted, except in the situations of patient safety (for further details, see Section 7.1).

Patients will be instructed to perform fasting blood glucose (FBG) measurements and to record all results in diaries; these results will be used for glucose management only.

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Section 9.2.1.2.4) will receive a new glucose-lowering intervention (or rescue therapy) based on clinical judgment of the investigator, and the patient will discontinue study drug. Patients who need rescue therapy for this reason will be asked to remain in the trial until they complete all study visits for collection of safety information. Patients who discontinue study drug due to AEs will also be asked to continue in the trial for collection of safety information. Patients who are unable or unwilling to continue in the study because of an AE or any other reason will perform

an early termination (ET) visit as their final study visit. If the patient is discontinuing during an unscheduled visit, that visit should be performed as the ET visit. If the patient is discontinuing during a scheduled visit, that visit should be considered the ET visit. At this visit, patients will perform procedures listed in the Schedule of Activities (Section 2).

Study Period III (Safety Follow-Up, Visit 801):

All randomized patients who complete the treatment period will complete the safety follow-up approximately 4 weeks after their last visit on treatment.

Patients randomized to LY3298176 who have treatment-emergent anti-LY3298176 antibodies or antibodies to native GIP or GLP-1 at the last visit may be monitored after the last visit (see Section 9.9).

5.2. Number of Participants

Approximately 150 participants will be screened to achieve 92 randomized and 80 evaluable participants for an estimated total of 20 evaluable participants per treatment group.

5.3. End of Study Definition

End of the trial is the date of the last visit or last scheduled visit shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

Study GPGF is a 3-month Phase 2 study designed to evaluate the efficacy, safety, and tolerability of 3 different titration schemes of LY3298176 compared with placebo in patients with T2DM inadequately controlled with diet and exercise with or without stable metformin monotherapy.

The titration algorithms to be used in Study GPGF have been chosen based on tolerability data from the Phase 1 study GPGA, and the highest dose and dose titration scheme being evaluated in the Phase 2 study GPGB. Study GPGF is designed to explore titration schemes different from those in Study GPGB. In Study GPGB, the 15 mg dose is attained using a dose titration of 5 mg for the first 2 weeks, followed by 10 mg for 4 weeks, before reaching 15 mg at Week 7. This approach for titrating a drug with GLP-1 RA activity is expected to allow patients to reach the 15 mg dose with minimal GI-related AEs. However, there may be other titration schemes that that are superior for minimizing the GI-related AEs that were observed in the Phase 1 study GPGA at the 15 mg dose. It is possible that giving patients a very low first dose of 2.5 mg may improve tolerability of higher doses; thus, a 2.5 mg dose will be utilized in Study GPGF. Study GPGF also contains 1 titration scheme with the highest LY3298176 dose level of 12 mg. The 12 mg dose was chosen in order to compare the tolerability and efficacy of 12 mg with 15 mg. The 12 mg dose may provide efficacy similar to that of the 15 mg dose but with superior tolerability, and this titration scheme provides additional data for dose and dose titration decisions for Phase 3. Efficacy, safety, and tolerability data from both Study GPGB and Study GPGF will be used to set doses and the titration scheme for the Phase 3 development program.

The current study will enroll patients with inadequate glycemic control based on HbA1c values ranging from 7.0% to 10.5%, inclusive. Similar ranges of screening HbA1c have been used in numerous studies of T2DM treatments.

Patients treated with diet and exercise alone, or in combination with stable metformin monotherapy (≥1000 mg/day), will be enrolled. Patients on a second oral antihyperglycemic medication (OAM) may also be eligible if the second OAM was discontinued ≥3 months prior to Visit 1 (refer to Section 6.2, Exclusion Criterion 35). Stable metformin treatment for at least 3 months is required to minimize glucose variability prior to study entry.

5.5. Justification for Dose

The highest dose to be evaluated in Study GPGF is 15 mg, which is the highest dose being evaluated in the Phase 2 study GPGB. Depending on the safety, tolerability, and efficacy data in Study GPGB, the LY3298176 15 mg dose may be the high dose tested in the Phase 3 program. The 15 mg dose was considered safe in the Phase 1 study GPGA although not well tolerated. Based on experience with other GLP-1 RAs, higher doses may be attained through dose titration to minimize GI-related AEs. The 3 titration schemes to reach either LY3298176 12 mg or 15 mg were selected based on the following:

- Phase 1 tolerability data in T2DM patients utilizing the dose titration scheme of QW LY3298176 doses of 5 mg for the first 2 weeks, 10 mg for the third week, and 15 mg the fourth week showed that this titration scheme to reach 15 mg was too rapid and resulted in more incidents of vomiting following the 15 mg dose than had been observed with other titration schemes with lower LY3298176 doses. Thus, a more gradual titration may be needed to reach 15 mg.
- The current titration scheme for Study GPGB is LY3298176 5 mg for the first 2 weeks, followed by 10 mg for 4 weeks before reaching the first 15 mg dose at Week 7, and continuing on 15 mg for the duration of the study. This titration scheme is expected to be tolerated; however, other titration schemes may have improved tolerability or patient and physician convenience. This will be explored in different titration schemes in Study GPGF.
- It is possible that a slightly lower dose (>10 mg but <15 mg) would have improved tolerability with comparable efficacy compared with 15 mg. Therefore, LY3298176 12 mg was chosen as the high dose for 1 titration scheme.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Type of Patient and Disease Characteristics

[1] Have T2DM for at least 6 months before screening based on the disease diagnostic criteria (Appendix 5).

[2] Have an HbA1c value at screening of ≥7.0% and ≤10.5% and treated with diet and exercise alone or a stable dose of metformin (either immediate release or extended release, ≥1000 mg/day and not more than the locally approved dose) for at least 3 months prior to screening/Visit 1.

Patient Characteristics

[3] Male or female patients 18 to 75 years of age, inclusive.

[3a] Male patients:

Male patients should be willing to use reliable contraceptive methods throughout the study and for at least 3 months after last injection (see Appendix 6).

[3b] Female patients:

Women not of child-bearing potential may participate and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
- postmenopausal – defined as
  - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either cessation of menses for at least 1 year; or
  - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) >40 mIU/mL; or
  - A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
  - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Women of child-bearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) may participate. In order to participate, they must:

- Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.
- Otherwise, women of child-bearing potential participating must agree to use 1 highly effective method (<1% failure rate) of contraception, or a combination of 2 effective methods of contraception for the entirety of the study:
  - Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit and followed by a negative urine pregnancy test within 24 hours prior to exposure. (Any pregnancy testing subsequent to this initial test should be based on compound specific concerns and is not mandated by this guidance.)
  - Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
- Not be breastfeeding.

[4] Have a body mass index (BMI) between 23 and 45 kg/m^2 (inclusive) at screening.

Informed Consent

[5] In the investigator's opinion, are well motivated, capable, and willing to:

- prepare (with assistance if necessary) study medication
- self-inject (with assistance if necessary) up to 3 injections each week
- complete study diary(ies), as required for this protocol
- are receptive to continuing their prestudy diet, activity levels, and follow simple dietary advice as appropriate
- perform SMBG using the provided glucose meter.

[6] Be willing to maintain metformin dose during the trial, if taking a stable dose of metformin at study entry. Patients experiencing hypoglycemia during the study may have their metformin dose reduced.

[7] Are reliable and willing to make themselves available for the duration of the study, and who will comply with the required study and dosing visits and abide by the clinical research site policy and procedure and study restrictions.

[8] Are able and willing to give signed informed consent and have given written informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing their site.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

[9] Have type 1 diabetes mellitus or latent autoimmune diabetes in adults.

[10] Have uncontrolled diabetes defined as an episode of ketoacidosis or hyperosmolar state requiring hospitalization.

[11] Have had an episode of severe hypoglycemia, as defined by the occurrence of neuroglycopenic symptoms requiring the assistance of another person for recovery, within 6 months prior to Visit 1, or have a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any patient that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded.

[12] Have a history of acute or chronic pancreatitis or elevation in serum lipase/amylase (greater than 2 times the upper limit of normal [>2× ULN]) or fasting serum triglyceride level of >500 mg/dL at screening.

[13] Have a diagnosis of gastroparesis or history of bariatric surgery or a clinically significant gastric emptying abnormality, in the opinion of the investigator.

[14] Have active proliferative diabetic retinopathy.

[15] Have known liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or alanine aminotransferase (ALT) levels >2.5× ULN at Visit 1, as determined by the central laboratory at screening.

[16] Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.

[17] Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to patient safety. Subjects on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.

[18] Have a screening calcitonin ≥20 pg/mL as determined by the central laboratory at Visit 1.

[19] Have had any of the following within the last 6 months prior to screening: myocardial infarction (MI), unstable angina, coronary artery bypass graft, percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischemic attack (TIA), cerebrovascular accident or decompensated congestive heart failure, or currently have New York Health Association Class III or IV heart failure.

[20] Have an electrocardiogram (ECG) with abnormalities that may interfere with the interpretation of changes in ECG intervals at screening in the opinion of the investigator. A QTc (Fridericia) interval >450 ms in men and >470 ms in women is specifically excluded.

[21] Known significant autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea.

[22] Have a personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, sibling, or children) before the age of 40 years, or a personal history of unexplained syncope within the last year. Use of prescription or over-the-counter (OTC) medications known to significantly prolong the QT or QTc interval at screening is prohibited.

[23] Have poorly controlled hypertension (ie, mean seated systolic blood pressure [BP] ≥160 mm Hg or mean seated diastolic BP ≥95 mm Hg) at screening, or a change in antihypertensive medications within 30 days of screening, renal artery stenosis, or evidence of labile BP including symptomatic postural hypotension.

[24] Random fasting triglycerides >500 mg/dL (5.7 mmol/L). If the patient is on lipid-lowering therapies, doses must be stable for 30 days prior to screening.

[25] Have an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, as determined by the central laboratory at Visit 1, or a level of eGFR that would contraindicate the use of metformin per the label in the respective country. Patients on metformin must meet local label requirements.

[26] Have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).

[27] Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for <5 years prior to screening.

[28] Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies historically or at screening.

[29] Evidence of hepatitis B and/or positive hepatitis B surface antigen or evidence of active hepatitis C.

[30] Have a history of a transplanted organ (corneal transplants [keratoplasty] allowed).

[31] Have evidence of a significant active, uncontrolled medical condition or a history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the screening investigator at screening.

[32] Have had a significant change in weight, defined as a gain or loss of at least 5% body weight in the 3 months prior to screening.

[33] Have had a blood donation of ≥450 mL in the prior 3 months of screening or any blood donation within the prior month, or a blood transfusion or severe blood loss within the prior 3 months, or have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c methodology.

[34] Have any other condition (including known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol.

Prior/Concomitant Therapy

[35] With the exception of stable doses of metformin, patients on another OAM (including, but not limited to, sulfonylureas, dipeptidyl peptidase-4 inhibitor [DPP-4i], sodium–glucose cotransport 2 inhibitors, alpha-glucosidase inhibitors, meglitinides) in addition to metformin therapy may be randomized if the additional OAM treatment was discontinued at least 3 months prior to screening.

[36] Have used insulin for diabetic control within the prior year; however, short-term use of insulin for acute conditions is allowed (≤14 days) in certain situations, such as during a hospitalization or perioperatively (see Section 7.7).

[37] Have had any exposure to GLP-1 analogs or other related compounds within the prior 12 months or any history ever of allergies to these medications. Patients who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability or lack of efficacy should not be randomized.

[38] Have been treated or plan to be treated with drugs that promote weight loss (eg, Saxenda [liraglutide 3.0 mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion] or similar other body weight loss medications including OTC medications [eg, allī®]) within 3 months prior to Visit 1.

[39] Are receiving chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have received such therapy within 4 weeks immediately prior to screening.

[40] Are currently taking a central nervous system stimulant (eg, Ritalin-SR®) with the exception of caffeinated beverages at screening.

[41] Within 30 days of the initial dose of study drug, have received treatment with a drug that has not received regulatory approval for any indication. If the previous study drug has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[42] Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) [1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits].

[43] Evidence of regular use of known drugs of abuse in the opinion of the investigator.

Prior/Concurrent Clinical Trial Experience

[44] Have previously completed or withdrawn from this study or any other study investigating LY3298176.

[45] Previous exposure or known allergies to LY3298176.

[46] Are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other Exclusions

[47] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[48] Are Eli Lilly and Company employees or are employees of any third party involved in study who require exclusion of their employees.

[49] Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study or for 60 days following the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened only once at the discretion of the investigator. Before rescreening is performed, the patient must sign a new informed consent form (ICF) and receive a new identification number. If, in the opinion of the investigator, an ineligible lab test result is the result of an error or extenuating circumstance, then that parameter can be retested once (if feasible within the time constraints of the screening period) without the patient having to be rescreened. However, screen failures for HbA1c may not be retested or rescreened.

7. Treatments

7.1. Treatments Administered

In this study, patients will receive treatment with 1 of 3 LY3298176 titration schemes for 3 months to assess the reduction in HbA1c compared with placebo. The titration doses of LY3298176 will range from 2.5 mg through 15 mg to reach either 12 mg or 15 mg as the highest titrated maintained dose. Study drug will be supplied as lyophilized drug in a vial and each vial will contain 5 mg. There will be matching placebo vials. Patients will receive 1 to 3 injections of study drug per week depending on which dose the patient is scheduled to receive in the titration schedule. At the highest dose attained, 12 mg or 15 mg, patients will receive 3 injections per week (to be taken at the same time). Each SC dose administration of study drug should be in different quadrants of the abdomen. If the recommendation following the first interim analysis of Study GPGB is to lower the highest dose of 15 mg to 12.5 mg, then the highest dose administered for Groups 1 and 2 of this study, GPGF, will also be lowered to 12.5 mg from 15 mg. The high dose for Group 3, 12 mg, will be unchanged. If this change occurs, it will be prior to the first patient visit for Study GPGF. Furthermore, patient user materials will be modified to indicate that the highest titrated LY3298176 dose for Groups 1 and 2 will be 12.5 mg.

This study will involve dose titration in 2.5 mg, 4 mg, 5 mg, or 7.5 mg dose increments (Table GPGF.3). Although the investigators and patients will know which titration group the patients are assigned, they will not know whether they are receiving LY3298176 or a complementary volume of placebo.

Patients will be required to dilute study drug in the vials and administer injections of the study drug or matching placebo at approximately the same time each week. The study site will send vials, diluent (Sterile Water for Injection), and syringes with needles home with patients. For all clinical site visits, the patient should dilute the vials and administer the study drug at the clinical research site under the supervision of study personnel in order to reinforce patient understanding and confidence. Patients will be diluting study drug in the vials and self-injecting at home during weeks without a clinical site visit and instructions will be provided. The investigator or site staff may assist patients with vial reconstitution and study drug injection any time they deem necessary.

Table GPGF.3. Study Treatments and Dose Titration

Study Phase	Random-ization	Treatment Phase										
Visit	3	4	5	N/S	6	N/S	N/S	N/S	8	N/S	N/S	N/S
Week	0	1	2	3	4	5	6	7	8	9	10	11
Dose number	1	2	3	4	5	6	7	8	9	10	11	12
Titration schemes (dose in mg)												
Group 1	2.5	2.5	5	5	10	10	10	10	15	15	15	15
Group 2	2.5	2.5	2.5	2.5	7.5	7.5	7.5	7.5	15	15	15	15
Group 3	4	4	4	4	8	8	8	8	12	12	12	12

Abbreviation: N/S= none scheduled.

Note: For each of the groups, visits are scheduled to occur on the day of the next scheduled titrated dose. For non-scheduled visits, it is expected that the patient will dilute study drug and self-inject at home. However, the investigator may have the patient come to the site for an unscheduled visit to dilute the vials and self-inject at any time the investigator feels that the patient would benefit from added instruction and supervision. Visit 10 (not shown) will occur 1 week after the last dose of study drug (Dose 12).

Patients taking background metformin (either immediate release or extended release) are strongly encouraged to remain on the same type of metformin during the trial, if possible. Changing formulations or manufacturers of metformin during the study participation should be minimized. If a dose change (ie, conversion of extended release to immediate release or vice versa) is required, the investigator should determine the most appropriate clinically equivalent metformin dose. The metformin dose should be at least 1000 mg/day and not more than the highest dose allowed per local label.

The patient receiving metformin should continue the baseline dose of metformin, unless the patient experiences documented hypoglycemia, in which case the dose may be reduced.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agents to the patient or the patient's legal representative
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law.

Patients will be instructed to contact the investigator as soon as possible if he/she has a complaint or problem with the study drug so that the situation can be assessed.

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the regulatory requirements. LY3298176 and the matched placebos will be supplied by Lilly. CCI [redacted]

CCI [redacted] Patients will inject the dose volume appropriate for their treatment group, including placebo patients within a group. LY3298176 vials must always be stored in a secure location with access limited to designated study staff members.

Instructions for the reconstitution of study drug will be provided separately to each patient and the investigator. CCI [redacted] The reconstituted LY3298176 or placebo solution should be used immediately after reconstitution.

Study drug must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). Temperature logs must be maintained to verify correct storage conditions at the investigator site, throughout the study. Patients should be instructed to store the study drug in their refrigerator but are not required to maintain temperature logs. Sterile water vials may be stored at room temperature.

7.1.2. Medical Devices

The manufactured medical devices provided for patient use in the study are glucose meters and lancet devices.

7.2. Method of Treatment Assignment

A unique 4-digit patient number will be assigned to each patient when the patient signs the ICF.

Patients will be assigned to placebo or 1 of 3 LY3298176 titration groups. Patients who meet all criteria for enrollment will be randomized at Visit 3 and assigned to their respective treatment arms via IWRS using the following stratification variables: baseline HbA1c (<8.5%, ≥8.5%), metformin use (Yes, No), and BMI (<30, ≥30). There will be approximately an equal randomization to the treatment arms (1:1:1:1).

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

7.2.1. Selection and Timing of Doses

Assignment to 1 of 3 LY3298176 titration groups or placebo will occur at randomization. There are no restrictions on the time of day each QW dose is given, but it is advisable to administer SC injections on the same day and same time each week. Patients should be instructed to record the actual date and time of all dose administrations in the diary provided. The actual date and time of all dose administrations will be recorded in the subject's case report form (CRF). If a dose of study drug, including placebo, is missed, the patient should take it as soon as possible and contact the study site for further instructions on timing of the next scheduled dose.

7.2.2. Specific Restrictions/Requirements

Prior to beginning the study, patients will complete informed consent and baseline tests.

Throughout the study, patients may undergo medical assessments and compliance reviewed before continuing in the study.

Patients will report to the clinical research site for safety assessments and will remain in the clinic until all procedures for that visit are complete and the investigator has deemed it safe to release the patient from the clinic. There will be no inpatient stays.

Meals/Diet – Patients shall fast for at least 8 hours overnight prior to each outpatient visit where fasting samples are drawn or weight measurements taken.

Alcohol – Alcohol will not be permitted 8 hours prior to the dosing day, until the patient has been discharged from the clinical research site.

Exercise – Patients will be advised to maintain their regular levels of physical activity/exercise during the study. When certain study procedures are in progress at the site, patients may be required to remain recumbent or sitting.

Blood donation – Study participants should be instructed not to donate blood or blood products during the study or for 8 weeks following the study.

Contraception – Male patients or their female partners of child-bearing potential must use reliable contraception during intercourse throughout the treatment period and for 3 months after the last dose of study drug as the risk of LY3298176 to the unborn fetus is unknown. Female patients of child-bearing potential, if sexually active, should use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the trial and for 30 days thereafter. Please see Appendix 6 for further details regarding contraception.

7.3. Blinding

This is a double-blind study. Although the patient and the investigator will know which dose titration group (Group 1, Group 2, or Group 3) the patient is assigned to, they will not know whether the patient is receiving LY3298176 or placebo.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency codes, generated by a computer drug-labeling system, will be available to the investigator. These codes, which reveal the patient's treatment group when opened, may be opened during the study ONLY if the patient's well-being requires knowledge of the patient's treatment assignment.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient

remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP)/clinical research scientist (CRS) for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. Patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dosage Modification

Generally, no adjustment in study drug doses (LY3298176 or placebo) will be allowed. However, if a patient is unable to tolerate a titrated dose for 2 weeks due to vomiting or moderate to severe nausea, the site should call the study CRS/CRP to discuss whether the patient should have the dose lowered to the previous dose level. Dosing of required concomitant metformin is discussed in Section 7.7.

The highest dose of Groups 1 and 2, LY3298176 15 mg, may be reduced to 12.5 mg prior to first patient visit of this study, GPGF, if the first interim analysis of the large Phase 2 study GPGB indicates that the 15 mg dose is not well tolerated. In that case, sites will be informed at the start-up meeting and in training materials. Patients will be provided dosing instructions for the 12.5 mg dose rather than the 15 mg dose.

7.5. Preparation/Handling/Storage/Accountability

The study site must store the study drug in a locked and secure environment. The study drug must be refrigerated (not frozen) at 2°C to 8°C. Dry ice should not be used for cooling. Patients will be provided with double-blinded vials containing lyophilized LY3298176 or placebo and Sterile Water for Injection (along with syringes), at clinic visits according to the Schedule of Activities (Section 2). The patients will also receive insulated bags with cooling gel packs for use in transporting the study drug from the site to the home. Study drug in each participating country will be labeled according to the country's regulatory requirements.

Commercial metformin may be made available during the treatment period to patients who entered the trial on this agent. Appropriate use and storage information will be available by referring to the package insert.

7.6. Treatment Compliance

During the study, patients will be asked to return their study drug vials and completed diaries to the site so that their compliance may be assessed.

Patients who are significantly noncompliant will be permanently discontinued from study medication. A patient will be considered significantly noncompliant if he/she misses ≥2 doses of study medication. Similarly, a patient will be considered significantly noncompliant if he/she is

judged by the investigator to have intentionally or repeatedly taken more or less than the prescribed amount of medication.

7.7. Concomitant Therapy

Treatment with drugs that are excluded in the entry criteria (Section 6.2) is not permitted.

The only concomitant antihyperglycemic medication permitted during this study is metformin, unless glycemic criteria for rescue therapy are met (see Section 7.8.1). Metformin treatment must be stable for at least 3 months prior to screening at a daily dose of ≥1000 mg/day. Patients who enter the study on diet and exercise alone will not be allowed to initiate metformin therapy after study entry unless criteria for rescue therapy are met.

Patients who are being treated with metformin upon entering this study should remain on the same (or equivalent if switching to sustained release) metformin dose throughout the course of the study unless a change in dose is required to protect patient safety.

If a patient switches from the immediate-release formulation of metformin to the sustained-release formulation, the change will be on a milligram-per-milligram basis.

In certain situations (such as during a hospitalization or perioperatively), it may be necessary for a patient to be treated with insulin(s). Treatment with insulin will be allowed for up to 14 consecutive days prior to or during the trial. If a patient requires treatment with insulin for >14 consecutive days, that patient will be considered a "rescue" patient and may remain in the study but will not receive additional study drug.

Doses of antihypertensive and lipid-lowering therapies must be stable for 30 days prior to screening. Doses of antihypertensive and lipid-lowering agents should not be changed during this study unless necessary to protect patient safety on an emergency basis (eg, hypertensive crisis).

Doses of other prescription medications (eg, thyroxine, estrogen or progesterone replacement, or selective estrogen receptor modulators) for treatment of concurrent medical conditions should remain constant during the study whenever possible.

If the need for additional concomitant medication arises, the patient may be continued in the study on study medication if, in the investigator's opinion, the addition of the new medication does not pose a safety risk. If an additional concomitant medication is started, the sponsor should be informed as soon as possible. Nausea and/or vomiting during this study may be treated with antiemetics but should not be used prophylactically. Nonsteroidal anti-inflammatory medications (including ibuprofen, aspirin), acetaminophen, cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis without notifying the sponsor and are not restricted by the stable dosing requirements listed above. Any additional medication used during the course of the study (including those not requiring sponsor notifications) must be documented on the appropriate electronic case report form (eCRF).

Specifically excluded concomitant medications include the following:

- Chronic use of drugs that directly reduce GI motility including but not limited to anticholinergics, antiemetics, and opiates (eg, metoclopramide, phenergan, dicyclomine, and morphine)
- Chronic use of medications that directly promote motility (eg, bethanechol and cisapride)
- Prescription or OTC medications to promote weight loss
- Systemic glucocorticoid therapy of >14 consecutive days' duration (with the exception of topical, intranasal, intraocular, intra-articular, and inhaled preparations)
- Central nervous system stimulants (eg, Ritalin-SR)
- Any drug, other than those provided in this study, that has not received regulatory approval.

7.8. Treatment after the End of the Study

7.8.1. Special Treatment Considerations (Rescue Therapy)

Investigators will be trained on how to apply decision criteria for the timing and method of intervention in patients who do not reach glycemic targets during the 12-week treatment period. An additional therapeutic intervention should be considered in patients who meet the following criteria:

- The patients are fully compliant with assigned therapeutic regimen.

  AND

- In the absence of any acute condition that raises blood glucose either of the following occurs:
  - During the first 6 weeks post-randomization: An average fasting glucose level >270 mg/dL (15.0 mmol/L) occurs over at least a 2-week period (at least 3 values/week must be available).

    OR

  - Any time after the first 6 weeks post-randomization: An average fasting glucose level >240 mg/dL (13.3 mmol/L) occurs over at least a 2-week period (at least 4 values/week must be available).

If these conditions are met, then patients may begin treatment with another antihyperglycemic agent as determined by their physician. If treatment with another antihyperglycemic agent is instituted, then study drug should be permanently discontinued. Patients may remain in the study for safety follow-up, but the date at which they begin rescue therapy will be the last date for collection of efficacy measures.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via case report form (eCRF).

  Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:

  - Abnormal liver tests or when a patient meets one of the following conditions:
    - ALT or aspartate aminotransferase (AST) >8× ULN
    - ALT or AST >5× ULN for >2 weeks
    - ALT or AST >3× ULN and total bilirubin level >2× ULN or prothrombin time >1.5× ULN
    - ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
    - Alkaline phosphatase (ALP) >3× ULN
    - ALP >2.5× ULN and total bilirubin >2x ULN
    - ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Investigator decision
  - The investigator decides that the patient should be discontinued from the study medication.
- Any medication for weight loss is given for >1 week.
- Adverse event.
- When any one of the following events occur, Lilly or its designee is to be alerted immediately:
  - Pancreatitis or pancreatic cancer (refer to Section 9.2.1.2.5 for details)
  - eGFR <30 mL/min/1.73 m^2
  - Any severe injection site reaction or ≥2 moderate injection site reactions occurring a week or more apart
  - Any study drug-related hypersensitivity reaction
  - Any nonfatal major CV events (refer to Section 9.2.1.2.6 for details)
  - Any other treatment-emergent adverse event (TEAE), serious adverse event (SAE), or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken.

- If the patient, for any reason (including protocol-mandated institution of rescue therapy; see Section 7.8.1), requires treatment for >1 week with another therapeutic agent that has been demonstrated to be effective for treatment of diabetes. Also, a change in dose of metformin is not allowed (except for incidences of hypoglycemia; see Section 7.1). However, a change to an equivalent dose strength from immediate-release to extended-release (or vice versa) formulation is allowed.
- If the patient misses ≥2 doses (consecutive or not) of study medication or intentionally or repeatedly takes more than the prescribed dose of study medication (see Section 9.3).
- If the patient develops any exclusion criteria, such as pregnancy or nursing.

If study drug is permanently discontinued, the patient should remain in the study if possible. Patients discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

After randomization, the investigator may temporarily discontinue study drug, for example, due to an AE (eg, nausea and vomiting), or a clinically significant laboratory value. If study drug discontinuation is due to an AE, the event is to be followed and documented. Every effort should be made by the investigator to maintain patients in the study and to restart study drug promptly after any temporary discontinuation, as soon as it is safe to do so. The dates of study drug discontinuation and restart will be documented. Patient noncompliance should not be recorded as temporary discontinuation of study drug on the eCRF. If ≥2 doses of study medication (consecutive or not) are missed for any reason, then the patient should be permanently discontinued from study medication.

In the event that the patient requires the discontinuation of the study drug, he/she may continue participation in the study, attend all visits, and undergo all protocol procedures, and patient data from the time of discontinuation of study drug will not be included in the primary analyses.

After study drug discontinuation, patients may commence any standard diabetes therapy in line with local or regional standards of care, and as considered appropriate by the investigator.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include the following:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Sponsor decision
    - Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).
- Investigator decision
    - The investigator decides that the patient should be discontinued from the study.
- Subject decision
    - The patient requests to be withdrawn from the study.

Patients discontinuing from the study prematurely for any reason should complete adverse event and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy measure is HbA1c, as determined by the central laboratory. Blood samples for HbA1c measurements will be collected at specific clinical visits as summarized in Section 2.

9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be collected at the times shown in Section 2.

- HbA1c target of <7.0%
- Body weight: Patients will be weighed on an electronic (digital) scale in a light hospital gown at approximately the same time in the morning after an overnight fast and evacuation of any bowel and bladder contents (see Appendix 7). The scale's performance will be monitored at least monthly using standard weights, and records of these assessments will be kept in the study binder.
- FBG
- Waist circumference: Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. The patient should stand with feet close together, arms at the side, and body weight evenly distributed, and should wear a hospital gown. The patient should be relaxed, and the measurements should be taken at the end of a normal expiration. The measurement should be repeated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

9.1.2.1. Exploratory Efficacy Assessments

Seven-point SMBG profiles consisting of blood glucose measurements should be obtained before each meal, approximately 2 hours after each meal, and at bedtime on a day during the week before the relevant scheduled clinic visit. Patients will record their SMBG levels in their diaries, according to instructions. The complete 7-point profile must be collected on a single day. If a patient does not complete the entire profile on a single day, all 7 points must be collected on a subsequent day.

9.1.3. Appropriateness of Assessments

All measures are widely used and generally recognized as reliable, accurate, and relevant with respect to the management of T2DM.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause-and-effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible the circumstances leading to any dosage modifications or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (ie, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- When a condition related to the investigational device necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed by official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure.

United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.2. Adverse Events of Special Interest

The following adverse events of special interest (AESIs) of varying clinical significance will be used to determine the tolerability of LY3298176 over the range of doses selected for this clinical trial. All AESIs should be captured and reported to Lilly on the AE eCRF or on a specific eCRF, if applicable (see below). Any AESI that meets the definition of an SAE (see Section 9.2.1) must be reported as an SAE.

When any one of the following events occur, Lilly or its designee must be alerted immediately, whether it is assessed as an SAE or not:

- Confirmed pancreatitis or pancreatic cancer
- Any severe injection site reaction or ≥2 moderate injection site reactions occurring a week or more apart
- Any study drug-related hypersensitivity reaction
- Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken.

9.2.1.2.1. Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea events will be recorded on a specific eCRF. They should not be recorded as AEs unless the event meets an SAE criterion. For each event, assessment of severity, duration, and investigator's opinion of relatedness to study drug and protocol procedure will be captured.

9.2.1.2.2. Injection Site Reactions

All injection site reactions, including reports of pain and burning, and information regarding their time of day, time relative to injection, size, amount of erythema, induration, and pruritus, as well as severity, will be recorded on specific eCRFs. In addition, if the reaction is clinically significant, the site should attempt to contact the sponsor for potential follow-up procedures. Injection site reactions do not need to be recorded as AEs unless they meet SAE criteria.

9.2.1.2.3. Hypersensitivity Reactions

All hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Study drug should be temporarily discontinued for any individual suspected of having a severe or serious allergic/hypersensitivity reaction to study drug. Study drug may be restarted if, in the opinion of the investigator, the event was not related to study drug and when/if it is safe to do so. If study drug is permanently discontinued, the patient should remain in the study.

9.2.1.2.4. Hypoglycemia

Hypoglycemia episodes will be recorded on a specific eCRF. Information regarding severity, time of day, and investigator's opinion of relatedness to study drug and procedure will be recorded. Hypoglycemia episodes should not be recorded as AEs unless the event meets serious criteria. Hypoglycemia will be classified as follows (American Diabetes Association 2005):

- **Documented Symptomatic Hypoglycemia:** Any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia and has a plasma glucose level of ≤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]).

9.2.1.2.5. Acute Pancreatitis

Acute pancreatitis is defined as an AE of interest for this study. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks et al. 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases [Banks et al. 2006; Koizumi et al. 2006]; the pain is often associated with nausea and vomiting);
- serum amylase (total and/or pancreatic) and/or lipase ≥3× ULN;
- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with investigational product, but will continue in the study on another glucose-lowering regimen (see Section 7.8.1 for details on rescue intervention). The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each case of AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug.

In addition to the diagnostic assessment in patients who develop symptoms of acute pancreatitis, each patient will have measurements of pancreatic amylase and lipase at screening, baseline, and during the study, including follow up, to assess any potential effects of LY3298176 on the exocrine pancreas (refer to Section 2, Schedule of Activities). Further diagnostic assessment per Lilly algorithm for assessment of asymptomatic pancreatic hyperenzymemia will be required whenever lipase and/or pancreatic amylase are ≥3× ULN at any time during the study. If this situation occurs at Visit 801 (Week 15), the patient will be required to undergo this additional workup, and the data will be collected in the clinical trial database.

All suspected cases of acute or chronic pancreatitis, as well as cases of confirmed lipase or pancreatic amylase values ≥3× ULN, will be adjudicated by an independent committee of expert physicians. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis, those with severe or serious abdominal pain, and those that undergo additional assessments due to confirmed hyperenzymemia will be entered into a specifically designed eCRF page by study site or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

9.2.1.2.6. Major Adverse Cardiovascular Events

Deaths (CV and non-CV), nonfatal MIs, supraventricular arrhythmias, and nonfatal strokes that occur during the treatment period or follow-up period will be adjudicated by an independent adjudication committee in compliance with a study-specific adjudication charter. Investigative sites will also be asked to submit any cases of TIA or hospitalization for unstable angina for adjudication as well to ensure that all true stroke and MI events are captured. Hospitalizations for heart failure and coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention) will also be submitted for adjudication.

Cardiovascular event definitions will be based on the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials (Hicks et al. 2015) and the ESC/ACCF/AHA/WHF Expert Consensus Document Third Universal Definition of Myocardial Infarction (Thygesen et al. 2012). An adjudication committee will enter the results of adjudication in the corresponding eCRF page.

9.2.1.2.7. Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Individuals with personal or family history of certain thyroid or nonthyroid endocrine abnormalities or certain preexisting laboratory and genetic characteristics will be excluded from the study (see Section 6.2). The assessment of thyroid safety during the trial will include reporting of thyroid TEAEs and measurements of calcitonin according to Section 2 at screening

and Visit 10 (end of treatment) or ET visit. The purpose of calcitonin measurements is to assess the potential of LY3298176 to affect thyroid C-cell function, which includes development of C-cell hyperplasia and neoplasms.

Patients who develop serum calcitonin increases ≥50% of the mean of the screening values AND an absolute value ≥20 pg/mL and <35 pg/mL at Visit 10 (end of treatment) or at ET will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be encouraged to undergo additional endocrine assessment and longer term follow-up by an endocrinologist to exclude a serious adverse effect on the gland.

For patients who require additional endocrine assessment because of increased calcitonin concentration per criteria provided in this section, data from the follow-up assessment will be collected in the specific section of the eCRF.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he/she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

For patients with suspected or confirmed overdose with LY3298176, there is no specific antidote. The patient should be watched for GI symptoms and hypoglycemia. Treatment is supportive, depending on the patient's symptoms.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, 12-lead ECGs should be collected according to Section 2. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

Electrocardiograms should be recorded in triplicate using standardized equipment provided by the sponsor.

Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the subject meets entry criteria and for

immediate subject management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE. The investigator (or qualified designee) is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of evaluation.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the patient will be assessed by the investigator for symptoms (eg, palpitations, near syncope, and syncope) and to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (eg, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report-writing purposes, unless a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

In addition, for each patient, a single ECG will be recorded at screening and if the patient discontinues from the study prematurely (Section 2) for immediate patient management. These ECGs will be stored at the investigation site.

Any treatment-emergent clinically significant ECG finding resulting in a diagnosis should be reported as an AE in the eCRF.

9.4.2. Vital Signs

Sitting BP and PR will be measured using standardized equipment provided by the sponsor. Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required (see Section 2). The participant should be required to sit quietly for 5 minutes before vital sign measurements are taken. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of BP measurements. The arm used for the BP measurement should be supported at heart level. At Visit 1 (screening), to determine which arm should be used to collect BP and PR throughout the study, BP and PR will be measured once in each arm, and the arm that had the higher systolic BP should be used to collect all 3 measurements of both BP and PR at all study visits. For each parameter (PR, systolic BP, and diastolic BP), 3 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart, and each

measurement of sitting PR and BP will be recorded in the eCRF. Any AE related to changes in BP and PR should be reported.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE.

9.4.4. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. In addition, the study team will review safety reports in a blinded fashion according to the schedule provided in the Trial-Level Safety Review plan. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly CRP/CRS will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

In addition, specific safety measures are included in the protocol to ensure appropriate monitoring of pancreatic, thyroid, and liver safety. Laboratory findings that trigger pancreatic and thyroid safety monitoring per Lilly standards are provided in Sections 9.2.1.2.5 and 9.2.1.2.7, respectively. Details of liver safety monitoring are provided in Section 8.1.1. If a study patient experiences elevated ALT ≥3× ULN or elevated total bilirubin ≥2× ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Appendix 4).

9.5. Pharmacokinetics

Blood samples for PK analyses will be collected from all randomized patients in accordance with the Schedule of Activities (Section 2) and at ET. However, only samples from patients assigned to treatment with LY3298176 will be analyzed for drug concentration.

Date and time of each sample and the most recent LY3298176 dose prior to PK blood draw must be recorded. Scheduled PK samples must be collected prior to dose administration at scheduled visits.

Drug concentration information that would unblind the study will not be reported to study sites or blinded personnel while the study is blinded.

Bioanalytical samples collected to measure study drug concentration will be retained for a maximum of 1 year following the last patient visit for the study.

9.6. Pharmacodynamics

Samples to evaluate the PD properties of LY3298176 are included in the secondary efficacy measures and not applicable here.

9.7. Pharmacogenomics

Not applicable.

9.8. Biomarkers

Collection of samples for other biomarker research is part of this study. Blood samples will be collected as specified in Section 2.

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurements of biomolecules, including DNA, RNA, proteins, lipids, and other cellular elements.

Serum and plasma ethylenediaminetetraacetic acid (EDTA) samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3298176, pathways associated with diabetes, mechanism of action of LY3298176, and/or research method or in validating diagnostic tools or assay(s) related to diabetes.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3298176 or after LY3298176 becomes commercially available.

9.9. Health Economics

Not applicable.

9.10. Samples for Immunogenicity Research

Samples from all patients will be tested for antidrug antibodies (ADA) against LY3298176. A blood sample will be collected at specific study visits according to the Schedule of Activities (Section 2). All samples for immunogenicity should be taken predose when applicable. To interpret the results of immunogenicity, a PK sample should be collected at the same time point as an the immunogenicity sample. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

Immunogenicity will be assessed using a validated ligand-binding assay designed to detect and titer ADA in the presence of LY3298176 at a laboratory approved by the sponsor. Confirmed positive samples for LY3298176 ADA will be titrated and then evaluated for cross-reactive binding to native GIP and GLP-1 using a validated ligand-binding assay. They may also be tested for their ability to neutralize the activity of assigned treatment (LY3298176-neutralizing antibodies) in separate cell-based neutralizing assays over-expressing the GIP and GLP-1 receptors. Antidrug antibody samples that test positive for neutralizing activity against LY3298176 and/or for cross-reactive binding to native GIP and GLP-1 may then be further tested for neutralizing activity against native GLP-1 and GIP using cell-based neutralizing assays.

All patients will have an ADA sample measured at ET or at the follow-up visit (Visit 801) approximately 1 month after the last dose of LY3298176. A risk-based approach will be used to monitor patients who have clinically significant treatment-emergent antidrug antibodies (TE-ADA) at the last visit. Treatment-emergent ADA are defined as those with a titer 2‑fold (1 dilution) greater than the minimum required dilution if no ADA were detected at baseline or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADA were detected at baseline. Clinically significant TE-ADA will be defined as any TE-ADA at the follow-up visit (Visit 801) with:

- A high titer (≥1280) or an increasing titer from last measured value
- An association of TE-ADA with a moderate to severe injection site reaction or infusion-related reaction
- Cross-reactive and/or neutralizing binding of an ADA with endogenous GLP-1 or GIP.

Patients who have clinically significant TE-ADA should be followed with ADA testing every 3 months for approximately 1 year or until the ADA titers have returned to baseline ADA titer (defined as ADA titer within 2-fold of baseline). A PK sample may be collected at the follow-up immunogenicity assessment(s) if warranted and agreed upon between both the investigator and sponsor.

Every attempt should be made to contact patients for the follow-up immunogenicity assessment; however, if patients are unwilling or unable to return for the visit, this is not considered a protocol violation.

Patients followed for at least 1 year since last dose who have not returned to baseline, as defined above, will be assessed for safety concerns and, if no clinical sequelae is recognized by the clinical team, no further follow-up will be required.

Patients who have clinical sequelae that are considered potentially related to the presence of TE-ADA may also be asked to return for additional follow-up testing.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by Lilly. The duration allows the sponsor to respond to future regulatory requests related to LY3298176. Any samples remaining after 15 years will be destroyed.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 92 patients will be randomized to placebo or 1 of 3 LY3298176 titrations arms assuming a 13% dropout rate resulting in approximately 20 completers per arm.

Assuming a standard deviation of 1.1, 20 patients per arm will provide at least 90% power to detect a statistically significant difference between LY treatments to placebo with a dose response assumption as shown in Table GPGF.4.

Table GPGF.4. Dose–Response Assumption Used in Sample Size Determination

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

Abbreviations: CFBL = change from baseline; LY = LY3298176.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined in Table GPGF.5.

Table GPGF.5. Definitions of Populations to Be Analyzed in Study GPGF

Population	Description
Enrolled	All participants who sign informed consent.
ITT (intention-to-treat)	All randomized patients.
mITT (modified ITT)	All randomized patients with at least 1 postbaseline measurement according to the treatment the patients were assigned.
PP (per-protocol)	All randomized patients who were compliant with study drug and completed the protocol.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be included in the treatment group to which they were randomized. In the event of a treatment error, participants will be analyzed according to the treatment they actually received.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the statistical methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the statistical analyses and the justification for the change will be described in the statistical analysis plan (SAP) and/or clinical study report (CSR). Additional exploratory analyses of the data may be performed as deemed appropriate. Analyses will be fully detailed in the SAP.

The intention-to-treat (ITT) population is defined as all randomized patients. Statistical analyses (including the primary analysis) will be conducted on the modified ITT (mITT) population. The mITT population is defined as all randomized patients with at least 1 postbaseline measurement according to the treatment the patients were assigned. The per-protocol (PP) population is defined as all randomized patients who were compliant with study drug and completed the

protocol and is a subset of the mITT population. The safety population is defined as all randomized patients who have received at least 1 dose of study drug. Safety analyses will be performed on the safety population.

Some efficacy measures will also be analyzed on the PP dataset. The PP analysis will include patients who meet the following additional criteria:

- Have been appropriately randomized
- Have not discontinued from the study for any of the early discontinuation criteria
- Have not missed ≥2 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.

Patients who have had rescue therapy will be included in the mITT population, but not the PP population. The efficacy measures will be censored at the time of rescue for analyses using mITT population.

No adjustments for multiplicity will be performed.

All tests of treatment effects will be conducted at a one-sided alpha level of 0.1 and/or one-sided 90% confidence interval, unless otherwise stated.

The baseline value used for the analyses will be the last scheduled baseline value obtained for each patient prior to randomization.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

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

10.3.2.2. Patient Characteristics

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

10.3.2.3. Concomitant Therapy

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

10.3.2.4. 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 doses of the assigned treatment at any point in the study. Patients who miss ≥2 doses at any point during the study will be considered significantly noncompliant and will be permanently discontinued from study medication. These patients will not be included in the PP analysis.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary outcome is the difference in HbA1c change from baseline between treatment groups based on the mITT population at the planned end of the treatment period of 3 months. The primary analysis model will be a mixed model for repeated measures (MMRM) for HbA1c change from baseline to 3 months in the mITT population with treatment, visit, treatment-by-visit, baseline BMI category, and metformin use (yes, no) as fixed effects, and baseline HbA1c as a covariate. The dependent variable will be the postbaseline change from baseline values. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the following covariance structures will be tested in order:

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

The first covariance structure that converges will be used.

The treatment p-value will be used as evidence of difference between active drug and placebo, while the comparison of least-squares (LS) means versus placebo (unadjusted for multiple comparisons) will provide magnitude and significance of this difference. The primary analysis model, MMRM, will be repeated using the PP population. If the conclusion differs from that of the mITT population, the data and analyses will be further investigated.

Descriptive statistics by treatment for HbA1c and HbA1c change from baseline at the 12-week endpoint will be presented using all observed data with no imputations and no elimination of patients with protocol violations. The descriptive statistics will be presented by visit and will include sample size, mean, SD, median, minimum, and maximum.

10.3.3.2. Secondary Analyses

10.3.3.2.1. Analyses on Secondary Efficacy Endpoints

In addition to the primary efficacy analysis of HbA1c, the following secondary efficacy outcomes will be analyzed on the mITT population:

- Body weight change from baseline to 3 months
- Percentage of patients reaching the HbA1c target of ≤7.0%
- Change from baseline of FBG at 3 months

- Change from baseline of waist circumference at 3 months.

The secondary continuous efficacy measures (change from baseline in body weight, waist circumference, and FBG) will also be analyzed using the MMRM models described above (with censoring data collected after initiation of rescue intervention). The MMRM model will include the model terms given for the previously described primary analysis model except the baseline of the corresponding variable replacing the baseline of HbA1c, and with the addition of the HbA1c strata (<8.5% or ≥8.5%). Baseline BMI category will be dropped from the analysis models for body weight change from baseline.

The percentage of patients reaching the HbA1c target of ≤7.0% at 3 months will be analyzed using a logistic regression analysis with fixed effects of treatment and stratification factors, and baseline as a covariate.

In addition to change from baseline in weight and waist circumference, change from baseline in BMI will be listed and summarized.

Descriptive statistics for each outcome will be presented by treatment group. For continuous variables, the descriptive statistics will include sample size, LS means, LS means standard error, mean, SD, median, minimum, and maximum. For categorical variables, the descriptive statistics will include sample size, frequency, and percentage.

10.3.3.3. Exploratory Analyses

The change from baseline of 7-point SMBG profiles will be analyzed using analysis of covariance model (ANCOVA) with treatment, baseline strata (metformin category, BMI category, and HbA1C category) as fixed effects, and the corresponding baseline as covariate.

10.3.4. Safety Analyses

10.3.4.1. Clinical Evaluation of Safety

The safety population will be used for safety analyses.

Safety measures will include vital signs, body weight, TEAEs (including SAEs and AESIs), and laboratory measures (including anti-LY3298176 antibodies). Summary statistics will be presented by treatment for the safety measures.

The summary statistics for continuous variables will be sample size, mean, SD, median, minimum, and maximum.

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

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

In addition, percent of patients requiring rescue therapy will be summarized.

Additional analysis, such as concentration–safety lab plots, may be performed if warranted upon review of the data.

10.3.4.2. Adverse Events

Adverse events will be listed by patient, actual term, preferred term, severity, and relationship to the treatment. Adverse events will be summarized as TEAEs (defined as events that are newly reported after randomization or reported to worsen in severity from baseline). The incidence of patients with at least 1 TEAE and the incidence of TEAEs by preferred term and system organ class will be presented by treatment group. The frequency and percentage of TEAEs will be presented. The incidence of patients with at least 1 TEAE assessed as possibly related to the investigational drug will be summarized by treatment group, in addition to the incidence of these possibly related TEAEs by preferred term. In addition, a summary of TEAEs by severity will be presented descriptively by treatment group.

Reported thyroid and adjudicated CV and pancreatic-related AEs will be listed by patient, and if there are a sufficient number of cases, they may be summarized by treatment group.

All SAEs will be listed by patient. If a sufficient number of SAEs are reported, incidence summaries similar to incidence of TEAEs will be included.

Discontinuations due to TEAEs will be listed by patient and summarized by treatment group.

10.3.4.3. Vital Signs

All vital signs will be listed using all randomized patients.

Descriptive statistics for the actual measurements and changes from baseline for systolic and diastolic BP and PR will be presented by treatment arm and visit. Corresponding figures may be presented.

Vital signs will be analyzed using a similar MMRM-based model as for the primary analysis.

10.3.4.4. Laboratory Measures

Summary statistics will be provided for laboratory measures, by visit.

A listing of laboratory measurements for individual patients will be presented by visit. An additional listing will be presented for all laboratory measurements that are outside the normal range.

Descriptive statistics for the laboratory analyses will be presented by treatment group and visit, including safety off-treatment visits.

Laboratory analyses with categorical responses will be summarized by visit and treatment group using frequency and percentage.

Shift tables will be evaluated at endpoint (last observation carried forward [LOCF]); the maximum/minimum postbaseline observation (as applicable for a lab) will be compared to the baseline observation by examining the proportion of patients whose test values are within and outside the reference ranges.

10.3.4.5. Evaluation of Immunogenicity

The frequency of antibody formation (including titers) to LY3298176 will be determined. If a cross-reactivity or neutralization assay is performed, the frequency of antibodies will be

determined. If there are a sufficient number of patients with positive antibodies to LY3298176, the change of antibodies (negative to positive) will be summarized using shift tables.

The relationship between the presence of antibodies, antibody titers, and clinical parameters (eg, AEs, efficacy measures) may be assessed. Likewise, the relationship between antibody titers, the PK parameters, and PD response to LY3298176 may be assessed.

10.3.4.6. Adverse Events of Special Interest

Hypoglycemia, hypersensitivity reactions, injection site reactions, acute pancreatitis, major adverse CV events, and selected GI events such as nausea, vomiting, and diarrhea, are defined as AESIs.

Descriptive statistics for the AESIs will be presented by treatment group and visit. Continuous responses will be summarized using sample size, mean, SD, median, minimum, and maximum, whereas categorical responses will be summarized using frequencies and percentages.

Summaries and analyses for incidence, time to onset, duration, and severity of GI events (nausea, vomiting, and diarrhea) will be provided for each treatment group during the 12-week treatment period and by visit. The planned reports will be detailed in the statistical analysis plan.

Additional analyses will be performed if necessary.

10.3.4.7. Hypoglycemic Episodes

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.

The total hypoglycemia monthly rate per patient will be summarized where 1 month is defined as a 30-day period. This will be calculated by dividing the total number of hypoglycemic events by the total number of days between visits and multiplying by 30 days. This rate will also be calculated per patient for nocturnal hypoglycemia episodes, and summarized by treatment.

The incidence and rate of total hypoglycemic episodes and nocturnal hypoglycemic episodes will be presented for each visit (incidence between visits) and overall. Nocturnal hypoglycemia episodes are episodes that occur between bedtime and waking. The incidence of hypoglycemic episodes during a time period on treatment is defined as patients with at least 1 hypoglycemic episode occurring within that period of time.

Listings of hypoglycemic episodes and severe hypoglycemic episodes will be presented by visit for each patient. If a sufficient number of severe hypoglycemic episodes are reported, then incidence summaries similar to incidence of hypoglycemic episodes will be included.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

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

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

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

10.3.6. Other Analyses

10.3.6.1. Subgroup Analyses

Subgroup analyses of important factors, including age, race, ethnicity, gender, duration of diabetes, baseline HbA1c (<8.5%, ≥8.5%), metformin use (Yes/No) at baseline, BMI, and other factors to be specified in the SAP are planned for the key outcomes of HbA1c.

These will be conducted using the ANCOVA model with strata, treatment, factor, treatment-by-factor interaction as fixed effects, and baseline as covariate.

Other exploratory subgroup analyses may be performed as deemed appropriate.

10.3.6.2. Interim Analyses

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

11. References

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

Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131–2157.

Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379–2400.

Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384(9951):1349–1357.

Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care*. 2015;38(12):2241–2249.

Herbst R, Bolton W, Shariff A, Green JB. Cardiovascular Outcome Trial Update in Diabetes: New Evidence, Remaining Questions. Current Diabetes Reports. 2017; 17:67.

Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL; American College of Cardiology; American Heart Association. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (writing committee to develop cardiovascular endpoints data standards). *Circulation*. 2015;132(4):302–361.

Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. *Diabetes Metab Res Rev*. 2016;32(8):776–790.

Koizumi M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, Sekimoto M, Hirota M, Kimura Y, Takeda K, Isaji S, Otsuki M, Matsuno S; JPN. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25–32.

Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, During M, Matthews DR; LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care*. 2009;32(1):84–90.

Nauck MA, Petrie JR, Sesti G, Mannucci E, Courreges JP, Lindegaard ML, Jensen CB, Atkin SL; Study 1821 Investigators. A Phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care*. 2016;39(2):231–241.

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020–2035.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BG	blood glucose
BMI	body mass index
BP	blood pressure
CFBL	change from baseline
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CRF	case report form
CRP	clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, CRS, global safety physician, or other medical officer.
CRS	clinical research scientist

CT	computed tomography
CV	cardiovascular
documented symptomatic hypoglycemia	Defined as 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).
DPP-4i	dipeptidyl peptidase 4 inhibitor (an OAM)
ECG	electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
eGFR	estimated glomerular filtration rate
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ET	early termination
ET	early termination
FBG	fasting blood glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (ie, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	Interactive Web Response System
LH	luteinizing hormone
LOCF	last observation carried forward
LS	least squares
MI	myocardial infarction
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
OAM	oral antihyperglycemic medication
OTC	over-the-counter
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol dataset: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PR	pulse rate
QTc	corrected QT interval
QW	once weekly
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

SD	standard deviation
SMBG	self-monitoring of blood glucose
SUSAR	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus
TE-ADA	treatment-emergent antidrug antibodies
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
TIA	transient ischemic attack
ULN	upper limit of normal (reference range)

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology:
- Hemoglobin
- Hematocrit
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Neutrophils, segmented
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets

Hemoglobin A1c

Urinalysis:
- pH
- Protein
- Glucose
- Blood
- Urine leukocyte esterase

Lipid Panel (Fasting)
- Total Cholesterol
- Triglycerides
- HDL-C
- LDL-C (calculated)

Immunogenicity:
- Anti-LY3298176 antibodies
- Anti-LY3298176 antibody neutralization assay

Optional urine drug screen (local, at the discretion of the investigator)

Clinical Chemistry:

Serum Concentrations of:
- Sodium
- Potassium
- Total bilirubin
- Direct bilirubin
- ALP
- ALT
- AST
- BUN
- Creatinine
- Uric acid
- Calcium
- Total Protein
- Lipase
- Amylase
- eGFR[b]
- Glucose, fasting or random
- Albumin
- Calcitonin

Hormones (females):
- Pregnancy Test, serum and/or urine[c]
- Serum FSH[d]

Serology[e]
- Hepatitis B Surface Ag
- Hepatitis C Ab
- HIV Ab

GIP and GLP-1 (total and active)

Nonpharmacogenetic Stored Samples
- EDTA plasma
- Serum

Abbreviations: Ab = antidrug antibody; Ag = antigen; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; HIV = human immunodeficiency virus; LH = luteinizing hormone; RBC = red blood cells; UACR = urine albumin-to-creatinine ratio; WBC = white blood cells.

a All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.

b eGFR will be calculated by the central laboratory at all visits and included in lab result reports.
c Serum pregnancy test will be performed by central laboratory at Visit 1 for women of child-bearing potential; urine pregnancy tests may be performed at the investigator's discretion during the study. A local laboratory may be used for urine pregnancy tests. Of note, women of child-bearing potential must have a local (urine) pregnancy test prior to the first dose of study drug (Visit 3) to confirm lack of pregnancy.
d Performed at screening by central laboratory to establish menopausal status. Women who meet the criteria for postmenopausal status in Section 6.1 by age and/or cessation of menses do not need to have postmenopausal status confirmed with hormone tests.
e Performed at screening only.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his/her participation in the trial.

Appendix 3.1.2. Ethical Review

The investigator or an appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB, and updates during the course of the study
- ICF
- relevant curricula vitae.

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

1. consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. applicable ICH GCP Guidelines
3. applicable laws and regulations.

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.4. Investigator Information

Physicians with a specialty in diabetes/endocrinology, internal medicine, or family medicine will participate as investigators in this clinical trial.

Appendix 3.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his/her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.6. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instructions on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in InForm. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (eg, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

The following hepatic monitoring tests should be considered for patients with treatment-emergent hepatic abnormalities in Lilly- or its designee-sponsored clinical trials to ensure patient safety and comply with regulatory guidance.

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required during follow-up with patients in consultation with Lilly or its designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
ALP isoenzymes	
ALT	Antinuclear antibody[a]
AST	Anti-F actin antibody[a]
GGT	Anti-smooth muscle antibody[a]
CPK	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Criteria for Diagnosing Type 2 Diabetes Mellitus (American Diabetes Association 2017)

Criteria for Diabetes Diagnosis: 4 Options

- Fasting blood glucose (FBG) ≥126 mg/dL (7.0 mmol/L)
  Fasting is defined as no caloric intake for at least 8 hours.*
- 2-hr plasma glucose (PG) ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT)
  The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
- A1c ≥6.5% (48 mmol/mol)
  The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP)-certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.*
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Reference:

American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care*. 2017;40(Suppl. 1):S11–S24.

Appendix 6. Contraceptive Methods

Men

Male patients with female partners of child-bearing potential will be required to use a condom in conjunction with a spermicidal gel, foam, cream, or suppository. In addition, the female partner, will be requested to use an additional effective form of contraception, which can be any of the following:

- diaphragm with spermicide
- cervical sponge
- cervical cap with spermicide
- combined oral contraceptive pill and mini-pill
- NuvaRing
- implantable contraceptives
- injectable contraceptives (such as Depo-Provera®)
- intrauterine device (such as Mirena® and ParaGard®)
- true abstinence, when in line with the preferred and usual lifestyle of the patient.

Men who have had a vasectomy with appropriate postvasectomy documentation of the absence of sperm in the ejaculate are not required to use contraception. In addition, Inclusion Criterion 3b (Section 6.1) provides a specific definition of women not of child-bearing potential; these subjects will not be required to use contraception. Male patients with a female partner meeting the definition of a woman not of child-bearing potential will not be required to use contraception.

Women of Child Bearing Potential

Women of child-bearing potential will be required to use contraception, which can be any of the following:

- Abstinence: If this is complete abstinence, as their preferred and usual lifestyle or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.
- Birth Control: Use of 1 highly effective method (<1% failure rate) of contraception, or a combination of 2 effective methods of contraception for the entirety of the study:
  - Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device)
  - A combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide.

It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Appendix 7. World Health Organization Standardized Protocols for the Measurement of Height and Weight

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2017).

Measuring Height

Step 1. Ask the patient to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the patient at every clinic visit when their weight is measured).

Step 2. Ask the patient to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the back board or the stadiometer or the wall.

Step 3. Ask the patient to look straight ahead without tilting their head up.

Step 4. Ask the patient to breathe in and stand tall. If using a stadiometer or fixed measuring device, move the device's measurement arm gently down onto the top of the patient's head. Record the patient's height in centimeters (cm).

Measuring Weight

Body weight measurements should be done in a consistent manner using a calibrated scale (digital). All weights for a given patient should be measured using the same scale, whenever possible, after the patient has emptied their bladder. Patients should wear a light hospital gown while their weight is measured.

Step 1. Ask the patient to remove their outer clothing and footwear (underwear may remain on), and change into a light hospital gown.

Step 2. Make sure the scale is placed on a firm, flat, even surface (not on carpet or on a sloping surface or a rough uneven surface).

Step 3. Ask the patient to step onto the scale with one foot on each side of the scale.

Step 4. Ask the patient to stand still with their arms by their sides and then record their weight in kilograms (kg).

Reference:

[WHO] World Health Organization. STEPwise approach to Surveillance (STEPS). Updated 2017.Available at: http://www.who.int/chp/steps/Part3_Section3.pdf. Accessed 31 July 2017.

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