Protocol H9X-MC-GBGE(b)

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

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(AWARD-10: Assessment of Weekly AdministRation of LY2189265 in Diabetes – 10)

Dulaglutide (LY2189265)

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

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1. Protocol Synopsis

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

Rationale:
Combined use of glucose-lowering pharmacological agents is common in patients with type 2 diabetes (T2D) and often includes 2, 3, or more classes of therapeutics. The sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide -1 receptor agonists (GLP-1 RAs) are indicated in similar populations and their combined use is of clinical interest; however, clinical data is currently limited.

An important aspect of the concomitant treatment with these 2 classes of agents is a potential for additive or synergistic actions on blood glucose due to their complementary mechanisms of actions; SGLT2 inhibitors lower blood glucose by increasing excretion of glucose in the urine, while GLP-1 RAs enhance glucose-mediated insulin secretion and also suppress glucagon. Similarly, both may lower body weight and blood pressure; therefore, combined use of these agents may provide T2D patients with a treatment regimen that is associated with an acceptable safety profile, in addition to clinically relevant glucose-lowering effects.

It is also of particular interest to assess the overall tolerability of the combination therapy, including hemodynamic and renal parameters. SGLT2 inhibitors may cause volume depletion due to their osmotic effect in kidney tubules and may be associated with impairment in renal function. GLP-1 RAs may also cause loss of body fluid when severe, protracted vomiting occurs.

Objectives/Endpoints:

Objectives	Endpoints
Primary: To demonstrate that once-weekly dulaglutide (1.5 mg and/or 0.75 mg) is superior to placebo as measured by hemoglobin A1c (HbA1c) at 24 weeks (change from baseline) in patients with inadequately controlled T2D on concomitant SGLT2 inhibitor therapy.	• The change in HbA1c from baseline to 24 weeks
Secondary: Key secondary efficacy objectives (controlled for type 1 error) are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks.	• Proportion of patients with HbA1c target values of <7.0% at 24 weeks • The change in fasting blood glucose (FBG) (central laboratory) from baseline to 24 weeks • The change in body weight from baseline to 24 weeks

Summary of Study Design:

Study H9X-MC-GBGE is a randomized, double-blind, placebo-controlled, parallel-arm, multicenter, Phase 3b trial that investigates the effect of the addition of once-weekly dulaglutide 1.5 mg or 0.75 mg to SGLT2 inhibitors, with or without concomitant use of metformin, on glycemic control and safety over a 24-week treatment period in patients with inadequately controlled T2D.

Treatment Arms and Duration:

After completing screening, a 1-week lead-in period, and if necessary, a 12-week stabilization period, patients will be randomized 1:1:1 to a weekly injection of placebo, dulaglutide 0.75 mg, or dulaglutide 1.5 mg, all in combination with at least minimum-required doses of SGLT2 inhibitor (± metformin). Study participants will be treated for 24 weeks after randomization.

Number of Patients:

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

Statistical Analysis:

Two analysis models will be used for the primary objective. The primary analysis will be mixed-model repeated measure (MMRM) analysis using restricted maximum likelihood (REML) with treatment, country, SGLT2 inhibitor dose ("low" vs "high"), metformin use ("yes" vs "no"), visit and treatment-by-visit as fixed effects, baseline value as a covariate, and patient as random effect. An unstructured covariance structure will be used to model the within-patient errors. The secondary analysis for the primary objective will be analysis of covariance (ANCOVA) using a similar model as described above with treatment, country, SGLT2 inhibitor dose ("low" vs "high"), and metformin use ("yes" vs "no") as factors and baseline value as a covariate. Missing endpoints will be imputed with the last (postbaseline)-observation-carried-forward (LOCF). For the key secondary continuous measures (body weight and FBG), both models (with HbA1c strata included), will also be used. The percent to goal, ie, the percentage of patients achieving target HbA1c of <7.0% at 24 weeks, will be analyzed using a longitudinal logistic regression with repeated measurements including independent variables for treatment, country, visit, treatment-by-visit, and baseline HbA1c as a covariate.

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

alternative antihyperglycemic agents. Both estimands will use the same primary analysis model, and each will be tested at the full significance level of 0.05.

A graphical testing approach for each estimand separately will be used to strongly control for type I error to test for superiority of each of the dulaglutide doses versus placebo at 24 weeks for the following measures: (1) change from baseline in HbA1c, (2) change from baseline in FBG, (3) percent achieving HbA1c <7.0%, and (4) change from baseline in body weight.

The primary analysis population will be the ITT population, defined as all patients randomized who have taken at least 1 dose. This is also the safety population. A select number of measurements (HbA1c, percent to goal in HbA1c, FBG, and body weight) will also be evaluated in the per-protocol population.

2. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been developed for use as monotherapy or in combination with 1 or more oral antihyperglycemia medications (OAMs) and/or insulin for treatment of type 2 diabetes mellitus (T2D) (Bydureon® USPI, 2015; Byetta® USPI, 2015; Tanzeum™ USPI, 2015; Trulicity™ USPI, 2015; Victoza® USPI, 2015). Expected adverse events (AEs) of the GLP-1 RA class are mostly those from the gastrointestinal (GI) system organ class. Dulaglutide is a once-weekly GLP-1 RA approved as a monotherapy or in combination with OAMs and/or insulin for treatment of T2D (Trulicity USPI, 2015). Based on the experience from completed dulaglutide trials, similar to the GLP-1 RA class, GI AEs are the most common AEs associated with dulaglutide treatment. These AEs are mostly mild to moderate in severity, transient, and their incidence decreases over time. More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of dulaglutide may be found in the Investigator's Brochure (IB).

Inhibitors of the active sodium-glucose co-transporter 2 (SGLT2) are a new class of glucose-lowering agents that act by promoting glucose excretion in the urine. The SGLTs are carrier proteins that are located in proximal or distal kidney tubules and are involved in active reabsorption of glucose from the tubular fluid back into the bloodstream (Jardiance® USPI, 2014; Farxiga® USPI, 2015; Invokana® USPI, 2015). There are two types of SGLTs, SGLT1 and SGLT2; they differ in their binding capacity and binding affinity for glucose. It has been shown that pharmacological inhibition of SGLT2 decreases blood glucose without increasing the risk of hypoglycemia, and reduces systolic blood pressure and body weight (Jardiance USPI, 2014; Farxiga USPI, 2015; Invokana USPI, 2015). The effect of SGLT1 inhibition on urinary glucose loss is much smaller, and its contribution to blood glucose lowering is considered to be limited. The SGLT2 inhibitors are indicated as monotherapy or in combination with 1 or 2 other OAMs and/or insulin for treatment of T2D. The most commonly reported AEs with inhibitors of SGLT2 are urinary tract infections and female genital mycotic infections.

There are no published data from randomized clinical trials on the effects of combined use of SGLT2 inhibitors and GLP-1 RAs. Due to their mostly complementary mechanisms of action, except for opposing action on glucagon secretion, combined treatment with these agents may provide an option for patients with T2D that is effective for glucose lowering without increasing hypoglycemia risk, and may decrease body weight and blood pressure.

Study H9X-MC-GBGE (GBGE; AWARD-10) is designed to assess the efficacy and safety of dulaglutide versus placebo, both added to the existing therapy of a stable dose of SGLT2 inhibitor (with or without a stable dose of metformin) in patients with T2D. The primary objective is to show superiority of the dulaglutide 1.5-mg dose and/or dulaglutide 0.75-mg dose to placebo for change from baseline in hemoglobin A1c (HbA1c) at 24 weeks. Key secondary objectives are to compare both dulaglutide doses to placebo with respect to their effect on the proportion of patients reaching HbA1c targets (<7.0%), body weight, and fasting blood glucose (FBG) at 24 weeks. The primary objective and all key secondary objectives will be analyzed using a family-wise strategy to control for type 1 error.

2.1. Background

A GLP-1 RA, dulaglutide is a biosynthetic fusion protein molecule produced using mammalian cell cultures, and consists of 2 identical, disulphide-linked chains, each containing an N-terminal glucagon-like peptide-1 (GLP-1) analogue sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain by a small peptide linker (Trulicity™ USPI, 2015). These structural features of the dulaglutide molecule (1) decrease the rate of clearance, (2) increase the duration of pharmacologic activity, (3) may reduce immunogenic potential, and (4) may decrease unwanted antibody-mediated effect or function (Barrington et al. 2011; Trulicity USPI, 2015).

Dulaglutide exhibits GLP-1 mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss (Trulicity USPI, 2015). Preclinical and clinical experience to date support the use of dulaglutide as a once-weekly injection to improve glycemic control in patients with T2D (Barrington et al. 2011). Dulaglutide received regulatory approval in the United States on 18 September 2014 and in the European Union on 21 November 2014 for use as monotherapy, in combination with OAMs or with insulin for treatment of adult patients with T2D.

2.2. Study Rationale

Treatment of T2D starts with lifestyle measures followed by stepwise addition of oral and injectable glucose-lowering agents. Combined use of pharmacological agents is common and often includes 2, 3, or more classes of therapeutics. The SGLT2 inhibitors and GLP-1 RAs are indicated in similar populations and their combined use is of clinical interest; however, clinical data are currently limited (Inzucchi et al. 2015).

An important aspect of the concomitant treatment with these 2 classes of agents is a potential for additive or synergistic actions on blood glucose due to their complementary mechanisms of action; SGLT2 inhibitors lower blood glucose by increasing excretion of glucose in the urine, while GLP-1 RAs enhance glucose-mediated insulin secretion and also suppress glucagon (Jardiance USPI, 2014; Bydureon USPI, 2015; Byetta USPI, 2015; Farxiga USPI, 2015; Invokana USPI, 2015; Tanzeum USPI, 2015; Trulicity USPI, 2015; Victoza USPI, 2015). Similarly, both may lower body weight and blood pressure; therefore, combined use of these agents may provide T2D patients with a treatment regimen that is associated with an acceptable safety profile, in addition to clinically relevant glucose-lowering effects.

It is also of particular interest to assess the overall tolerability of the combination therapy, including hemodynamic and renal parameters. Sodium-glucose co-transporter 2 inhibitors may cause volume depletion due to their osmotic effect in kidney tubules and may be associated with impairment in renal function. It has been suggested that this excessive water loss in insulinopenic T2D patients may increase the risk of ketoacidosis in the absence of severe hyperglycemia. In patients taking a GLP-1 RA, the presence of vomiting or decreased appetite may be associated with changes to the patient's volume status.

3. Objectives and Endpoints

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

Table GBGE.1. Objectives and Endpoints

Objectives	Endpoints
Primary To demonstrate that once-weekly dulaglutide (1.5 mg and/or 0.75 mg) is superior to placebo as measured by HbA1c at 24 weeks (change from baseline) in patients with inadequately controlled T2D on concomitant SGLT2 inhibitor therapy.	• The change in HbA1c from baseline to 24 weeks
Secondary Key secondary efficacy objectives (controlled for type 1 error) are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks	• Proportion of patients with HbA1c target values of <7.0% at 24 weeks • The change in FBG (central laboratory) from baseline to 24 weeks • The change in body weight from baseline to 24 weeks
Other secondary efficacy objectives are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks	• Proportion of patients with HbA1c target values of ≤6.5% at 24 weeks • The change in 6-point SMPG profile from baseline to 24 weeks • The change in fasting glucagon from baseline to 24 weeks
Secondary safety objectives are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks	Incidence of: • Treatment-emergent adverse events (TEAEs) • Early discontinuations due to AEs • Adjudicated cardiovascular and pancreatic AEs • Thyroid neoplasms AEs • AEs related to kidney failure, eGFR • Systemic hypersensitivity AEs • Local injection site reactions • The change in systolic and diastolic blood pressure, heart rate, and lipids from baseline to 24 weeks • Incidence and rate of hypoglycemic episodes • Ketoacidosis, and initiation of rescue therapy for severe persistent hyperglycemia

Objectives and Endpoints

Objectives	Endpoints
Exploratory Exploratory efficacy objectives are to compare dulaglutide 1.5 mg and 0.75 mg to placebo at 24 weeks	• Proportion of patients meeting the composite endpoint of HbA1c <7.0%, no weight gain, and no documented symptomatic hypoglycemia • Proportion of patients meeting the composite endpoint of HbA1c <7.0%, body weight loss >5%, and no documented symptomatic hypoglycemia

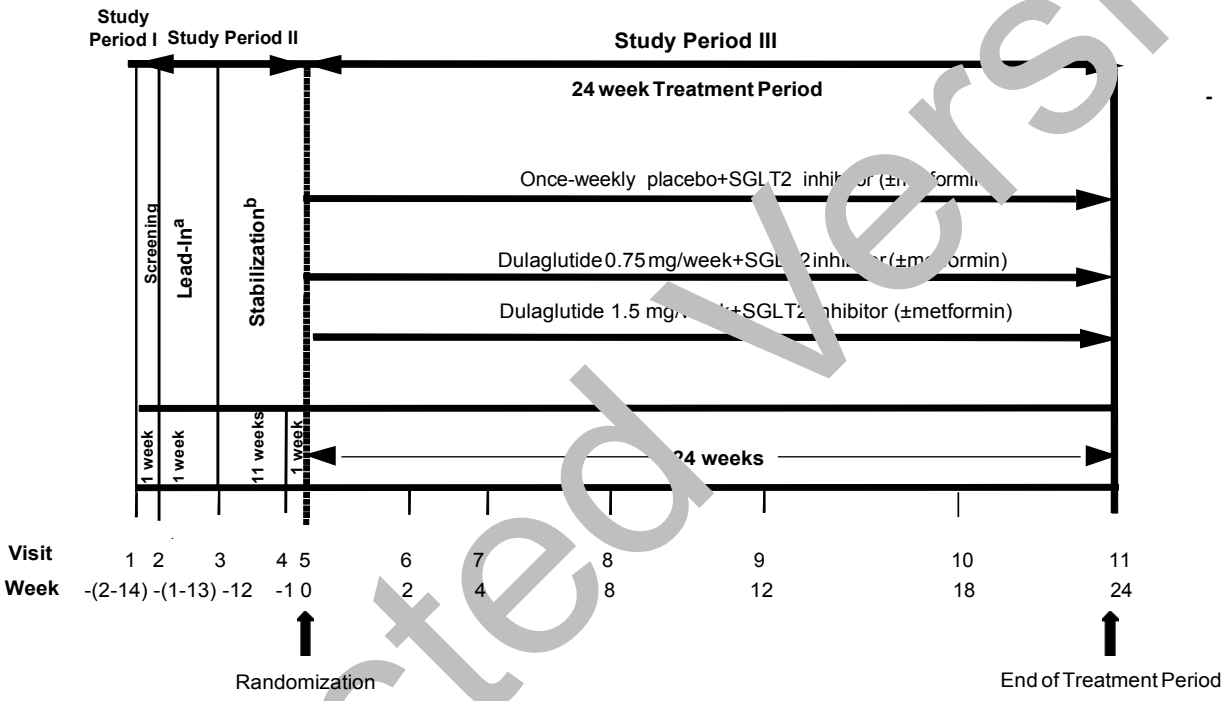
Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; SGLT2 = sodium-glucose co-transporter 2; SMPG = self-monitored plasma glucose; T2D = type 2 diabetes.

4. Study Design

4.1. Overview of Study Design

Study GBGE is a randomized, double-blind, placebo-controlled, parallel-arm, multicenter, Phase 3b trial that investigates the effects of the addition of once-weekly dulaglutide 1.5 mg or 0.75 mg to SGLT2 inhibitors, with or without concomitant use of metformin, on glycemic control and safety in patients with inadequately controlled T2D.

Figure GBGE.1 illustrates the study design.



Abbreviations: OAM = oral antihyperglycemia medication; SGLT2 = sodium-glucose co-transporter 2.

[a] Patients who require adjustment of their OAM regimen to meet eligibility criteria will implement treatment changes during the lead-in period (between Visit 2 and Visit 3), all other patients will continue with their prestudy regimen without changes.

[b] Patients who adjust their OAM regimen during lead-in and/or need to stabilize the regimen will perform Visit 3 (end of lead-in) as their next visit and will then enter 1 to 12-weeks stabilization, as needed. All other patients will skip Visit 3 and 4 and will perform Visit 5 as their next visit (approximately 1 week after Visit 2).

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

Study Periods

For each study period and each visit, study procedures are provided in the Schedule of Activities (Appendix 2).

Study Period I: Screening (Visit 1)

The purpose of Visit 1 is to initiate the assessment of patient eligibility for participation in the trial. Patients who meet all applicable inclusion criteria and none of the applicable exclusion criteria at Visit 1 (Section 5.1) will proceed to Visit 2 using the same OAMs (type and dose).

Study Period II: Lead-In and Stabilization (Visits 2 to 4)

The purpose of Visit 2 is to confirm patient eligibility, assess the need for stabilization of the OAM regimen, and provide trainings on study procedures. The need for stabilization of a patient's OAM regimen should be based on the requirements for minimum required and stable doses of SGLT2 inhibitors and metformin (see Section 5.1 and Section 6.8.1).

Those patients who meet all enrollment requirements for treatment with stable and minimum required doses of SGLT2 inhibitor and metformin at Visit 2 will have blood drawn for baseline HbA1c at this visit, followed by a 1-week lead-in using the same treatment regimen (same OAM type and dose). They will then proceed to Visit 5 (randomization visit).

For patients not meeting dose requirements for allowed OAMs at Visit 2, or who require OAM regimen adjustments for other reasons, the investigator will advise the patient on how to adjust the OAM regimen between Visit 2 and 3 to meet the study requirements (see Section 6.8.1 for details). Those patients not accepting required changes will be considered as ineligible and will be discontinued immediately from the trial.

The patients whose OAM regimen has been changed between Visit 2 and 3 or whose doses of SGLT2 inhibitor and/or metformin prior to Visit 2 have not been stable long enough to meet eligibility requirements at Visit 5 will perform a stabilization that will last 1 to 12 weeks (±3 days), that is, until the time these requirements are met. A blood sample for baseline HbA1c for patients who need stabilization will be drawn at Visit 4, approximately 1 week prior to Visit 5. They will then proceed to Visit 5 (randomization visit).

At Visit 2, eligible patients will receive training on study procedures (Schedule of Activities, Appendix 2) including the need to continue in the study and complete all study visits, the self-monitoring of plasma glucose (SMPG) plan (daily fasting plasma glucose and weekly 4-point SMPG profile [consisting of fasting, pre-lunch, pre-dinner, and bedtime PG measurements]), 6-point SMPG profile (before and 2 hours after each main meal), lifestyle treatment measures (Section 5.4), signs and symptoms and treatment of hyperglycemia (Section 6.6.1.3) and hypoglycemia (Section 6.6.1.2), and use of the study diary. Single-dose pen (SDP) injector training will be completed with the demonstrator device, which does not include a needle.

Study Period III: Randomization and Treatment Period (Visits 5 through 11)

At Visit 5, investigators will first review the diary and assess patient eligibility. Patients with baseline HbA1c <7.0% or >9.5% will be excluded. Those patients who continue to be eligible will be randomized to 1 of the following treatment groups in a blinded fashion: (1) once-weekly dulaglutide 1.5-mg injection, (2) once-weekly dulaglutide 0.75-mg injection, or (3) once-weekly

placebo injection (1:1:1 randomization ratio). Patients should inject their first dose of study drug while in the clinic for Visit 5.

Study participants will be treated for 24 weeks (treatment period). Study procedures for each visit are provided in the Schedule of Activities (Appendix 2).

Participants are required to continue using their concomitant OAMs throughout the treatment period. Discontinuation of these medications or changes in their dose is not permitted, except in situations where dose adjustment or complete discontinuation is required per country -specific label or when allowed per study protocol, for example, in the case of hypoglycemic episodes (see Sections 6.6.1.2 and 6.8.1.1).

Patients who develop persistent, severe hyperglycemia based on pre-specified thresholds (see Section 6.6.1.3) will continue administering study drug and will receive a new glucose-lowering intervention (rescue) based on the clinical judgment of the investigator. These patients, as well as those who receive rescue therapy after discontinuation of study drug due to an AE or any other reason, will be asked to perform all study visits to collect planned efficacy and safety measurements.

Those patients who are unable or unwilling to continue in the study because of an AE (see Section 7.1.2 for details) or any other reason, will perform an early termination (ET) visit as their final study visit (for procedures at the ET visit , see the Schedule of Activities [Appendix 2]). 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.

4.2. End of Trial Definition

End of the trial is the date of the last visit at which data for the primary analysis are collected for the last patient (Appendix 2).

4.3. Scientific Rationale for Study Design

This trial is designed to be consistent with recommendations provided in a position statement of the American Diabetes Association and the European Association for the study of Diabetes "Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach" (Inzucchi et al. 2015). Placebo comparator was chosen because it will enable characterization of efficacy and safety effects of dulaglutide when added to existing therapy with SGLT2 inhibitors, with or without metformin. Compared to a design which utilizes active comparator, comparison to placebo will allow assessment of the effect attributable to dulaglutide alone, which is of importance especially for the safety aspect of the combined use. The results are expected to enable physicians to choose patients suitable for the combination therapy in the clinical setting. To protect the safety of patients in the placebo arm who will enter Study GBGE with HbA1c above the <7% target, several design features are introduced for this purpose: (a) short trial duration (24 week-long treatment period), (b) exclusion of patients considered to have unacceptably high baseline HbA1c (>9.5%), and (c) additional glucose-lowering intervention (rescue) for patients with unacceptably high glycemia during the treatment period.

Allowed concomitant medications are chosen because the combined use of dulaglutide with SGLT2 inhibitors is of significant clinical interest, but available clinical data are very limited. Metformin is an OAM expected to be used in all patients with T2D as the starting OAM, if tolerated and no contraindications for its use are present.

The parallel group design is an appropriate way to compare treatments as it avoids carry-over effect that commonly occurs with cross-over designs, while the proposed randomization scheme with stratification is included to minimize between -group heterogeneity. The planned duration of treatment (24 weeks) is considered appropriate as the full effect of randomized treatments on blood glucose is expected after approximately 12 weeks of therapy, supported by the results of the 6 completed Phase 3 AWARD trials (Dungan et al. 2014; Giorgino et al. 2014; Nauck et al. 2014; Umpierrez et al. 2014; Wysham et al. 2014; Blonde et al. 2015). The additional 12 weeks of treatment will allow for stable HbA1c values to be achieved and is needed because of the delay in effect on this parameter, the primary endpoint measure in this trial.

HbA1c is chosen as the primary efficacy measure as it is the most well accepted surrogate of the long-term effect of a treatment regimen on blood glucose and has been shown to be a reliable predictor of the long-term outcomes of diabetes (UKPDS 1998; DCCT 1993). Other key efficacy measures (proportion of patients with HbA1c <7%, body weight change, and FBG) are standard clinical parameters that are relevant for patients and physicians when assessing the effects of treatment in the clinical setting. Similarly, other efficacy and safety measures are standard for trials that evaluate glucose-lowering agents and are relevant in clinical decision-making.

The statistical plan will include a graphical testing scheme to strongly control for type 1 error and will be applied in the analysis of the primary and the key secondary objectives. This approach has been well studied in the scientific literature and has been accepted by regulatory agencies for labeling (Bretz et al. 2009).

4.4. Justification for Dose

The approved Product Information for dulaglutide includes 2 approved doses, 1.5 and 0.75 mg once weekly (Trulicity™ Summary of Product Characteristics [SPC], 2014; Trulicity USPI, 2015). Doses of SGLT2 inhibitors and metformin are chosen based on the approved regulatory labeling for these agents.

4.5. Benefit/Risk Assessment

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of dulaglutide are to be found in the IB, US prescribing information (USPI), and SPC.

5. Study Population

Study participants should be instructed not to donate blood or blood products during the study or for 4 weeks following their last study visit.

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

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at study entry (Visit 1), and/or, when explicitly indicated below for specific criteria, at other visits during the lead-in/stabilization period (Visits 2 -5):

[1] are men or non-pregnant women aged ≥18 years at screening;

[2] have T2D (based on the World Health Organization's [WHO] diagnostic criteria [Appendix 6]);

[3] have been treated with an SGLT2 inhibitor, with or without metformin, for at least 3 months prior to study entry (minimum required doses for that period for allowed SGLT2 inhibitors: empagliflozin 10 mg, dapagliflozin 5 or 10 mg [per country-specific label], canagliflozin 100 mg [see also Table GBGE.3 for details]); minimum required dose for metformin, if used, is ≥1500 mg/day and must be reached by **Visit 3** (or highest tolerated dose which is acceptable with documented GI intolerability, see Section 6.8.1.1.2 for further details);

[4] daily doses of all allowed OAMs must have been stable for at least 12 weeks (±3 days) prior to randomization at **Visit 5** (study enrollment); daily doses of SGLT2 inhibitor and metformin, if used, will be considered stable during this period if:

  [a] all prescribed daily doses were in the range between the minimum-required dose (see Inclusion Criterion [3]) and maximum-approved dose per country-specific label; and

  [b] >90% of prescribed daily doses were equal to the dose at **Visit 5**;

[5] have HbA1c ≥7.0% and ≤9.5% at study entry (**Visit 1**) and at **Visit 2** for patients without stabilization; HbA1c ≥7.0% and ≤9.5% at study entry (**Visit 1)** and **Visit 4** for patients with stabilization;

[6] have body mass index (BMI) ≤45 kg/m^2 and agree to not initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment (see Section 5.4);

[7] are able and willing to administer once-weekly injections;

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

[a] perform finger-stick plasma glucose (PG) monitoring including scheduled daily PG profile with up to 6 measurements in 1 day;

[b] learn how to self-inject treatment, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug);

[c] maintain a study diary, as required for this protocol;

[9] Women of childbearing potential participating must agree to remain abstinent, use 1 highly effective method of contraception or use a combination of 2 effective methods for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration until 4 weeks after the last dose of study drug.

[a] Women of childbearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit (**Visit 1**) followed by a negative urine pregnancy test within 24 hours prior to exposure (**Visit 5**).

[b] Either 1 highly effective method of contraception (eg, combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives [such as Depo-Provera®], intrauterine devices [such as Mirena® and ParaGard®]) or a combination of 2 effective methods of contraception (eg, male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, cervical cap with spermicide) will be used. The patient may choose to use a double-barrier method of contraception. Each barrier method must include use of a spermicide (ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide). Note: 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.

[c] Women must not be breastfeeding.

Women not of childbearing potential may participate and are defined as:

[a] infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or

[b] postmenopausal woman at least 50 years of age with an intact uterus, who has not taken hormones or oral contraceptives within 1 year, AND

i) who has had either cessation of menses for at least 1 year, OR

ii) 6 months of spontaneous amenorrhea with follicle-stimulating hormone >40 mIU/mL (central laboratory; Appendix 2)

Men participating are not required to use contraception during the study. Specific local government requirements that require contraception during the study are to be complied with to participate.

[10] have given written and informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing the study site.

5.2. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria at Visit 1 (study entry), and/or when explicitly indicated below for specific criteria, at other visits during the screening and lead-in/stabilization periods (Visits 2-5):

[11] have type 1 diabetes mellitus;

[12] have been treated with ANY other OAMs (other than SGLT2 inhibitors and metformin), GLP-1 RA, pramlintide or insulin 3 months prior to study entry, or between study entry and **Visit 5**; or initiate metformin between study entry and **Visit 5**; short-term use of insulin for acute care (≤14 days) during the 3-month period prior to entry is not exclusionary;

[13] have any condition that is a contraindication for use of the GLP-1 RA class or the SGLT2 inhibitor class (per country-specific labels) at study entry or develop such condition between study entry and **Visit 5**;

[14] for patients using metformin, if a condition that is a contraindication for its use develops between **Visit 3** and **Visit 5**;

[15] discontinue therapy with SGLT2 inhibitors any time prior to **Visit 5** and/or metformin, if used, between **Visit 3** and **Visit 5**, based on the Exclusion Criteria described under [13] and [14] above, or any other reason;

[16] have a history of ≥1 episode of ketoacidosis or hyperosmolar state/coma prior to study entry;

[17] have a history of hypoglycemia unawareness within the 6 months prior to study entry;

[18] have been treated with drugs that promote weight loss (eg, Saxenda® [liraglutide 3.0 mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Adipex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], or similar over-the-counter [OTC] medications [eg, allī®]) or have received a diet and/or exercise program with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment (see Section 5.4) within 3 months prior to study entry or between study entry and **Visit 5**;

[19] are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) any time between entry and **Visit 5** or have received such therapy within 1 month prior to study entry;

[20] have had any of the following cardiovascular (CV) conditions within 2 months prior to study entry: acute myocardial infarction (MI), New York Heart Association (NYHA) Class III or Class IV heart failure, or cerebrovascular accident (stroke);

[21] have a known clinically significant gastric emptying abnormality (eg, severe diabetic gastroparesis or gastric outlet obstruction) at study entry, or have undergone bariatric surgery (gastric bypass procedure, sleeve gastrectomy, adjustable gastric band or biliopancreatic diversion with duodenal switch) in the past;

[22] have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine transaminase (ALT) level >2.5 times the upper limit of the reference range, as determined by the central laboratory at study entry; patients with NAFLD are eligible for participation in this trial;

[23] had chronic or acute pancreatitis any time prior to study entry;

[24] have an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2, calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) equation, as determined by the central laboratory at study entry and confirmed at **Visit** 2;

[25] have evidence of a significant, uncontrolled endocrine abnormality (eg, thyrotoxicosis, adrenal crisis) at study entry, in the opinion of the investigator;

[26] have any self or family history of type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) in the absence of known C-cell hyperplasia (this exclusion includes patients with a family history of MEN 2A or 2B, whose family history for the syndrome is rearranged during transfect [RET]-negative; the only exception for this exclusion will be for patients whose family members with MEN 2A or 2B have a known RET mutation and the potential patient for the study is negative for the RET mutation);

[27] have any self or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial, or part of MEN 2A or 2B syndrome);

[28] have a serum calcitonin ≥20 pg/mL as determined by the central laboratory at study entry;

[29] have evidence of a significant, active autoimmune abnormality (eg, lupus, rheumatoid arthritis) at study entry;

[30] have a history of transplanted organ (corneal transplants [keratoplasty] are allowed);

[31] have a history of an active or untreated malignancy, or are 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) during the last 5 years prior to study entry;

[32] have a history of any other condition (eg, known drug or alcohol abuse or psychiatric disorder) at study entry, that, in the opinion of the investigator, may preclude the patient from following and completing the protocol;

[33] have any hematologic condition that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle-cell disease) at study entry;

[34] 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;

[35] are Lilly employees;

[36] have participated within the last 30 days in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed;

[37] 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;

[38] have previously screen failed, withdrawn, discontinued or completed this study or been randomized in any other study investigating dulaglutide.

5.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

5.4. Lifestyle and/or Dietary Requirements

Per the Schedule of Activities (Appendix 2), qualified medical staff will provide diabetes management counseling, which includes diet, exercise, and education about the signs, symptoms, and treatment of hypoglycemia, should it occur. Patients should continue their usual exercise habits and generally follow a stable meal plan (with consistent meal size and time of day) throughout the course of the study. Instruction on how to assess carbohydrate content and caloric content of meals may be incorporated into the counseling. Dietary counseling may be reviewed throughout the study, as needed.

6. Treatment

6.1. Treatments Administered

This study involves a comparison of dulaglutide 1.5 mg and dulaglutide 0.75 mg versus placebo, given once weekly as a subcutaneous injection in patients with T2D who are already treated with a stable dose of SGLT2 with or without stable dose of metformin. Table GBGE.2 shows the treatment regimens.

Table GBGE.2. Study Treatments and Concomitant Medications

Name of Drug	Dosage	Frequency	Drug Formulation	Route of Administration
Investigational Compound				
Dulaglutide	1.5 mg	Once weekly	Single-dose pen	Subcutaneous injection
Dulaglutide	0.75 mg	Once weekly	Single-dose pen	Subcutaneous injection
Comparator				
Placebo	Placebo	Once weekly	Single-dose pen	Subcutaneous injection
Concomitant SGLT2 inhibitor for all treatment arms				
Canagliflozin	100 mg or 300 mg	Once daily	Tablet	Oral
Dapagliflozin	5 mg or 10 mg	Once daily	Tablet	Oral
Empagliflozin	10 mg or 25 mg	Once daily	Tablet	Oral
Concomitant metformin for all treatment arms				
Metformin	1500 mg to 3000 mg[a]	Variable	Tablet/liquid	Oral

Abbreviations: GI = gastrointestinal; SGLT2 = sodium-glucose co-transporter 2.

[a] Range between minimum required dose of ≥1500 mg/day (lower [or highest tolerated] dose is acceptable with documented GI intolerability) and maximum approved dose for metformin per country-specific label. Maximum approved dose may vary across labels.

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

- explaining the correct use of the investigational agent(s) to the patient or patient representative, and SDP training with a demonstration device
- explaining the correct use of concomitant SGLT2 inhibitors and metformin (if used) to the patient, including any contraindications and appropriate dosing per country-specific labeling
- verifying that instructions described above are followed properly
- maintaining accurate records of investigational product dispensing and collection

Patients should return all unused study drug to the site according to the Schedule of Activities (Appendix 2). The patients should be instructed to discard all used SDPs in a closeable, puncture-resistant container, and dispose according to local regulations. Sites may be authorized to destroy used and unused SDPs locally per applicable local or national requirements.

6.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 5. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign cartons containing double-blind investigational product to each patient. Site personnel will confirm that they have located the correct cartons by entering a confirmation number found on the carton label into the IWRS.

Block randomization will be used at the country level. Patients will be randomized in a 1:1:1 ratio. Stratification for baseline HbA1c (≤8.0%, >8.0%), dose of SGLT2 inhibitor ("low" or "high"), and metformin use ("yes" or "no") will be used to mitigate against baseline heterogeneity between treatment groups. For the purpose of patient stratification, low dose of SGLT2 inhibitor is defined as the lowest dose approved in any of the participating countries (canagliflozin 100 mg, dapagliflozin 5 mg, empagliflozin 10 mg); high dose is defined as any dose higher than the low dose.

6.2.1. Selection and Timing of Doses

Details of the dosing strategy and administration timing for injectable study drug that are provided in this section and the following sections are designed to achieve HbA1c <7.0% without hypoglycemia, a standard treatment goal in this population.

6.2.1.1. Dulaglutide or Placebo Injections

All patients will inject study drug subcutaneously in the abdomen or thigh using the injection supplies provided; a caregiver may administer the injection in the patient's upper arm. A new SDP will be used for each injection.

Study drug will be administered once weekly. It is recommended that patients inject the study drug at approximately the same time of day on the same day each week. If the injection is not given on the scheduled day, the missed dose should be given as soon as possible after the scheduled day if there are at least 3 days (72 hours) until the next injection. If fewer than 3 days remain before the next scheduled injection, the missed dose should be skipped and the next dose given at the regularly scheduled time and day.

6.3. Blinding

This is a double-blind study.

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 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) 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. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

6.4. Packaging and Labelling

The sponsor will provide dulaglutide and placebo in SDPs, which will be dispensed via an IWRS. Each SDP (0.75 mg dulaglutide in 0.5 mL OR 1.5 mg dulaglutide in 0.5 mL OR placebo in 0.5 mL) is packaged in cartons of 4 pens. Each carton contains a 4-week supply, as each pen is a weekly dose.

Clinical trial materials will be labeled according to the country's regulatory requirements.

6.5. Preparation/Handling/Storage

The study site must store the SDP cartons in a locked and secure environment. The SDPs must be refrigerated (not frozen) at 2°C to 8°C until use. Dry ice should not be used for cooling. Patients will be provided with cartons contain ing 4 dulaglutide or placebo SDPs, as required, at clinic visits per the Schedule of Activities (Appendix 2). They will receive insulated bags with cooling gel packs for use in transporting the SDP carton from the site to home. Investigational products in each participating country will be labeled according to the country's regulatory requirements.

Where appropriate, SGLT2 inhibitors and metformin may be obtained locally by the Lilly affiliate in the participating country from local commercial supplies and distributed to sites. It is acceptable for patients to continue obtaining metformin by previous prescribing process. In the case of individual countries, with study team approval, it is acceptable for patients to continue obtaining SGLT2 inhibitors by previous prescribing process. In the United States and Puerto Rico, a prescription card will be available for patients to obtain these medications, with a prescription.

Clinical trial materials in each participating country will be labeled according to the country's regulatory requirements.

Dulaglutide demonstration pens will be provided for subcutaneous injection training at the site; these pens do not have needles and do not contain study drug.

Patients will also be provided with a commercially available PG meter and test strips to use during the study. Sufficient study drug material and glucose testing supplies will be dispensed, as needed, at each visit.

Study site staff must regularly assess whether the patient is correctly administering the assigned study drug and storing the study drug according to the provided instructions.

6.6. Dose Modification

No adjustment in injectable study drug dose (dulaglutide or placebo) will be allowed.

During the 24-week treatment period, participants are required to continue using their concomitant OAMs. Discontinuation of these medications or changes in their dose is not permitted, except in situations where dose adjustments or complete discontinuation is required per country-specific label or when allowed per study protocol, for example, in the case of hypoglycemic episodes (Section 6.8.1.1).

6.6.1. Special Treatment Considerations

6.6.1.1. Standards of Medical Care

Maintenance of adequate glycemic control in study participants may be enhanced but should not be compromised due to trial participation. Investigators and other study team members are expected to treat patients according to the nationally established standards of care for diabetes management in respective participating countries, except where that treatment would be in conflict with the protocol-provided treatment requirements. If there are no local standards of care for diabetes, the investigators should follow current published standards of care from the American Diabetes Association and the European Association for Study of Diabetes (Inzucchi et al. 2015) during their patients' participation in this study.

This section provides guidance on management of episodes of hypoglycemic events and severe, persistent hyperglycemia. For effective implementation of measures described here, it is important that patients, and their caregivers, if applicable, be well-educated about the signs and symptoms of hyperglycemia (eg, severe thirst, dry mouth, frequent micturition, or dry skin) and hypoglycemia (eg, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders). Patients should be instructed to contact the investigative site in the event of severe, persistent hyperglycemia or severe hypoglycemia between study visits.

6.6.1.2. Management of Increased Hypoglycemia Risk

If a hypoglycemic event occurs, the patient should record in the study diary the PG level measured during the episode and prior to administration of treatment (if taken), as well as associated symptoms, and treatment administered. Site personnel should educate and encourage patients to measure and record PG values during the symptoms of hypoglycemia and enter the results into their study diaries. Patients should be instructed to call the investigative site as soon as possible if they experience a hypoglycemic event that requires assistance to administer treatment.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia: (the PG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and

Laboratory Medicine plasma-equivalent glucose meters and strips) (American Diabetes Association 2005):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of ≤70 mg/dL (≤3.9 mmol/L).
- **Asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured PG of ≤70 mg/dL (≤3.9 mmol/L).
- **Probable symptomatic hypoglycemia** is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by a PG concentration of ≤70 mg/dL [≤3.9 mmol/L]).
- **Severe hypoglycemia** is defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

Cases of relative hypoglycemia, defined as symptomatic events during which the person reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but a measured PG concentration of >70 mg/dL (>3.9 mmol/L), will also be collected.

If a hypoglycemic event meets the criteria of severe, it needs to be recorded as serious on the AE case report form (CRF) and reported to Lilly as an SAE.

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The patient should receive additional education, if deemed appropriate.

Because of its mechanism of action, no adjustment of dulaglutide dose should be made to counteract increased risk of hypoglycemia. If, in the opinion of the investigat or, treatment regimen requires adjustment because of repeated episodes of hypoglycemia, initial step should be dose reduction of metformin, followed by its complete withdrawal, if needed. In the case of continuously increased risk of hypoglycemia despite discontinuation of metformin, dose reduction or complete withdrawal of the SGLT2 inhibitor is permitted.

Investigators are responsible for their patients' management and well-being; therefore, it is their responsibility to implement these generally recommended interventions provided above, taking into account clinical and other relevant criteria.

6.6.1.3. Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period

An additional therapeutic intervention should be considered in patients who develop persistent, severe hyperglycemia after randomization based on the following criteria:

a) Average daily PG from the 4-point SMPG profile >240 mg/dL over at least a 2-week period any time during the first 4 weeks postrandomization; or
b) Average daily PG >200 mg/dL over a 2-week period at any time after the first 4 weeks postrandomization.

Investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that they do not have an acute condition causing severe hyperglycemia. The investigator will decide in consultation with the patient on an appropriate glucose-lowering intervention (rescue) after considering relevant clinical criteria. Other GLP-1 RAs must not be included in the rescue intervention. Patients who receive a new intervention should also continue administering study drug for the remaining period in the trial.

6.7. Treatment Compliance

The assessment of treatment compliance with study drug (dulaglutide or placebo) will be determined by the following:

- Information about the administration of once weekly study drug injections will be entered into the patient diary by the patient and reviewed by the site personnel at each study visit; this information will be collected in the eCRF;
- Study drug accountability will be checked at every visit. For that purpose, patients will be instructed to return the study drug carton at the next study visit. They will also be instructed to return any unused study drug at the next study visit;
- In both treatment arms, treatment compliance for once weekly study drug for each visit interval is defined as taking at least 75% of the required doses of study drug as assessed by site personnel; this information will be entered in the eCRF.

Other aspects of compliance with the study treatments will also be assessed at each visit based on the patient's adherence to the visit schedule, compliance with the concomitant SGLT2 inhibitor and metformin and requirements for non-study glucose-lowering agents, completion of study diaries, results of SMPG, and any other parameters the investigator considers necessary. Patients considered to be poorly compliant with their medication and/or the study procedures (for example, missed visits or specific diagnostic tests) will receive additional training and instructions, as required in the protocol.

6.8. Concomitant Therapy

Patients are permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study drug.

Investigative site staff will inform patients that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study,

except when initiated for treatment of medical emergencies . Any additional medication initiated during the course of the study (including OTC drugs, such as paracetamol or aspirin) must be documented, and the name of the drug and the date(s) of administration must be recorded in the patient's diary and on the "Concomitant Medications" section of the eCRF. In addition, for allowed concomitant glucose-lowering agents, the dosage will also be documented and collected (SGLT2 inhibitors and metformin).

Nonstudy medications taken by patients who are screened but not randomized will not be reported to Lilly unless an SAE or AE occurs that the investigator believes may have been caused by a study procedure.

6.8.1. Antihyperglycemia Medications

The only glucose-lowering agents that are allowed 3-months prior to study entry and during the study are study drug and concomitant SGLT2 inhibitors and metformin. In addition, short-term insulin use for management of medical emergencies is allowed prior to study entry and after randomization (Visit 5), but not during screening and lead-in/stabilization (Sections 5.1 and 5.2). Rescue therapy with other glucose-lowering agents, including insulin, may be medically indicated in certain situations after randomization. These situations are described in Section 6.6.1.3 (severe, persistent hyperglycemia) and in Section 7.1.1 (early discontinuation of study drug). If any such situation occurs, the patient may be treated with any locally-approved glucose-lowering agent, except other GLP-1 RAs. If insulin is prescribed as a rescue therapy, it must be differentiated from short-term use of insulin therapy for medical emergencies when reported in the eCRF.

Patients who receive any glucose-lowering agents 3 months prior to entryor during the screening or lead-in/stabilization periods, other than those allowed, will not be eligible for further participation in the trial. The patients not using metformin prior to study entry (Visit 1) are not allowed to initiate this therapy between study entry and Visit 5 . Patients who violate this requirement will be considered as ineligible and will be discontinued from further participation in this trial.

If any new glucose-lowering medication is initiated after randomization at Visit 5, other than rescue therapy or short-term use of insulin for medical emergencies, the patient will be required to immediately discontinue the medication and the appropriate study deviation report will be generated. Any such violation of the protocol that lasted longer than 14 days will exclude the patient from the per-protocol (PP) population. Patients who receive insulin therapy for management of medical emergencies >14 days as well as those who receive rescue therapy, will also be excluded from the PP population.

6.8.1.1. Allowed Concomitant OAMs

The key requirements for use of SGLT2 inhibitors and metformin, the allowed OAMs in Study GBGE, are provided in Section 5.1 and Section 5.2. Table GBGE.3 provides minimum required and maximum approved doses for these agents (Note: for SGLT2 inhibitors, these are the only approved doses per country-specific labels ["low" and "high" dose]; therefore, no other doses should be used during this study). The minimum required doses correspond to the lowest

recommended dose per country-specific label and may not be the same dose in all participating countries. All prescribed doses to the study participants must comply with country-specific labels for these medications.

Table GBGE.3. Required Doses of Concomitant SGLT2 Inhibitors and Metformin in Study GBGE for Patients Already Using These Agents

Drug Class	Minimum-Required Dose[a]	Maximum Dose[a]
Canagliflozin		
eGFR >60 mL/min/1.73 m^2	100 mg QD	300 mg QD
eGFR 45-60 mL/min/1.73 m^2	100 mg QD	100 mg QD
eGFR <45 mL/min/1.73 m^2	**Contraindicated**	**Contraindicated**
Dapagliflozin		
eGFR ≥60 mL/min/1.73 m^2	5 or 10 mg QD[b]	10 mg QD
eGFR <60 mL/min/1.73 m^2	**Contraindicated**	**Contraindicated**
Empagliflozin		
eGFR >60 mL/min/1.73 m^2	10 mg QD	25 mg QD
eGFR 45-60 mL/min/1.73 m^2	10 mg QD	10 or 25 mg QD[b]
eGFR <45 mL/min/1.73 m^2	**Contraindicated**	**Contraindicated**
Metformin		
eGFR ≥60 mL/min/1.73 m^2	1500 mg[c]	2550 mg or 3000 mg[b]
eGFR <60 mL/min/1.73 m^2	**Contraindicated**	**Contraindicated**

Abbreviations: eGFR = estimated glomerular filtration rate; QD = once-daily; SGLT2 = sodium-glucose co-transporter 2.

[a] Based on the labels approved in participating countries.

[b] These doses may differ in different countries, and country-specific labels are required to be followed to reach decisions appropriate for individual patients.

[c] Lower dose allowed in the case of documented intolerability.

Note: eGFR calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) equation and will be provided by the central laboratory.

6.8.1.1.1. SGLT2 Inhibitors

Patients in this study are required to be treated with an SGLT2 inhibitor for at least 3 months prior to Visit 1. The dose during this time must be at least the minimum required dose, per country-specific label. The dose may be adjusted between Visit 2 and Visit 3, if required per label and to comply with the protocol requirements. Dose adjustment may be considered in the following situations:

a) For patients who are on the minimum-required doses of SGLT2 inhibitors that is lower than the maximum approved dose at study entry (Visit 1); no further dose increase for these patients is required; however, if judged by the investigator as clinically appropriate and if allowed per label, dose increase is not prohibited;

b) For patients with a confirmed eGFR 45 to 59 mL/min/1.73 m^2 (see Appendix 2 for further details on handling of low eGFR): dapagliflozin, if used, should be immediately discontinued when required per label; for these patients, they could either be discontinued from the study, or if the local label allows, patients could be prescribed another SGLT2

inhibitor to maintain eligibility; the dose of canagliflozin and empagliflozin, if used, would need to be reduced if required per local label (see Table GBGE.3).

For patients who adjust their SGLT2 inhibitor regimen between Visit 2 and Visit 3 for reasons described under a) and b), or for any other reason per product label, they will be required to undergo stabilization. The type and dose of SGLT2 inhibitor should remain unchanged during stabilization. For all randomized patients, the type and dose of the SGLT2 inhibitor should remain unchanged during the treatment period other than as described below.

Those patients who discontinue therapy with SGLT2 inhibitors prior to randomization at Visit 5 will be discontinued from the trial.

After randomization, dose adjustment or discontinuation of SGLT2 inhibitors is allowed u nder the following circumstances:

- in situations that require short-term treatment interruption consistent with the product labeling for each respective country;
- in situations that require dose adjustment or discontinuation per country-specific label, for example, in the case of reduced eGFR;
- in the case of increased hypoglycemia risk during the treatment period (as described in Section 6.6.1.2).

Dose reduction/discontinuation of SGLT2 inhibitors during the trial should be properly documented.

In patients who require rescue therapy, dose increase of SGLT2 inhibitors is allowed, but the dose and the reason for change must be properly documented in the eCRF.

6.8.1.1.2. Metformin

Patients in this study are not required to be treated with metformin to be eligible for participation, but if used for at least 3 months prior to study entry, metformin therapy should be continued during the entire trial. Those patients not using metformin prior to study are not allowed to initiate this medication after entry. Patients who use metformin should have been on at least the minimum-required dose for at least 12 weeks prior to randomization at Visit 5. If metformin therapy adjustment is required at Visit 2 per label and/or to meet protocol dosing requirements, the site personnel will instruct the patient on the changes needed prior to Visit 3. Metformin treatment adjustments may be considered in the following situat ions:

a) If the dose of metformin is less than the minimum-required (≥1500 mg/day) at Visit 1; the dose should be up-titrated based on efficacy and safety parameters per label; a lower dose will be acceptable only in the case of documented (ie, recorded in the patient's medical file) poor GI tolerability of the minimum required dose (that is, the highest tolerated dose) prior to Visit 1 or between Visit 2 and Visit 3;

b) For patients who are on the minimum-required doses of metformin that is lower than the maximum approved dose at study entry(Visit 1), no further dose increase is required;

however, if judged by the investigator as clinically appropriate and if allowed per label, dose increase is not prohibited;

c) For patients with a confirmed eGFR 45 to 59 mL/min/1.73 m^2 (see Appendix 2 for further details on the handling of low eGFR); metformin should be immediately discontinued when required per country-specific label (see TableGBGE.3);

For patients who change their metformin regimen between Visit 2 and Visit 3 for reasons described under a), b) and c), or for any other reason per product label, the patient will be required to undergo stabilization and the dose should remain unchanged during stabilization. For all randomized patients, the dose of metformin should remain unchanged during the entire study other than as described below.

Those patients who discontinue metformin between Visit 3 and Visit 5 will be discontinued from the trial. Discontinuation of metformin, if required per label, is allowed prior to Visit 3, in which case, the patient will perform stabilization.

Dose adjustment or discontinuation of metformin is allowed after randomization under the following circumstances:

- in situations that require short-term treatment interruption in line with the product labeling for each respective country;
- in situations that require dose adjustment or discontinuation per country-specific label, for example, in the case of reduced eGFR;
- in the case of increased hypoglycemia risk during the treatment period (as described in Section 6.6.1.2).

Dose reduction/discontinuation of metformin during the trial should be properly documented.

In patients who require rescue therapy, dose increase or initiation of metformin is allowed, but the dose and the reason for change/initiation must be properly documented in the eCRF.

6.8.2. Medications that Promote Weight Loss

Prescription or OTC medications that promote weight loss are exclusionary if used 3 months prior to study entry, or between study entry and randomization at Visit 5 (see Section 5.2). These medications are also not allowed at any time during the treatment period. If started, they should be immediately withdrawn. Patients who use any medication from these groups during the treatment period will not be included in the PP analysis if the duration of use is >14 days (cumulative). In addition, patients should not receive a diet/exercise program with the intent of reducing body weight at any time during the study, other than the lifestyle and dietary measures for diabetes treatment (see Section 5.4).

6.8.3. Systemic Glucocorticoids

Chronic systemic glucocorticoid therapy (with the exception of topical, intraocular, intra-articular, or intranasal preparations) is exclusionary if used >14 consecutive days during the 1-month period before study entry or between study entry and randomization at Visit 5. This

therapy is not allowed during the treatment period and patients who require >14 days of therapy with these medications will not be included in the PP analysis.

6.8.4. Antihypertensive Medications

If used, antihypertensive therapy should be kept stable throughout the trial to allow assessments of the effect of randomized therapies on blood pressure. If initiation of any new blood pressure lowering agent is required at any time during the study, the type and dose of medication must be documented in the eCRF.

6.9. Treatment after Study Completion

6.9.1. Continued Access

After study treatment is discontinued, an appropriate diabetes treatment regimen will be initiated by the investigator.

7. Discontinuation Criteria

7.1. Discontinuation from Study Treatment

Study drug may be interrupted temporarily or discontinued permanently.

7.1.1. Permanent Discontinuation of Study Treatment

Patients will be permanently discontinued from study drug in the following circumstances:

- For inadvertently enrolled patients for whom it was determined that continued treatment with study drug would not be medically appropriate (see Section 7.1.4);
- Exclusion Criteria [31] and [38] develop(s), after randomization (see Section 5.2);
- The patient is diagnosed by the investigator with an AE of acute or chronic pancreatitis;
- A patient is diagnosed with C-cell hyperplasia or medullary thyroid carcinoma after randomization;
- If a patient develops an eGFR <30 mL/min/1.73m^2 as calculated by CKD-EPI;
- If the patient or the patient's designee, for example, legal guardian, requests to be withdrawn from study drug;
- If the investigator or sponsor decides that the patient should be withdrawn from study drug; if the sponsor decides to permanently discontinue study treatment because of an SAE or a clinically significant laboratory value, Lilly or its designee should be alerted immediately [see Section 8.2.1]);
- 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:
    - ALT or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
    - ALT or AST >5X ULN for more than 2 weeks
    - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or prothrombin time >1.5X ULN
    - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
    - Alkaline phosphatase (ALP) >3X ULN
    - ALP >2.5X ULN and TBL >2X ULN
    - ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Those patients who stop the study drug permanently will receive another glucose-lowering intervention (rescue) and will continue participation in the trial according to the protocol, to collect all planned efficacy and safety measurements. The rescue intervention must not include another GLP-1 RA.

7.1.2. Permanent Discontinuation from the Study

Every attempt should be made to keep patients in the trial irrespective of their adherence to treatment with study drug in order to minimize the amount of missing data and to enable assessment of study objectives as planned by the study protocol (Fleming 2011). Patient discontinuation from the study early may be warranted in the following situations for ethical or legal reasons:

- Exclusion Criterion [11]
- When a female patient becomes pregnant;
- When a patient is enrolled in another clinical trial involving an investigational product or is enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

Patients may also discontinue from the study due to:

- Sponsor or Investigator Decision
    - If Lilly or its designee stops the study or if Lilly or the investigator stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Patient Decision
    - The patient or the patient's designee, for example, legal guardian, requests to be withdrawn from the study

Prior to early study discontinuation, the patient will discontinue study drug and will have end -of-study procedures (ET visit) performed as shown in the Schedule of Activities (Appendix 2). During the ET visit the patient will be prescribed an appropriate glucose-lowering regimen and glucose self-monitoring plan.

7.1.3. Temporary Interruption of Study Treatment

In certain situations after randomization, t he investigator may need to temporarily discontinue (interrupt) study drug (for example, due to an AE or a clinically significant laboratory value). If study drug interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 8.2 of this protocol. Investigators should inform the Sponsor that study drug has been temporarily interrupted. Every effort should be made by the investigator to maintain patients on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so. The data related to temporary interruption of study treatment will be documented in source documents and entered in the eCRF.

7.1.4. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP and the investigator to determine if the patient may continue in the st udy. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with

investigational product. An inadvertently enrolled patient may be allowed to continue treatment with study drug only if the principal investigator and Lilly study physician responsible for medical monitoring of this trial agree that it is safe for the patient to do so.

7.1.5. Patients Lost to Follow-Up

A patient will be considered lost to follow-up if he or 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.

8. Study Assessments and Procedures

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

Appendix 3 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the 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 (Sections 8.7 and 8.8).

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

The primary efficacy measure is change in HbA1c from baseline at 24 weeks.

8.1.2. Secondary Efficacy Assessments

The following key secondary efficacy measures will be evaluated at 24 weeks:

- Proportion of patients achieving HbA1c target of <7.0%
- Changes in FBG from baseline measured at the central laboratory
- Changes in body weight from baseline

Other secondary efficacy measures will also be evaluated at 24 weeks:

- Proportion of patients achieving HbA1c target of ≤6.5%
- Changes from baseline in PG from 6-point SMPG profile
- Changes in fasting glucagon from baseline

8.1.3. Exploratory Assessments

The following exploratory measures will be evaluated at 24 weeks:

- Percentage of patients achieving HbA1c target <7.0%, with no weight gain and no documented symptomatic hypoglycemia
- Percentage of patients achieving HbA1c target <7.0%, with body weight loss >5%, and no documented symptomatic hypoglycemia

8.1.4. Appropriateness of Assessments

Efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with T2D.

8.2. 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 treatment effect.

After the informed consent form (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 via eCRF 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 study procedure, investigational product, and study device via eCRF.

The investigator decides whether he or she interprets the observed AEs as reasonably possibly related to disease, to the investigational product, study device, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AEs, the following is defined:

> **Reasonably Possibly Related:** Reasonable possibility 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.

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 .

8.2.1. 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 (that is, 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 result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs after signing the ICF are recorded in the eCRF, SAE reporting 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, it needs to be reported ONLY 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 with 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 CRF 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.

Requirements for the reporting of severe hypoglycemia episodes, AEs of pancreatitis, and AEs of systemic hypersensitivity as SAEs are found in Section 8.2.2.

8.2.1.1. 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.

8.2.2. Adverse Events of Interest

8.2.2.1. Hypoglycemia and Hyperglycemia

Patients will collect information on episodes of hypoglycemia between Visit 2 and the last study visit (Visit 11 or ET visit). For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia in the study diary (see Section 6.6.1.2) according to the Schedule of Activities (Appendix 2). Site personnel will enter this information into the eCRF at each visit after Visit.

Events of interest related to hyperglycemia (rescue therapy for severe, persistent hyperglycemia, per criteria specified in Section 6.6.1.3, and ketoacidosis) will be collected during the trial to assess the risk of extreme disbalance in glycemic control.

8.2.2.2. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with dulaglutide, including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

1. Abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases [Banks and Freeman 2006; Koizumi et al. 2006]; the pain is often associated with nausea and vomiting);
2. Serum amylase (total and/or pancreatic) and/or lipase ≥3×ULN; or
3. 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 supports 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 6.8.1 and Section 7.1.1 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 pancr eatitis, each patient will have measurements of pancreatic amylase and lipase at screening, baseline, and the last study visit (Visit 11 [Week 24] or ET visit), to assess any potential effects of dulaglutide on the exocrine pancreas (refer to the Schedule of Activities, Appendix 2). 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 11 (Week 24), the patient will be required to undergo this additional work-up, and the data will be collected in the clinical trial database.

All AEs 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.

8.2.2.3. 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 5.2). The assessment of thyroid safety during the trial will include reporting of thyroid treatment-emergent adverse events (TEAEs) and measurements of calcitonin according to the Schedule of Activities (Appendix 2) at screening, baseline, and Visit 11 (Week 24). The purpose of calcitonin measurements is to assess the potential of dulaglutide versus placebo to affect the thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Patients who develop serum calcitonin increases ≥50% of the mean of the baseline and screening values AND an absolute value ≥20 pg/mL and <35 pg/mL at Visit 11 (Week 24) will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be recommended that he or she undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude a serious adverse effect on the gland.

Patients with an increase in serum calcitonin ≥50% of the mean of the baseline and screening values AND an absolute value ≥35 pg/mL at Visit 11 (Week 24) will be recommended to immediately undergo additional e ndocrine assessments and longer-term follow-up by an endocrinologist.

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.

8.2.2.4. Cardiovascular Events

Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. The nonfatal CV AEs to be adjudicated include: MI; hospitalization for unstable angina; hospitalization for heart failure; coronary i nterventions (such as coronary artery bypass graft or percutaneous coronary intervention); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack (TIA).

8.2.2.5. Renal Events

Renal safety will be assessed based on repeated renal functional assessment, as well as assessment of AEs suggestive of acute and chronic renal failure.

8.2.2.6. Allergic/Hypersensitivity Reactions

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to study drug via a CRF created for this purpose. Study drug should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug (Section 7.1.3). Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug is permanently discontinued, the patient will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the patient's clinical status, and will continue in the trial to collect all planed efficacy and safety measurements (see Section 6.8.1 and Section 7.1.1).

8.2.3. 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 or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.3. Treatment of Overdose

Study drug overdose will be reported as an AE. In the event of overdose, refer to the IB and/or Product Label.

8.4. Safety Assessments

8.4.1. Electrocardiograms

Episodes of symptomatic hypotension have been reported in patients treated with SGLT2 inhibitors, while treatment with dulaglutide increases the mean heart rate (HR) (2 to 4 beats/min) and the mean duration of the PR interval (2 to 3 msec). To assess the effect of their combined

use on cardiac electrophysiology in Study GBGE , electrocardiograms (ECGs) will be collected according to the Schedule of Activities (Appendix 2) and centrally overread. Electrocardiograms should be recorded according to the study-specific recommendations included in the Manual of Operations for the study, using standardized equipment provided by the Sponsor.

Each ECG tracing will be assessed by the investigator immediately upon recording for clinical management purposes. 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 via eCRF. Results of the central overread will be entered into the clinical trial database and will be used for the statistical analysis of the effects of the randomized treatments. In addition, once the overread ECG is returned from the centralized ECG vendor, the investigator, or qualified designee, is responsible for determining if any change to the patient management is needed. The investigator, or qualified designee, must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

8.4.2. Blood Pressure and Heart Rate

Sitting blood pressure (BP) and HR will be measured according to the Schedule of Activities (Appendix 2), using standardized equipment provided by the Sponsor. Vital sign measurements should be taken before obtaining an ECG tracing, at visits where required (see Schedule of Activities, Appendix 2), and before collection of blood samples for laboratory testing. For each parameter, 2 measurements will be taken using the same arm. 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. Each measurement of sitting HR and BP is to be recorded in the eCRF. Any AE related to changes in BP and HR should be reported, per requirements provided in Section 8.2.

8.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 3 should be conducted according to the Schedule of Activities (Appendix 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 via eCRF.

8.4.4. Body Weight and Body Mass Index

Body weight will be measured at prespecified time points (see Schedule of Activities, Appendix 2). Each patient's weight should be measured according to a standardized protocol (Appendix 7). Body mass index will be computed from the patient's weight and height.

8.4.5. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods, including trends in safety variables, laboratory analytes, and AEs. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly study physician

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 prov ided in Section 8.2.2.2 and 8.2.2.3. Details of the liver safety monitoring are provided in Appendix 4. If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X 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/subject safety and comply with regu latory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information a nd follow-up laboratory tests.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

A blood sample will be collected for pharmacogenetic analysis where local regulations and ERBs allow (Appendix 2). These samples are not being collected to create a biobank for conducting unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable response to dulaglutide, and to investigate genetic variants thought to play a role in diabetes and diabetes-related complications. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to the genetic variants in drug target pathway (glucagon-like peptide 1 receptor [GLP1R]) genes and genes associated with diabetes and related complications (eg, transcription factor 7-like 2 [TCF7L2]). Samples will be retained for a maximum of 15 years after the last subject visit, or as local regulations and ERBs allow, for the study at a facility selected by the sponsor. 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 drug development or when the drug is commercially available. Molecular technologies are expected to improve during the 15 year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, genotyping data generated will be used only for the specific research scope described here.

8.8. Biomarkers

Serum and plasma samples for non-genetic biomarker research will be collected at the times specified in the Schedule of Activities (Appendix 2) where local regulations and ERBs allow.

Samples will be used for research on the drug target, disease process, pathways associated with T2D, mechanism of action of dulaglutide, and/or research method or in validating diagnostic tools or assay(s) related to T2D.

All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum 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 the sponsor. 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 drug development or when the drug is commercially available.

8.9. Health Economics

Not applicable.

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

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

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The primary analysis population will be the intent -to-treat (ITT) population, defined as all patients randomized who have received at least 1 dose. This is also the safety population. A select number of measurements (HbA1c, percent to goal in HbA1c, FBG, and body weight) will also be evaluated in the PP population and completer population. The PP population will be based on patients who were compliant with study medication, took no concomitant medications that would confound the interpretation of results (such as systemic steroids or non-study glucose-lowering agents used >14 days), and have an HbA1c measurement at the primary visit endpoint. The completer population will be based on patients who completed the treatment period.

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

Analyses of key secondary efficacy outcomes (percent to goal in HbA1c, FBG, body weight) and hypoglycemia will also be performed on the full dataset, excluding and including data collected after initiation of rescue with glucose -lowering therapy.

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

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

Two analysis models will be used for the primary and key secondary continuous efficacy measures. The primary analysis will be mixed-model repeated measure (MMRM) analysis using restricted maximum likelihood (REML) (Section 9.4.1). An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the following covariance structures will be tested in order:

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

The first covariance structure that converges will be used.

The secondary analysis for the primary and key secondary continuous endpoints will be analysis of covariance (ANCOVA) (Section 9.4.2). Missing endpoints will be imputed with the last (postbaseline) observation carried forward (LOCF). The percentage of patients achieving the target HbA1c of <7.0% at 24 weeks will be analyzed using a longitudinal logistic regression with repeated measurements (Section 9.4.2).

A graphical testing approach for each estimand separately will be used to strongly control for type 1 error to test for superiority of each of the dulaglutide doses versus placebo at 24 weeks for the following measures: (1) change from baseline in HbA1c, (2) change from baseline in FBG (central laboratory), (3) percent achieving HbA1c <7.0%, and (4) change from baseline in body weight.

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

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

9.3. Treatment Group Comparability

9.3.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study.

Frequency counts and percentages of all patients entered, randomized/enrolled, completing, discontinuing from the study drug early, and discontinuing from the study early will be presented for each of the treatment groups. The reasons for discontinuation from the study and/or study drug will be summarized by treatment group. A summary of discontinuations will also be presented by visit.

The overall percent discontinued comparisons among the treatment groups will be performed using a chi-square test.

9.3.2. Patient Characteristics

Demographic and baseline characteristics will be summarized for both treatment arms.

9.3.3. Concomitant Therapy

Glucose lowering agents will be summarized by treatment at entry, baseline (Visit 5), and for the entire 24-week treatment period. Doses of SGLT2 inhibitors and metformin will be summarized at baseline (Visit 5). Other prespecified concomitant medications of interest will be summarized by treatment at baseline (Visit 5). Frequency of use of non-study glucose-lowering medications will be summarized at baseline (Visit 5) and for the entire 24-week treatment period by treatment group.

9.3.4. Treatment Compliance

Treatment compliance for each visit interval is defined as taking at least 75% of required injections. Overall compliance is defined as being at least 75% compliant with study drug for at least 75% of the visits. The investigator will advise the patient that injections should be given at approximately the same time of the day, on the same day of the week. Compliance will be summarized by all treatment arms, by visits and overall. Listings will also be produced.

9.4. Primary and Secondary Analyses

9.4.1. Primary Outcome Measure and Analyses

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

The primary analysis model will be an MMRM for HbA1c change from baseline to 24 weeks in the ITT population (Visit 11) with treatment, country, SGLT2 inhibitor dose (“low” vs “high”; see Section 6.2), metformin use (“yes” vs “no”), visit and treatment-by-visit as fixed effects, baseline HbA1c as a covariate, and patient as a random effect.

9.4.1.1. Additional Analyses of the Primary Outcome

The primary analysis model, MMRM, will be repeated using the PP population and completer population to check the sensitivity of the analysis. If the conclusion differs from that of the ITT population, the data and analyses will be further investigated. The secondary analysis model will be an ANCOVA for HbA1c change from baseline to 24 weeks (Visit 11), using a similar model as described above with treatment, country, SGLT2 inhibitor dose (“low” vs “high”), and metformin use (“yes” vs “no”) as factors and baseline HbA1c as a covariate. Missing endpoints will be imputed with the LOCF using postbaseline data only.

To investigate departure from the missing at random (MAR) assumption for the primary analysis for both efficacy and treatment-regimen estimands, a sensitivity analysis using a particular missing not at random (MNAR) assumption will be performed. Specifically, a placebo multiple imputation (pMI) will be performed (Ayele et al. 2014), which assumes that the drug effect in missing data and postrescue data in both the placebo arm and dulaglutide arm was like the observed effect in the placebo arm (excluding postrescue data). This is essentially the “copy reference” approach as described in Carpenter et al. 2013. This approach is in essence assuming that the drug effect will decay over time, in accordance with the correlation structure implied by the data. Data imputed this way will be analyzed with the same MMRM model as the primary analysis. This particular MNAR assumption can be viewed as a “worst reasonable case” assessment of the 2 estimands. For both the efficacy estimand, and the treatment-regimen estimand, a tipping-point analysis will be performed in which the missing data are imputed with a MAR assumption. However, prior to analysis, in the dulaglutide arm, the imputed values will be replaced by the imputed value plus delta. Multiple values of delta will be tried until the value at which the conclusion from the MMRM analysis changes.

9.4.2. Secondary Outcome Measures and Analyses

The key secondary continuous efficacy measures will also be analyzed using both models, the MMRM and the ANCOVA with LOCF models described above (with and without censoring data collected after initiation of rescue intervention). Analysis of other secondary efficacy measures that are continuous variables, except glucagon (for glucagon, see Section 9.5.6), will be performed using MMRM on the ITT population. There will be no multiplicity adjustment for

pairwise comparisons. The MMRM and ANCOVA models will include the model terms given for the previously described primary analysis model with the addition of the HbA1c strata (≤8.0%, >8.0%).

For percentages of patients achieving target HbA1c of <7.0% (including exploratory composite endpoints with body weight and hypoglycemia) or ≤6.5% at 24 weeks, longitudinal logistic regression with repeated measurements will be used. The model will include independent variables treatment, country, SGLT2 inhibitor dose ("low" vs "high"), metformin use ("yes" vs "no"), visit, baseline HbA1c-by-visit interaction, treatment-by-visit, and baseline HbA1c as a covariate. These analyses will be performed with postrescue data excluded (considered missing), and separately with all postrescue data included. In addition, an analysis of percentage of patients on HbA1c targets will be performed where patients who have been rescued or have no postbaseline data being considered (imputed) as not having achieved the target.

9.5. Safety Analyses

The safety analysis will include measurements of AEs, SAEs, hypoglycemic and hyperglycemic episodes, and laboratory analytes. Unless otherwise specified, the ITT population will be used for analyses of safety measures.

9.5.1. Study Drug Exposure

Exposure to each study treatment will be calculated for each patient and summarized by treatment group. The time points for exposure summaries will be defined in the SAP.

9.5.2. Adverse Events

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported in preferred term and system organ class (SOC). Selected notable AEs of interest may be reported using high-level terms. All AEs and TEAEs, defined as postbaseline events that are new events or preexisting conditions that worsened in severity after randomization, will be listed by patient and visit. Information on treatment, actual term, preferred term, severity, seriousness, and relationship to study drug will also be reported.

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

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

9.5.3. Hypoglycemic Episodes

Section 6.6.1.2 contains definitions of categories of hypoglycemia. A listing of individual hypoglycemic episodes by patient will be presented. Summary reports will include both incidence and rates of hypoglycemia for the ITT population (with postrescue data censored, and without postrescue data censored). Hypoglycemia will be categorized as "documented

symptomatic," "asymptomatic," "probable," "severe," or "nocturnal," and for all events combined, "total hypoglycemia." Only "documented symptomatic" and "total hypoglycemia" will be analyzed inferentially.

Baseline hypoglycemia risk will be established based on hypoglycemia events recorded between Visit 2 and Visit 5. The incidence of hypoglycemic episodes will be summarized by frequencies and percentages for each treatment group, by visit as well as overall. Treatment differences in the incidence of hypoglycemic episodes will be assessed using Fisher's exact test or chi-square test for treatment comparison.

Treatment differences in rates of hypoglycemic episodes (episodes/patient/30 days; episodes/patient/year) will be assessed by the likelihood-based model for repeated measures. The model will include the same terms as in the primary analysis model with baseline hypoglycemia as a covariate instead of baseline HbA1c. The logarithm of days between visit s will be adjusted as an offset to account for possible unequal duration between visits and between patients. Certain categories of hypoglycemia may also be evaluated using a PG cutoff <54 mg/dL (<3.0 mmol/L).

9.5.4. Hyperglycemic Episodes

Listings and summaries (if appropriate) will be provided for events of severe, persistent hyperglycemia resulting in initiation of rescue therapy, as well as events of ketoacidosis.

9.5.5. Special Safety Topics

9.5.5.1. Pancreas Safety

Listings and summaries of adjudicated pancreatic events will be provided.

9.5.5.2. Cardiovascular Safety

Listings and summaries of adjudicated CV events will be provided. Heart rate and systolic and diastolic blood pressure from vital signs will be summarized as well as ECG data. Adverse events suggestive of hypotension will be provided.

9.5.5.3. Thyroid Safety

Listings of AEs of interest associated with the thyroid gland (benign and malignant neoplasms) will be produced, as well as a listing of biopsy reports.

9.5.5.4. Renal Safety

To assess renal safety, summary and analyses will be provided for eGFR, as well as shift tables. Listing of AEs suggestive of acute and chronic kidney failure will also be provided. Other reports may also be generated if deemed appropriate.

9.5.5.5. Allergic/Hypersensitivity Reactions

Summaries and listings of allergic and other hypersensitivity AEs will be provided.

9.5.6. Laboratory Analytes

Laboratory measurements will be listed by patient and visit. An additional listing will be presented for laboratory measurements that are outside the normal range.

Laboratory measurements will also be summarized. For continuous (numeric) laboratory analytes, including glucagon, the change from baseline to endpoint will be analyzed using an analysis of variance (ANOVA) on the rank-transformed data, with treatment as fixed effects. Last observation carried forward will be used to impute missing postbaseline values.

For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using chi-square tests.

9.6. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

9.7. Other Analyses

9.7.1. Subgroup Analyses

A subgroup analysis will be performed on the primary endpoint using the efficacy estimand and the same model as the primary analysis model with an added term for t he 3-way interaction visit-by-treatment-by- [subgroup]. The 2-way interaction of treatment -by-[subgroup] at the primary time point of 24 weeks will be evaluated to assess an interaction in the treatment effect with the subgroup levels. Significance will be evaluated at alpha=0.10. The following are candidate subgroups that might be analyzed. This list is not necessarily all-inclusive:

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

When analyzing baseline HbA1c as a subgroup, the baseline HbA1c will not be included as a covariate to avoid confounding.

A subgroup analysis will also be performed for the change from baseline in body weight by baseline glucagon only, using a similar approach as described for HbA1c above. Other subgroups may be assessed when considered appropriate.

For all subgroup analyses, if the MMRM fails to converge, then the corresponding ANCOVA model (LOCF) will be used.

9.8. 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.

10. Study Governance Considerations

10.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1.1. 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 or her participation in the trial.

10.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference on 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 or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae
- study diary

10.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- 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
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization (TPO).

10.1.4. Investigator Information

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

10.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or 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.

10.1.6. Final Report Signature

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

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

10.2. 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 instruction 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.

10.2.1. 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 a clinical trial database. 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 generic labs system.

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 measures (for example, 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.

10.3. Study and Site Closure

10.3.1. 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.

10.3.2. 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.

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Appendix 1. Abbreviations and Definitions

Term	Definition
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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
blinding/masking	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 patients are aware of the treatment received
BMI	body mass index
BP	blood pressure
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.
CI	confidence interval
CRF/eCRF	case report form/electronic 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, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
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.

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
fasting	abstaining from food and drink (except water) for approximately 8 hours (typically, overnight), no significant physical activity and no administration of glucose-lowering agents during this period
FBG	fasting blood glucose
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on 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	intent 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 (that is, 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
LOCF	last observation carried forward
LS mean	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia
MI	myocardial infarction
MMRM	mixed-model repeated measures

MNAR	missing not at random
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
OAM	oral antihyperglycemia agent
OTC	over the counter
PG	plasma glucose
PP	per protocol: 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.
QD	once daily
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
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
SDP	single-dose pen
SGLT1/SGLT2	sodium-glucose co-transporter 1/sodium-glucose co-transporter 2
SMPG	self-monitored plasma glucose
SPC	summary of product characteristics
SUSARs	suspected unexpected serious adverse reactions
T2D	type 2 diabetes
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
USPI	United States prescribing information

Appendix 2. Schedule of Activities

Schedule of Activities, Protocol H9X-MC-GBGE

Perform procedure as indicated.

	Study Period I	Study Period II			Study Period III							
	Screening	Lead in	Stabilization[a]		Treatment Period							
Visit	**1**	**2**[a]	**3**	**4**	**5**[b]	**6**	**7**	**8**	**9**	**10**	**11**	**ET**
Week of Treatment	**-(2-14)**	**-(1-13)**	**-12**	**-1**	**0**	**2**	**4**	**8**	**12**	**18**	**24**	
Allowable Deviation (Days)	**±3**	**±3**	**±3**	**±3**		**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	
Informed consent	**X**											
Randomization[c]					**X**							
Clinical Assessments												
Medical history	**X**											
Physical	**X**										**X**	**X**
Height[d]	**X**											
Weight[d]	**X**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Electrocardiogram[e]	**X**				**X**						**X**	**X**
Vital signs (BP and HR measurements)[f]	**X**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Preexisting conditions/adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Review/record hypoglycemic events			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Patient summary											**X**	**X**

Schedule of Activities, Protocol H9X-MC-GBGE

	Study Period I	Study Period II			Study Period III							
	Screening	Lead in	Stabilization[a]		Treatment Period							
Visit	**1**	**2[a]**	**3**	**4**	**5[b]**	**6**	**7**	**8**	**9**	**10**	**11**	**ET**
Week of Treatment	**-(2-14)**	**-(1-13)**	**-12**	**-1**	**0**	**2**	**4**	**8**	**12**	**18**	**24**	
Allowable Deviation (Days)	**±3**	**±3**	**±3**	**±3**		**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	
Patient Education and Management												
Diet and exercise and SMPG trainings		**X**										
PG meter training		**X**										
Subcutaneous injection training		**X**		**X**								
Review of subcutaneous injection training					**X**							
Dispense PG meter/supplies[g]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Dispense study diary, instruct in use		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Review/return study diary			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Review/record 6-point SMPG values[h]					**X**				**X**		**X**	**X[i]**
Dispense study drug and/or injection supplies					**X**	**X**	**X**	**X**	**X**	**X**		
Observe patient inject study drug					**X**							
Patient returns study drug and injection supplies						**X**	**X**	**X**	**X**	**X**	**X**	**X**
Assess study drug compliance						**X**	**X**	**X**	**X**	**X**	**X**	**X**

Schedule of Activities, Protocol H9X-MC-GBGE

	Study Period I	Study Period II			Study Period III							
	Screening	Lead in	Stabilization[a]		Treatment Period							
Visit	**1**	**2[a]**	**3**	**4**	**5[b]**	**6**	**7**	**8**	**9**	**10**	**11**	**ET**
Week of Treatment	**-(2-14)**	**-(1-13)**	**-12**	**-1**	**0**	**2**	**4**	**8**	**12**	**18**	**24**	
Allowable Deviation (Days)	**±3**	**±3**	**±3**	**±3**		**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	
Laboratory Tests[j]												
Pregnancy test[k]	**X**				**X**							
Chemistry panel	**X**				**X**						**X**	**X**
Urinalysis panel					**X**						**X**	**X**
Urinary albumin/creatinine ratio					**X**						**X**	**X**
eGFR (CKD-EPI)[l]	**X**				**X**						**X**	**X**
Calcitonin	**X**				**X**						**X**	**X**
Hematology	**X**				**X**						**X**	**X**
Lipid panel					**X**						**X**	**X**
HbA1c	**X**	**X**[m]		**X**[n]			**X**		**X**		**X**	**X**
Pancreatic amylase, lipase	**X**				**X**						**X**	**X**
Fasting glucagon					**X**						**X**	**X**
Follicle-stimulating hormone test[o]	**X**											
Stored Samples:												
Pharmacogenetic					**X**							
Nonpharmacogenetic					**X**		**X**		**X**		**X**	**X**

Abbreviations: BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; CRF = case report form; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ET = early termination; HbA1c = hemoglobin A1c; HR = heart rate; OAM = oral antihyperglycemia medication; PG = plasma glucose; SMPG = self-monitored plasma glucose.

[a] Visit 2: Lead-in

- Patients who require adjustment of their OAM regimen will implement treatment changes between Visits 2 and 3 (the lead-in period), all other patients will continue with their prestudy regimen without changes;
- Patients who adjust their OAM regimen during lead-in and/or need to stabilize the regimen will perform Visit 3 (end of lead-in) as their next visit and will then run 1 to 12-week stabilization. All other patients will skip Visit 3 and Visit 4 and will perform Visit 5 as their next visit.

[b] The final visit window is determined by the dates of the previous visit(s). The visit calculator should be used to determine the exact visit window for all subsequent visits.

[c] Baseline assessments must be completed before processing in the interactive web-response system (IWRS).

Schedule of Activities, Protocol H9X-MC-GBGE

[d] Refer to Protocol Appendix 7 for standardized procedure.

[e] Refer to Protocol Section 8.4.1 for standardized procedure.

[f] Refer to Protocol Section 8.4.2 for standardized procedure.

[g] Dispense only as needed.

[h] One 6-point SMPG profile should be performed by patient during the week prior to this visit.

[i] If performed prior to the visit.

[j] For Visits 5 and 11, and the ET Visit, patients should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity and before taking their OAMs.

[k] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only. A urine pregnancy test must be performed at Visit 5 with the result available prior to randomization and first injection of study drug for women of childbearing potential only. Additional urine pregnancy tests may be performed at the investigator's discretion during the study.

[l] The CKD-EPI equation will be used by the central lab to estimate and report eGFR. Values that are below important thresholds (60 mL/min/1.73 m^2 or 45 mL/min/1.73 m^2) must be first confirmed at the next visit before any protocol-required treatment adjustment or other protocol-required action is implemented. The higher of the 2 available values should be used when making clinical decisions. For example, if a patient's eGFR value is <45 mL/min/1.73 m^2 at Visit 1 but the value at Visit 2 is ≥45 mL/min/1.73 m^2, the patient will be allowed to continue in the trial.

[m] HbA1c blood draw only for patients who do **NOT** require stabilization of the OAM regimen.

[n] HbA1c blood draw only for patients whose OAM regimen needs to be stabilized due to changes made between Visit 2 and Visit 3 and/or to meet requirements for stable doses of OAMs.

[o] Follicle-stimulating hormone test performed at Visit 1 for postmenopausal woman at least 50 years of age with an intact uterus, who has not taken hormones or oral contraceptives within 1 year and has had 6 to 12 months of spontaneous amenorrhea.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

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

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Leukocyte esterase

Albumin/creatinine ratio (urine)[e]

Endocrine
- Calcitonin[c]
- Fasting glucagon

Stored Samples
- Pharmacogenetic stored sample
- Biomarker stored sample

Clinical Chemistry
- Sodium
- Potassium
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Alanine aminotransaminase (ALT/SGPT)
- Aspartate aminotransaminase (AST/SGOT)
- Gamma-glutamyl transferase (GGT)
- Blood urea nitrogen (BUN)
- Creatinine
- Creatine kinase (creatine phosphokinase; CPK[b])
- Uric acid
- Calcium
- Albumin
- Glucose

Pancreas (Exocrine)[c]
- Serum pancreatic amylase
- Serum lipase

HbA1c

Pregnancy test serum and urine[d]

Follicle-stimulating hormone

Lipid Panel
- Total cholesterol
- LDL[f]
- HDL
- VLDL
- Triglycerides

Abbreviations: CK-MB = creatine kinase-MB; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; RBC = red blood cells; WBC = white blood cells; VLDL = very low density lipoprotein cholesterol.

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

[b] CK-MB is to be assayed if the creatine kinase result is >1000 IU/L.

[c] Additional samples may be collected based on the investigator's judgment.

[d] A serum screening pregnancy test will be performed at Visit 1 for women of childbearing potential only by a Lilly-designated laboratory. A urine pregnancy test must be performed at Visit 5 for women of childbearing potential with the result available prior to randomization and first injection of study drug. A local urine pregnancy test may be performed at the investigator's discretion during the study.

[e] Urinary albumin and creatinine are measured; the ratio is calculated.

[f] This value will be calculated. If triglycerides >400 ng/mL, then direct LDL will be assayed.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests[a]

Hematology[b]
- Hemoglobin
- Hematocrit
- Erythrocyte count (RBC)
- Leukocytes (WBC)
- Neutrophils, segmented
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets

Hepatic Chemistry[b]
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Alanine transaminase (ALT/SGPT)
- Aspartate transaminase (AST/SGOT)
- Gamma-glutamyl transferase (GGT)
- Creatine phosphokinase (CPK)

Haptoglobin[b]

Hepatic Coagulation[b]
- Prothrombin Time
- Prothrombin Time, INR

Hepatic Serologies[b]
- Hepatitis A antibody, total
- Hepatitis A antibody, IgM
- Hepatitis B surface antigen
- Hepatitis B surface antibody
- Hepatitis B Core antibody
- Hepatitis C antibody
- Hepatitis E antibody, IgG
- Hepatitis E antibody, IgM

Anti-nuclear antibody[b]

Alkaline phosphatase isoenzymes[b]

Anti-smooth muscle antibody (or anti-actin antibody)[b]

Abbreviations: IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalised ratio (for blood clotting time); RBC = red blood cells; WBC = white blood cells.

a Hepatic safety will be assessed and monitored throughout the study, based on clinical and laboratory parameters. Any patient who develops abnormalities that meet standard criteria for hepatic assessment will be referred for clinical assessment in accordance with Lilly standards. Hepatic assessment may include the tests listed above, or others as clinically indicated, as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

b Assayed by Lilly-designated or local laboratory.

Appendix 5. Sampling Summary

This table summarizes the approximate number of samples (venipunctures) and volumes for all sampling (screening, standard laboratory, pharmacogenetic, biomarker, and exploratory) and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol H9X-MC-GBGE Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening tests[a]	Blood	10 mL	1	10 mL
Standard laboratory tests[a]	Blood	20 mL	6	120 mL
Pharmacogenetic samples	Blood	10 mL	1	10 mL
Other exploratory Nonpharmacogenetic samples	Blood	20 mL	4	80 mL
Total blood				220 mL
Hepatic monitoring[b]	Blood	3-30 mL	-	-

a Additional samples may be drawn if needed for safety purposes.

b Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

Appendix 6. Protocol GBGE World Health Organization Classification of Diabetes and Diagnostic Criteria

Type 1 Diabetes Mellitus (T1DM): Type 1 diabetes mellitus is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death.

Type 2 Diabetes Mellitus (T2DM): Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in type 2 diabetes but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with type 2 diabetes later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

Appendix 7. Protocol GBGE 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 2008).

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 (mechanical or digital scales are acceptable). All weights for a given patient should be measured using the same scale, whenever possible, after the patient has emptied their bladder. Patients should be lightly clothed but not wearing shoes while their weight is measured.

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 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).

Appendix 8. Protocol Amendment H9X-MC-GBGE(b) Summary – A Randomized, Parallel-Arm, Double-Blind Study of Efficacy and Safety of Dulaglutide When Added to SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus

Overview

Protocol H9X-MC-GBGE, A Randomized, Parallel-Arm, Double-Blind Study of Efficacy and Safety of Dulaglutide When Added to SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

Based on a request from the US Food and Drug Administration, changes were made to the protocol to include an additional primary ITT estimand (treatment regimen estimand) which will include postrescue data. This additional ITT estimand measures the benefit of treatment as actually taken, while the existing efficacy estimand measures the benefit of treatment when taken as directed by excluding postrescue data. Analyses will be performed for both the efficacy estimand and the treatment regimen estimand. In addition, the sample size estimate was revised to increase the overall number of patients enrolled.

The overall changes made to this protocol are as follows:

- Added text in Section 4.1 stating that eligible patients will receive training on study procedures, including the need to continue in the study and complete all study visits.
- Added citation to Fleming 2011 publication to Section 7.1.2.
- Modified text in Section 9.1 to increase the number of patients screened, enrolled, the number of patients in each arm, and the number of completers. Amended the assumed percentage difference between dulaglutide and placebo to 0.55%.
- Added text in Section 9.2 to advise that in addition to the PP population, the completer population will also be evaluated for HbA1c, percent to goal in HbA1c, FBG, and body weight. A definition for the completer population has been added.
- Added a paragraph in Section 9.2 to advise that there are now 2 primary analyses for this study, including the rationale for the change, the analysis model to be used, and the level of significance for the analysis.
- Modified text in Section 9.2 to advise that analyses of key secondary efficacy outcomes (percent to goal in HbA1c, FBG, body weight) and hypoglycemia will also be performed

on the full dataset with or without censoring. Deleted text stating that these analyses will be performed without censoring postrescue data as sensitivity analyses.

- Modified text in Section 9.2 to advise that a separate graphical testing approach will be conducted for each estimand.
- Deleted text in Section 9.4.1 stating that the primary outcome is an efficacy estimand with postrescue data censored (excluded), to align with the change to 2 primary outcomes.
- Added text in Section 9.4.1.1 stating that the primary analysis model (MMRM) will also be repeated using the completer population.
- Added text in Section 9.4.1.1 clarifying that departure from the MAR assumption is to be investigated for both the efficacy and treatment regimen estimands, and deleted text stating that this excludes postrescue data, as this applies only to the efficacy estimand.
- Deleted text in Section 9.4.1.1 defining the efficacy estimand as this is now defined earlier in the text.
- Deleted text in Section 9.4.1.1 describing the ITT estimand (treatment regimen estimand) as this is now described earlier on in the text.
- Deleted wording in Section 9.4.1.1 defining the efficacy estimand and the ITT (treatment regimen) estimand for the tipping point analysis.
- Added text in Section 9.4.2 for the percentages of patients achieving target HbA1c of <7%, to include additional independent variables of SGLT2 inhibitor dose ("low" vs "high"), metformin use ("yes" vs "no"), and baseline HbA1c-by-visit interaction.
- Added text in Section 9.5.3 advising that treatment differences in the incidence of hypoglycemic episodes will be assessed using Fisher's exact test or chi-square test.
- Deleted text in Section 9.5.3 stating that treatment differences in the incidence of hypoglycemic episodes will be assessed using logistic regression.
- A reference (Fleming 2011) was added to Section 11.

Minor editorial changes to the text were made to correct typographical errors.

Revised Protocol Sections

- **Note:** Deletions have been identified by ~~strikethroughs~~.
  Additions have been identified by the use of underscore.

1. Synopsis

…

Number of Patients:

~~The study will need 101completers~~ With 120 completers per arm, the study will ~~in order to~~ have 90% ~~probability of achieving statistical significance for~~ power for demonstrating superiority of either dulaglutide 1.5 mg or 0.75 mg versus placebo in change from baseline in mean HbA1c at 24 weeks, assuming a standard deviation of 1.2%, a difference between dulaglutide and placebo of ~~0.6%~~ 0.55%, and a 2-sided significance level of 0.025. Assuming that the dropout rate is 15% for the entire study period, the study will ~~need to~~ enroll approximately ~~at least 119~~ 142 patients in each arm for a total of ~~357~~ 426 patients enrolled. Assuming a screen fail rate of 40%, ~~595~~ approximately 710 patients will need to be screened to meet these enrollment number requirements.

Statistical Analysis

…

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

A graphical testing approach for each estimand separately will be used to strongly control for type I error to test for superiority of each of the dulaglutide doses versus placebo at 24 weeks for the following measures: (1) change from baseline in HbA1c, (2) change from baseline in FBG, (3) percent achieving HbA1c <7.0%, and (4) change from baseline in body weight.

The primary analysis population will be the ~~intent-to-treat (~~ITT~~)~~ population, defined as all patients randomized who have taken at least 1 dose. This is also the safety population. ~~For the primary analysis, all available data up to 24 weeks will be included except those collected after initiation of glucose-lowering rescue therapy. The primary analysis will be repeated with all available data included, including those collected after initiation of rescue therapy.~~ A select number of measurements (HbA1c, percent to goal in HbA1c, FBG, and body weight) will also be evaluated in the ~~Per Protocol~~ per-protocol population.

4.1. Overview of Study Design

…

Study Period II: Lead-In and Stabilization (Visits 2 to 4)

…

At Visit 2, eligible patients will receive training on study procedures (Schedule of Activities, Appendix 2) including the need to continue in the study and complete all study visits, the self-monitoring of plasma glucose (SMPG) plan (daily fasting plasma glucose and weekly 4-point SMPG profile [consisting of fasting, pre-lunch, pre-dinner, and bedtime PG measurements]), 6-point SMPG profile (before and 2 hours after each main meal), lifestyle treatment measures (Section 5.4), signs and symptoms and treatment of hyperglycemia (Section 6.6.1.3) and hypoglycemia (Section 6.6.1.2), and use of the study diary. Single-dose pen (SDP) injector training will be completed with the demonstrator device, which does not include a needle.

7.1.2. Permanent Discontinuation from the Study

Every attempt should be made to keep patients in the trial irrespective of their adherence to treatment with study drug in order to minimize the amount of missing data and to enable assessment of study objectives as planned by the study protocol (Fleming 2011). Patient discontinuation from the study early may be warranted in the following situations for ethical or legal reasons:

…

9.1. Determination of Sample Size

~~The study will need 101~~ With 120 completers per arm, the study will ~~in order to~~ have 90% ~~probability of achieving statistical significance for~~ power for demonstrating superiority of either dulaglutide 1.5 mg or 0.75 mg versus placebo in change from baseline in mean HbA1c at 24 weeks, assuming a standard deviation (SD) of 1.2%, a difference between dulaglutide and placebo of 0.~~6~~55%, and a 2-sided significance level of 0.025. Assuming that the dropout rate is 15% for the entire study period, the study will ~~need to~~ enroll ~~at least 119~~ approximately 142 patients in each arm for a total of ~~357~~ 426 patients enrolled. Assuming a screen fail rate of 40%, a total of ~~595~~ approximately 710 patients will be screened to meet these enrollment number requirements.

9.2. General Statistical Considerations

…

The primary analysis population will be the intent-to-treat (ITT) population, defined as all patients randomized who have received at least 1 dose. This is also the safety population. A select number of measurements (HbA1c, percent to goal in HbA1c, FBG, and body weight) will also be evaluated in the PP population and completer population. The PP population will be based on patients who were compliant with study medication, took no concomitant medications

that would confound the interpretation of results (such as systemic steroids or non-study glucose-lowering agents used >14 days), and have an HbA1c measurement at the primary visit endpoint. The completer population will be based on patients who completed the treatment period.

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

Analyses of ~~certain~~ key secondary efficacy outcomes (~~HbA1c,~~ percent to goal in HbA1c, FBG, body weight) and hypoglycemia will also be performed on the full dataset, ~~with censoring as primary (ie, to exclude~~ excluding and including data collected after initiation of rescue with glucose-lowering therapy ~~for reasons described in Section 6.6.1.3, Section 6.8.1, and Section 7.1.1). These same analyses will also be performed without censoring post rescue data as sensitivity analyses~~.

…

Two analysis models will be used for the primary and key secondary continuous efficacy measures. The primary analysis will be mixed-model repeated measure (MMRM) analysis using restricted maximum likelihood (REML) (Section 9.4.1). 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
- ~~Toeplitz, autoregressive~~
- compound symmetry without heterogeneous variances, by visit

…

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

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

9.4.1. Primary Outcome Measure and Analyses

The primary outcome is ~~an efficacy estimand defined as~~ the difference in HbA1c mean change from baseline to 24 weeks in the ITT population ~~with post-rescue data censored (excluded)~~. The primary hypothesis of interest in this placebo-controlled study is whether dulaglutide has superior efficacy compared to placebo, in patients already treated with SGLT2 inhibitors. ~~without confounding with rescue therapy~~.

…

9.4.1.1. Additional Analyses of the Primary Outcome

The primary analysis model, MMRM, will be repeated using the PP population and completer population to check the sensitivity of the analysis. If the conclusion differs from that of the ITT population, the data and analyses will be further investigated. The secondary analysis model will be an ANCOVA for HbA1c change from baseline to 24 weeks (Visit 11), using a similar model as described above with treatment, country, SGLT2 inhibitor dose ("low" ~~versus~~ vs "high"), and metformin use ("yes" ~~versus~~ vs "no") as factors and baseline HbA1c as a covariate. Missing endpoints will be imputed with the LOCF using postbaseline data only.

To investigate departure from the ~~Missing At Random~~ missing at random (MAR) assumption for the primary analysis ~~that excludes post-rescue data~~ for both efficacy and treatment-regimen estimands, a sensitivity analysis using a particular missing not at random (MNAR) assumption will be performed. Specifically, a placebo multiple imputation (pMI) will be performed (Ayele et al. 2014), which assumes that the drug effect in missing data and postrescue data in both the placebo arm and dulaglutide arm was like the observed effect in the placebo arm (excluding postrescue data). This is essentially the "copy reference" approach as described in Carpenter et al. 2013. This approach is in essence assuming that the drug effect will decay over time, in accordance with the correlation structure implied by the data. Data imputed this way will be analyzed with the same MMRM model as the primary analysis. This particular MNAR assumption can be viewed as a "worst reasonable case" assessment of the 2 estimands. ~~efficacy estimand, or as an effectiveness estimand that assumes patients with missing data or rescued patients received no drug benefit after dropout or rescue.~~

~~Also of interest is the effectiveness/treatment regimen estimand that evaluates the difference in mean HbA1c change from baseline to 24 weeks in the ITT population regardless of treatment discontinuation or use of rescue therapy (ITT estimand). Therefore as a supportive analysis, MMRM will be performed on the ITT population with all post-rescue data up to the primary endpoint of 24 weeks included.~~

For both the efficacy estimand ~~(missing data and post-rescue data both considered as missing)~~, and the treatment-regimen estimand ~~and the ITT estimand (post-rescue data not treated as missing)~~, a tipping-point analysis will be performed in which the missing data are imputed with a

MAR assumption. However, prior to analysis, in the dulaglutide arm, the imputed values will be replaced by the imputed value plus delta. Multiple values of delta will be tried until the value at which the conclusion from the MMRM analysis changes.

9.4.2. Secondary Outcome Measures and Analyses

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For percentages of patients achieving target HbA1c of <7.0% (including exploratory composite endpoints with body weight and hypoglycemia) or ≤6.5% at 24 weeks, longitudinal logistic regression with repeated measurements will be used. The model will include independent variables treatment, country, SGLT2 inhibitor dose ("low" vs "high"), metformin use ("yes" vs "no"), visit, baseline HbA1c-by-visit interaction, treatment-by-visit, and baseline HbA1c as a covariate. …

9.5.3. Hypoglycemic Episodes

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Baseline hypoglycemia risk will be established based on hypoglycemia events recorded between Visit 2 and Visit 5. The incidence of hypoglycemic episodes will be summarized by frequencies and percentages for each treatment group, by visit as well as overall. Treatment differences in the incidence of hypoglycemic episodes will be assessed using ~~a logistic regression~~ Fisher's exact test or chi-square test for treatment comparison.

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References

Fleming TR. Addressing missing data in clinical trials. *Ann Intern Med.* 2011;154(2):113-117.

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