

Protocol H9X-MC-GBGJ (a)

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

NCT02973100

Approval Date: 07-Nov-2016

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[Dulaglutide (LY2189265)]

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

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Protocol Electronically Signed and Approved by Lilly: 19 August 2016  
Amendment (a) Electronically Signed and Approved by Lilly  
on approval date provided below.

Approval Date: 07-Nov-2016 GMT

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## 1. Synopsis

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

**Rationale:**

Study H9X-MC-GBGJ (GBGJ) is a Phase 2 trial designed to assess the safety and efficacy of once weekly dulaglutide 3.0 mg and 4.5 mg in comparison to placebo in patients with type 2 diabetes mellitus (T2D) treated with metformin monotherapy. The trial will also include exploratory comparisons to dulaglutide 1.5 mg (the highest dose approved by regulatory agencies). The strategic objective is to obtain data to support the development of an additional higher dulaglutide dose than the currently approved 0.75 mg and 1.5 mg doses (Trulicity® United States Package Insert 2015), that could provide improved clinical benefits, including greater reduction in hemoglobin A1c (HbA1c) and greater body weight reduction, with an acceptable safety profile.

**Objectives/Endpoints:**

Objectives	Endpoints
<p><b>Primary</b> To demonstrate that once weekly dulaglutide (4.5 mg, 3.0 mg, 1.5 mg) is superior to placebo in HbA1c reduction at 18 weeks in patients with T2D on concomitant metformin monotherapy.</p>	<ul style="list-style-type: none"> <li>• The change in HbA1c from baseline</li> </ul>
<p><b>Secondary</b> <u>Efficacy</u></p> <ul style="list-style-type: none"> <li>• To compare each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) to the placebo arm at 18 weeks for secondary efficacy parameters</li> </ul> <p><u>Safety</u></p> <ul style="list-style-type: none"> <li>• To compare each dulaglutide arm (4.5 mg, 3.0 mg, 1.5 mg) to the placebo arm for selected safety parameters at 18 weeks</li> </ul> <p><u>Pharmacokinetics and Pharmacodynamics</u></p> <ul style="list-style-type: none"> <li>• To characterize the pharmacokinetics (PK) of dulaglutide and establish the relationships between dose/exposure and key safety and efficacy measures</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of patients achieving HbA1c target of &lt;7.0%</li> <li>• The change in fasting serum glucose (FSG; central laboratory) from baseline</li> <li>• The change in body weight from baseline</li> <li>• Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)</li> <li>• Discontinuation of study drug due to adverse events (AEs)</li> <li>• Incidence and rate of hypoglycemia (severe, total, documented symptomatic, and nocturnal)</li> <li>• PK parameters (eg, C<sub>max</sub>, AUC)</li> <li>• Pharmacodynamic evaluations will include HbA1c, FSG, body weight, QTcF interval, and heart rate</li> </ul>

Abbreviations: AUC = area under concentration-time curve; C<sub>max</sub> = maximum concentration; HbA1c = hemoglobin A1c; QTcF = Fridericia's corrected QT interval; T2D = type 2 diabetes mellitus.

**Summary of Study Design:**

Study GBGJ is a Phase 2, multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial with 3 study periods (lead-in, treatment, and safety follow-up) in patients who have T2D with inadequate glycemic control on metformin only.

**Treatment Arms and Duration:**

At Visit 3, patients will be randomized in a 1:1:1:1 ratio to weekly injections of dulaglutide 4.5 mg, 3.0 mg, or 1.5 mg, or placebo, in combination with stable doses of metformin. Within each of the investigational dulaglutide dose (3.0 mg and 4.5 mg) arms, patients will be randomly assigned in a 1:1 ratio to 1 of the dulaglutide dose titration algorithms (Algorithm 1 or Algorithm 2). Study participants will be treated for 18 weeks after randomization in a double-blind manner, followed by a 4-week safety evaluation.

**Number of Patients:**

A total of approximately 300 patients (~75 patients per arm and ~38 per algorithm) will be randomized and approximately 240 are expected to complete the treatment period (~60 per arm and ~30 per algorithm) to show that each dulaglutide dose arm is superior to placebo with at least 90% power. This sample size calculation assumes a treatment difference of 1.0% in HbA1c reduction, standard deviation of 1.2%, and dropout rate of 20%. The screen failure rate is estimated as 30%. Approximately 429 patients will be screened.

**Statistical Analysis:**

The primary analysis for the endpoint of the primary objective, change from baseline in HbA1c at 18 weeks, will be mixed-model repeated measures (MMRM) analysis. In this model, restricted maximum likelihood will be used to obtain model estimates with Kenward-Roger option to estimate denominator degrees of freedom. The corresponding baseline value will be used as a covariate, while pooled country, treatment, visit, and treatment-by-visit interaction will be fixed effects. The secondary analysis for the primary endpoint will use a Bayesian integrated 2-component prediction model (Fu and Manner 2010). Probabilities based on posterior distributions of parameters of interest will be generated from this model.

All secondary efficacy measures that are continuous variables (changes from baseline) will be analyzed using MMRM. Repeated measures logistic regression with generalized linear mixed model will be used to analyze percentages of patients achieving HbA1c targets of <7.0% and/or ≤6.5%. For the analysis of other categorical measures, Fisher's exact test will be used for treatment comparisons, unless 80% of cells have an expected value of at least 5, in which case the Chi-square test will be used.

Population pharmacokinetic (PK) analyses will be conducted using dosing data and dulaglutide concentrations obtained from all patients via commonly accepted pharmacostatistical methods (for example, nonlinear mixed-effects modeling), and covariate screening. The relationship between dulaglutide doses and/or PK concentrations and key safety and efficacy measures will be evaluated in PK/pharmacodynamics analyses. In addition, any relationship between dulaglutide PK concentrations and antibody formations will be evaluated for impact on dulaglutide clearance and, if applicable, drug effect(s).

## 2. Schedule of Activities

Visit	Screening and Lead-In		Treatment Period										Follow-Up	
	1	2	3	4	5	6	7	8	9	10	11	12	801	ET <sup>a</sup>
<b>Week of Treatment</b>	-2	-1	0	2	4	6	7	8	9	10	14	18	22	ET
<b>Allowable Deviation (Days)<sup>b</sup></b>	±3	±3		-3	-3	-3	±3	±3	±3	+4	±7	±7	±3	
Informed consent	X													
Randomization <sup>c</sup>			X											
<b>Clinical Assessments</b>														
Medical History	X													
Physical	X													
Height	X													
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (3 sitting BP and PR measurements)	X		X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram <sup>d</sup>	X					X		X		X		X		X
Adverse events		X	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	X	X
Review/record hypoglycemic events			X	X	X	X	X	X	X	X	X	X	X	X
Remind patients about 6-point SMPG		X									X			
Record 6-point SMPG values <sup>e</sup>			X									X		X <sup>f</sup>
Patient summary												X	X	X
<b>Patient Education and Management</b>														
Dispense study diary, instruct in use		X	X			X				X	X	X		
Review study diary			X	X	X	X	X	X	X	X	X	X	X	X
Return study diary			X			X				X	X	X	X	X
Diabetes management education <sup>g</sup>		X												
PG meter, SMPG training <sup>g</sup>		X	X											
Review SMPG values			X	X	X	X	X	X	X	X	X	X	X	X
Injection training <sup>g</sup>		X	X											
Dispense PG meter/supplies		X	X	X	X	X	X	X	X	X	X	X		
Dispense study drugs and/or injection supplies			X	X	X	X				X	X			
Observe patient inject study drug <sup>h</sup>			X											

Visit	Screening and Lead-In		Treatment Period										Follow-Up		
	1	2	3	4	5	6	7	8	9	10	11	12	801	ET <sup>a</sup>	
<b>Week of Treatment</b>	-2	-1	0	2	4	6	7	8	9	10	14	18	22	ET	
<b>Allowable Deviation (Days)<sup>b</sup></b>	±3	±3		-3	-3	-3	±3	±3	±3	+4	±7	±7	±3		
<b>Patient Education and Management (concluded)</b>															
Patient returns study drugs and/or injection supplies				X	X	X	X	X	X	X	X	X		X	
Assess study drug compliance <sup>i</sup>				X	X	X	X	X	X	X	X	X		X	
<b>Laboratory tests</b>															
Serum pregnancy test <sup>j</sup>	X														
Urine pregnancy test <sup>k</sup>			X												
Follicle-stimulating hormone test <sup>l</sup>	X														
Chemistry panel	X											X		X	
Lipid panel (fasting) <sup>m</sup>			X									X		X	
Urinalysis	X											X		X	
Albumin/creatinine ratio (urine) <sup>n</sup>	X											X		X	
eGFR (CKD-EPI) <sup>o</sup>	X											X		X	
Hematology	X											X		X	
Immunogenicity			X			X						X	X	X	
HbA1c	X		X			X				X		X	X	X	
Glucose (fasting) <sup>m</sup>			X			X				X		X	X	X	
Pancreatic amylase, lipase	X		X			X						X	X	X	
Serum insulin (fasting) <sup>m</sup>			X									X		X	
C-peptide			X									X		X	
Plasma glucagon (fasting) <sup>m,p</sup>			X			X						X		X	
Calcitonin	X		X									X		X	
Pharmacogenetic			X												
Nonpharmacogenetic biomarker (plasma and serum)			X		X	X						X		X	
<b>PK samples</b>															
PK samples			X <sup>q</sup>	X <sup>r</sup>	X <sup>q</sup>	X <sup>s</sup>					X <sup>t</sup>		X <sup>u</sup>	X <sup>u</sup>	X <sup>u</sup>

Abbreviations: BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemia medication; PG = plasma glucose; PK = pharmacokinetic; PR = pulse rate; SMPG = self-monitored plasma glucose.

- a Patients who are unable or unwilling to continue in the study because of an adverse event or any other reason will perform an ET visit as their final study visit. If the patient is discontinuing during an unscheduled visit, that visit should be performed as the ET visit. If the patient is discontinuing during a scheduled visit, that visit should be considered the ET visit.
- b The visit date is determined in relation to the date of the randomization visit ( $\pm$  the allowed visit window).
- c Baseline assessments must be completed before processing in the interactive web-response system (IWRS).
- d ECGs will be performed in triplicate. ECGs occurring on visits with PK collection should be measured at least 30 minutes prior to obtaining the sample for PK measurement.
- e 6-point SMPG consists of measurements before and 2 hours after each of 3 main meals within the same day. These SMPG profiles are collected by the patient within 1 week prior to the assigned visits.
- f If performed prior to visit.
- g All training should be repeated as needed to ensure patient compliance.
- h Patients should administer their first dose of study drug at the end of this visit, after other study procedures and randomization. Patients will be encouraged to administer their weekly dose of study drug in the clinic, when possible, at subsequent visits.
- i Study drug compliance will be reviewed for the time period from Visit 4 to Visit 12 and entered in the eCRFs at Visit 6, Visit 10, Visit 11, and Visit 12 for the interval after the previous compliance entry.
- j A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.
- k A urine pregnancy test will be performed at Visit 3 with the result available prior to randomization and first injection of study drug for women of childbearing potential only. Additional pregnancy tests may be performed at the investigator's discretion during the study.
- l Follicle-stimulating hormone test performed at Visit 1 for postmenopausal women at least 50 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months. After Visit 1, additional tests may be performed at the investigator's discretion during the study.
- m For Visit 3, Visit 6, Visit 10, Visit 12, Visit 801, 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 (if used).
- n Urinary albumin and creatinine are measured; the ratio is calculated.
- o The CKD-EPI equation will be used by the central laboratory to estimate and report eGFR. Values that are  $<60$  mL/min/1.73 m<sup>2</sup> at Visit 1 must be retested at Visit 2. If the highest of the 2 values is lower than the cutoff value for discontinuation of metformin per country-specific label (for example,  $<45$  mL/min/1.73 m<sup>2</sup> or  $<60$  mL/min/1.73 m<sup>2</sup>), the patient will be discontinued from the trial prior to randomization. After randomization (Visit 3), values that are  $<60$  mL/min/1.73 m<sup>2</sup> must be first confirmed on a retest before any protocol-required treatment adjustment is implemented.
- p Collect sample in P800 tube. Aliquot samples, 1 for glucagon and the remainder for nonpharmacogenetic biomarker.
- q PK samples at Visit 3 and Visit 5 should be collected 1-24 hours post-injection of study drug.
- r PK sample at Visit 4 should be collected immediately prior to administration of study drug.
- s PK sample at Visit 6 should be collected 5-7 days (120-168 hours) post-injection of Week 5 study drug or just pre-injection of Visit 6 study drug.
- t PK sample at Visit 10 should be collected 1-4 days (24-96 hours) post-injection of Visit 10 study drug.
- u PK samples at Visit 12, Visit 801, and the ET visit can be collected at any time during the visit.

## 3. Introduction

### 3.1. Study Rationale

Study H9X-MC-GBGJ (GBGJ) is a Phase 2 trial designed to provide initial safety and efficacy data for 2 investigational dulaglutide doses (3.0 mg and 4.5 mg) that are higher than the currently approved 0.75 mg and 1.5 mg doses (Trulicity<sup>®</sup> United States Package Insert [USPI] 2015 [WWW]). The trial objectives are expected to enable a feasibility assessment of further Phase 3 development of at least 1 of the 2 investigational doses to show improvement in the glycemic control efficacy in comparison to the 1.5 mg dose with an acceptable safety profile.

Patients with type 2 diabetes mellitus (T2D) treated with metformin monotherapy will be randomized to 1 of the following 4 treatment arms, each dosed once weekly: dulaglutide 3.0 mg or 4.5 mg (investigational doses), placebo, or dulaglutide 1.5 mg (the highest dose approved by regulatory agencies). The primary objective will compare the 3 dulaglutide doses to placebo in change from baseline in hemoglobin A1c (HbA1c) at 18 weeks. The secondary objectives will compare the 3 dulaglutide doses to placebo at 18 weeks for additional efficacy measures and for safety. The purpose of the primary and secondary objectives is to assess efficacy and safety characteristics of the 2 investigational dulaglutide doses. The exploratory objectives will compare the efficacy and safety of the 2 investigational dulaglutide doses to the approved 1.5 mg dose at 18 weeks. The purpose of these exploratory objectives is to provide scientific support for further Phase 3 development of 1 or 2 of the investigational doses. Additional exploratory objectives will assess the effect of 2 dulaglutide dose titration algorithms on gastrointestinal (GI) tolerability with the investigational dulaglutide doses to guide design of the Phase 3 dose titration algorithm for dulaglutide.

### 3.2. Background

Dulaglutide (Trulicity<sup>®</sup>) is a once weekly glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1 RA) that is approved for use as an adjunct to diet and exercise to improve glycemic control in patients with T2D. It exhibits GLP-1-mediated effects, including glucose-dependent potentiation of insulin secretion and inhibition of glucagon secretion, delay of gastric emptying, and weight loss. Treatment of patients with T2D with dulaglutide results in significant reductions in HbA1c with low risk of hypoglycemia, and reductions in body weight. Clinical studies to date support the use of once weekly injection of dulaglutide as monotherapy, in combination with oral antihyperglycemia medications (OAMs), or in combination with prandial insulin lispro to improve glycemic control in patients with T2D (Investigator's Brochure [IB]).

Two once weekly dulaglutide doses, 0.75 mg and 1.5 mg, were studied in the Phase 3 development program and received regulatory approval in the United States (US) and in the European Union in 2014 (Trulicity USPI [WWW], Summary of Product Characteristics [SmPC] [WWW]). While therapy with these doses of dulaglutide enabled the majority of patients included in the Phase 3 program to attain their glycemic targets along with other concomitant medications, up to 30% or potentially more of patients receiving approved therapies today, including dulaglutide, are not reaching glycemic control goals (Stark et al. 2013). Therefore, there remains an important medical need to provide enhanced efficacy of pharmaceutical agents

while also preserving an overall acceptable benefit/risk profile. The overall objective of Study GBGJ is to explore higher doses of dulaglutide for treatment of adult patients with T2D in order to provide greater glycemic efficacy compared to the currently approved doses with an acceptable safety profile.

The currently approved dulaglutide doses were selected in the Phase 2/3 Study H9X-MC-GBCF (GBCF), which initially included 7 doses in the range between 0.25 mg and 3.0 mg (Skrivanek et al. 2014). Final selection of the 0.75 mg and 1.5 mg doses for development was supported by: (a) favorable benefit/risk profile of these doses based on a clinical utility index that included HbA1c, body weight, pulse rate, and diastolic blood pressure (DBP); and (b) potentially concerning, short-term effects on pancreatic enzymes, GI tolerability, and heart rate (HR) observed with the 3.0 mg dose, which prompted early discontinuation of this arm (Skrivanek et al. 2014; Weinstock et al. 2015). In general, the effects noted with the 3.0 mg dose are now understood to be associated also with the GLP-1 RA class and are dose-dependent, occurring across the range of doses, and at doses lower than the 3.0 mg dose of dulaglutide. The Phase 3 dulaglutide development program, which included 0.75 mg and 1.5 mg doses, assessed these safety considerations and enabled their better understanding.

In dulaglutide registration trials, the risk of adjudicated pancreatitis and investigator-reported pancreatitis in patients treated with dulaglutide was similar to the risk observed with non-incretin comparators (data on file). In addition, the asymptomatic pancreatic enzyme elevations were observed in patients treated with 0.75 mg or 1.5 mg dulaglutide doses, but also in patients who received GLP-1 RA comparators, non-GLP-1 RA comparators or placebo. These elevations were not associated with adverse clinical outcomes based on the results of adjudication and do not require monitoring in the absence of signs and symptoms of acute pancreatitis (Trulicity USPI [WWW]; Umpierrez et al. 2014; Wysham et al. 2014; Blonde et al. 2015; Giorgino et al. 2015; Weinstock et al. 2015).

With respect to HR elevations, treatment with dulaglutide 0.75 mg or 1.5 mg for 26 weeks increases HR in the range between 2 and 4 beats per minute (bpm), with no clinically relevant cardiovascular (CV) safety findings (Trulicity USPI [WWW]; Ferdinand et al. 2016). The estimated effect of the 3.0 mg dose on HR at 26 weeks, based on a small number of patients with mean exposure of approximately 9.2 weeks in Study GBCF, was an increase of approximately 5 bpm (data on file). No safety data are available after 26 weeks of treatment for doses greater than 3.0 mg. Increases in HR with dulaglutide are time-dependent and diminish over time (data on file). The ongoing REWIND CV outcome trial (H9X-MC-GBDJ) will provide data on the long-term effect of dulaglutide on the CV risk.

The results from recently reported studies of dulaglutide described above have provided understanding of the clinical relevance of the pancreatic enzyme elevations and increases in HR, which was not available at the time of development of dulaglutide for initial registration (Egan et al. 2014). The additional data did not suggest association between these findings and long-term safety outcomes, providing support for re-evaluation of a range of once weekly dulaglutide doses higher than the currently approved 0.75 mg and 1.5 mg doses to assess whether an additional dose with favorable benefit/risk profile compared to the approved doses can be developed.

The investigational dulaglutide doses to be studied in Study GBGJ (3.0 mg and 4.5 mg) were chosen based on simulations which included data collected in Studies H9X-MC-GBCD (GBCD) and GBCF (Barrington et al. 2011, Skrivanek et al. 2014). The results of these simulations suggest that these doses may provide an incremental, clinically relevant improvement in Hb1Ac and body weight reduction in comparison to the 1.5 mg dose after 26 weeks. Further information on the rationale for the doses included in this study is provided in Section 5.5.

Potential poor tolerability due to GI side effects may pose a challenge to achieving the objective of development of higher dulaglutide doses, however, the currently approved doses of dulaglutide do not require dose-titration at treatment initiation. In 33 patients treated with 3.0 mg or higher doses in Phase 1 Study GBCD (5 week dosing) and in the dose-finding portion of Study GBCF (mean exposure 9.2 weeks), the incidence of GI adverse events (AEs) that are commonly related to the treatment with GLP-1 RAs (nausea: 17 patients [52%]; vomiting: 9 patients [27%]) was higher compared to the incidence reported with approved doses in registration trials (Barrington et al. 2011; Skrivanek et al. 2014; Umpierrez et al. 2014; Wysham et al. 2014; Blonde et al. 2015; Giorgino et al. 2015; Weinstock et al. 2015). Five out of these 33 patients (15%) discontinued treatment early due to GI AEs. It has recently been shown that a slow, stepwise dose titration upon initiation of GLP-1 RAs can attenuate the occurrence and severity of GI AEs, allowing the use of higher doses which provide greater glucose-lowering effects and robust body weight reduction. Simulation results discussed in Section 5.5, showing reduction in incidence of GI events with initial titration of dulaglutide, are consistent with these reports. In Study GBGJ, different titration options (algorithms) will be included to assess their effect on GI tolerability with the 2 investigational dulaglutide doses. Detailed rationale for titration algorithms can be found in Section 5.5.

### **3.3. Benefit/Risk Assessment**

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated AEs of dulaglutide may be found in the IB.

In addition, detailed information about the known and expected benefits and risks of dulaglutide may be found in the USPI and SmPC.

## 4. Objectives and Endpoints

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

**Table GBGJ.1. Objectives and Endpoints**

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

Objectives and Endpoints (continued)

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



## 5. Study Design

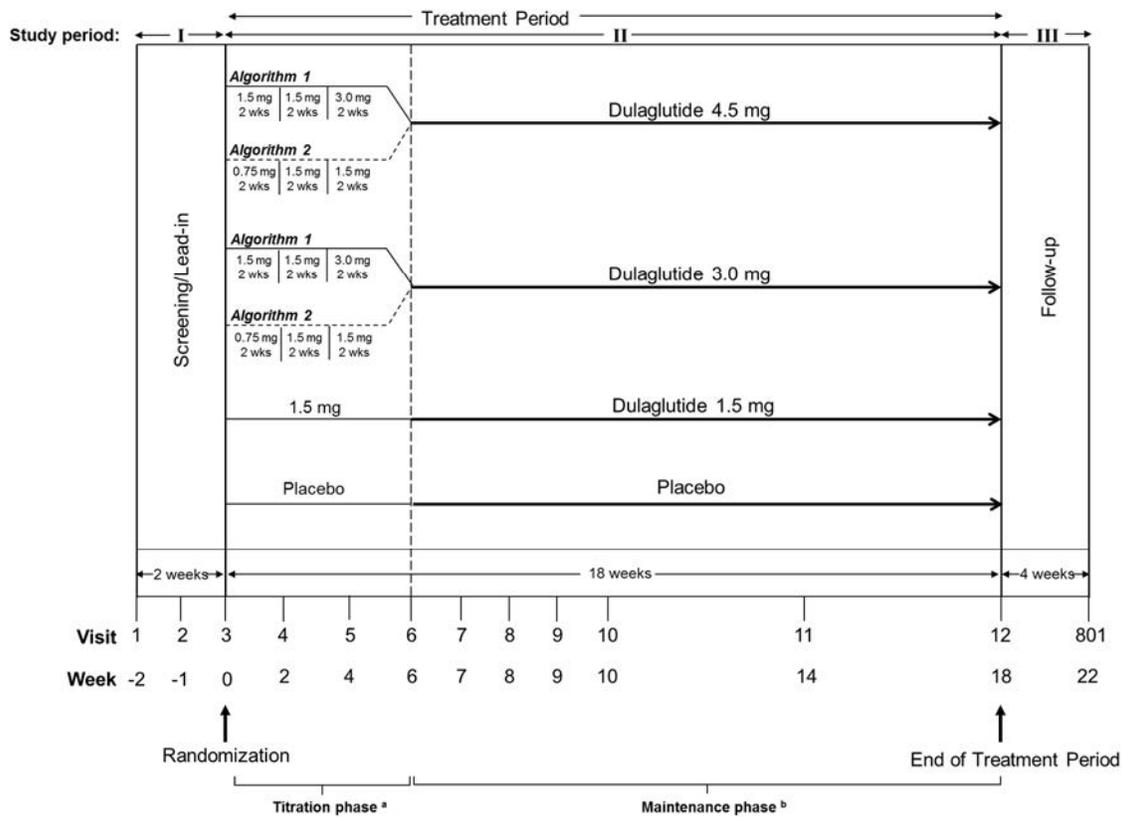
### 5.1. Overall Design

Study GBGJ is a randomized, multicenter, placebo-controlled, double-blind Phase 2 trial in T2D patients on metformin monotherapy. The study is designed to assess the efficacy and safety of once weekly dulaglutide 3.0 mg and 4.5 mg in comparison to placebo. In addition, the trial will explore how these dulaglutide doses compare to the approved dulaglutide 1.5 mg dose to support dose selection for further development in Phase 3 trials, and to guide design of these additional trials. Study GBGJ will also explore the effect of 2 dulaglutide dose titration algorithms on GI tolerability with investigational doses to guide design of the definitive algorithm to be evaluated in Phase 3 trials. The primary objective of this trial is to show superiority of the 3 dulaglutide doses (4.5 mg, 3.0 mg, 1.5 mg) to placebo in change in HbA1c at 18 weeks (see Section 4).

During the trial, an unblinded internal assessment committee (AC) will review data on safety and tolerability in study participants according to a prespecified schedule in order to assure the safety of randomized patients.

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

Figure GBGJ.1 illustrates the study design.



- a Patients will administer 1 injection per week in the first 4 weeks of the titration phase, and 2 injections per week in the remainder of the titration phase (see Section 7.1 and Table GBGJ.2).
- b During the maintenance phase, the assigned dose will require 3 injections (see Section 7.1 and Table GBGJ.2).

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

**Study Period I (Screening and Lead-In):**

**Screening (Visit 1)**

The purpose of screening procedures at Visit 1 is to establish initial eligibility (see Sections 6.1 and 6.2) and to obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2. Patients who meet all applicable inclusion criteria and none of the applicable exclusion criteria at Visit 1 will continue on their prestudy therapy (see Section 7.7.1.1) until Visit 2.

**Lead-In (Visit 2 to Visit 3)**

At Visit 2, the screening laboratory results will be reviewed and definite patient eligibility will be established. During the lead-in period, eligible patients should continue their prestudy therapy, metformin (same formulation and dose), in order to allow reliable assessment of HbA1c at baseline (Visit 3); see Section 7.7.1.1. If patients develop a condition that is a contraindication for the use of metformin or initiate other agents that are prohibited (see Table GBGJ.3 and

Sections 6.1 and 6.2 for further details) between entry (Visit 1) and randomization, they will be considered ineligible and will be discontinued from the trial before randomization. During this period, patients will be trained on disease monitoring and disease management procedures, study diaries, and study procedures. They will also receive education and training on how to perform subcutaneous injections; this should be reviewed as necessary throughout the study. The training should include information on appropriate injection site locations, injection technique, and the signs and symptoms of local adverse reactions, should that occur. Patients will receive instructions on timing of doses (Table GBGJ.2 and Section 7.2.1), and will be instructed to record the date and time of all injections administered throughout the study in their study diaries. Study site staff will observe each patient self-injecting for training purposes.

Visit-specific subject diaries will be dispensed at Visit 2 and at prespecified visits thereafter, until the last study visit (see Schedule of Activities, Section 2).

### **Study Period II (Treatment Period):**

#### **Randomization (Visit 3)**

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

Patients who continue to be eligible will then be randomized in a 1:1:1:1 ratio to 1 of the treatment arms: (1) dulaglutide 4.5 mg, (2) dulaglutide 3.0 mg, (3) dulaglutide 1.5 mg, or (4) placebo. Within each of the investigational dulaglutide dose (3.0 mg and 4.5 mg) arms, patients will be randomly assigned in a 1:1 ratio to 1 of the titration algorithms (Algorithm 1 or Algorithm 2). Immediately after randomization, the patient will inject the first dose of study drug at the study site. The Visit 3 pharmacokinetics (PK) sample must be collected 1-24 hours after the patient has injected study drug for the first time.

Following randomization, patients will participate in an 18-week treatment period that consists of a 6-week titration phase followed by a 12-week maintenance treatment phase at the final dosage.

#### **Titration Phase (end of Visit 3 to Visit 6)**

During the titration phase in the investigational dose dulaglutide arms, the dose of dulaglutide will be escalated according to 1 of 2 algorithms:

- Algorithm 1: patients will receive dulaglutide 1.5 mg once weekly for the first 4 weeks followed by dulaglutide 3.0 mg once weekly for the next 2 weeks, or
- Algorithm 2: patients will receive dulaglutide 0.75 mg once weekly for the first 2 weeks followed by dulaglutide 1.5 mg once weekly for the next 4 weeks.

#### **Maintenance Phase (end of Visit 6 to Visit 12)**

During the maintenance phase, patients will administer study drug at their final assigned dose once weekly for approximately 12 weeks.

### General considerations

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

In order to allow timely sampling for PK assessments, visits when collection of the PK samples are required will be scheduled within the required time windows for PK sampling provided in the Schedule of Activities (Section 2 and Section 9.5). Therefore, the scheduling of visits when these samples are to be collected should take into account visit intervals/windows, timing of study drug injections and PK sampling windows. The sponsor will provide appropriate training on these requirements to avoid protocol deviations.

Patients will continue to use concomitant metformin throughout the treatment period: discontinuation or changes to dose are not permitted, except in the situations where dose adjustment or complete discontinuation is required per country-specific label or when allowed per study protocol (for further details see Section 7.7.1.1).

Patients will be instructed to perform fasting plasma glucose (FPG) measurements once daily and 4-point self-monitoring plasma glucose (SMPG) measurements (consisting of fasting, pre-lunch, pre-dinner, and bedtime PG measurements) once weekly and to record all results in diaries; these results will be used for glucose management only. In addition, 6-point SMPG (prior to and 2 hours after the morning, midday, and evening meals) will be collected during the week preceding prespecified clinic visits as shown in the Schedule of Activities (Section 2) and will be used for efficacy analyses. During the weeks when the 6-point SMPG profiles are to be collected, patients will not be required to collect 4-point SMPG profiles, and the 6-point profiles will be used for glucose management instead.

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Section 7.4.1.3) will receive a new glucose-lowering intervention (or rescue therapy) based on clinical judgment of the investigator (see Table GBGJ.3) and will also continue to administer study drug. Patients who need rescue therapy for this reason will continue in the trial until they complete all study visits. Patients who discontinue study drug due to AEs will also be required to continue in the trial and will receive an appropriate rescue glucose-lowering regimen. Table GBGJ.3 provides details on the use of glucose-lowering medications for rescue and for treatment of acute conditions as well as other medication classes that may interfere with efficacy and safety assessments in this trial. Patients who are unable or unwilling to continue in the study because of an AE or any other reason will perform an early termination (ET) visit as their final study visit. If the patient is discontinuing during an unscheduled visit, that visit should be performed as the ET visit. If the patient is discontinuing during a scheduled visit, that visit should be considered the ET visit. At this visit, patients will perform procedures listed in the Schedule of Activities (Section 2).

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

All randomized patients who complete the treatment period will complete the safety follow-up visit at 22 weeks, approximately 4 weeks after their last visit on treatment. During the safety follow-up study period, patients will be treated with the appropriate glucose-lowering regimen decided on by the investigator and the patient. Glucagon-like peptide-1 receptor agonists and

dipeptidyl peptidase-4 (DPP-4) inhibitors will not be allowed during this period. Patients will also be required to return any remaining study diaries to the investigative site.

## 5.2. Number of Participants

Approximately 429 patients will be screened to achieve a total of approximately 300 randomized patients.

## 5.3. End of Study Definition

End of the trial is the date of the last visit or last scheduled procedure (ie, the end of the 4-week safety follow-up period) shown in the Schedule of Activities (Section 2) for the last patient.

## 5.4. Scientific Rationale for Study Design

Study GBGJ utilizes the parallel arm design as an appropriate option to collect data attributable to a specific randomized therapy without potential interference from other randomized treatments or the randomization sequence.

The 2 investigational dulaglutide doses (once weekly 3.0 mg and 4.5 mg) to be studied in this trial were chosen based on simulations which included data collected in Studies GBCD and GBCF (Barrington et al. 2011; Skrivanek et al. 2014), among other studies. Further details and the rationale for the choice of the doses are provided in Sections 3.2 and 5.5. The placebo comparator is considered appropriate for this trial to establish effects of the investigational doses on efficacy and safety measures that are attributable to dulaglutide. The active comparator dulaglutide 1.5 mg dose has been chosen to enable comparison of data collected under similar conditions to the investigational doses. Due to small sample size, the comparison between investigational doses and the dulaglutide 1.5 mg dose will use exploratory assessments with Bayesian-based methods to guide dose selection for Phase 3 development and design of confirmatory trials.

The 2 titration algorithms to be used in the dulaglutide 3.0 mg and 4.5 mg arms have been chosen based on simulations that included data from several Phase 2 and Phase 3 trials to assess the potential mitigating effect of doubling increases in titrated doses (ie, Algorithm 1) versus longer exposure at lower titration doses (ie, Algorithm 2). They differ with respect to the initial dose (0.75 mg or 1.5 mg) corresponding to the recommended starting doses in different country-specific labels, number of dose steps (2 or 3), and duration of exposure at the initiation dose (2 or 4 weeks). The exposure-response information for GI tolerability collected from this study will be combined with information from previous studies to guide design of the final algorithm to determine the starting dose(s), titration step(s), and duration of titration, to be taken into Phase 3 development if data suggests dose titration is necessary.

The study population, patients with T2D treated with metformin, is considered adequate since these patients have been shown in Phase 3 trials to respond well to dulaglutide due to preserved beta cell function, a key prerequisite for assessment of response to the GLP-1 RA class of agents. Metformin is a required concomitant OAM in this study since patients with T2D are treated with metformin from the very early stages of the disease. Due to its predominant mechanism of

action (suppression of hepatic glucose output), metformin is not expected to interfere with planned assessments in this trial, if used in stable doses over a longer time period, as required per study protocol.

The planned efficacy measures are accepted for assessment of the short- and long-term effects of glucose-lowering therapies on glycemic control. The safety measures included in the trial are considered suitable for a trial that investigates GLP-1 RAs, since they allow for assessment of general safety, as well as for assessment of safety issues that are of special interest with this class of medication (for example, pancreatic and thyroid safety). The schedule of electrocardiograms (ECGs) includes important time points with respect to dulaglutide dose increases or duration of exposure to the investigational doses to enable characterizations of the effects on electrocardiographic parameters, including HR. As explained in Section 3.2, monitoring of asymptomatic elevations in pancreatic enzymes does not predict clinical outcomes; multiple assessments of pancreatic enzymes are planned during the study to better understand the changes in enzyme concentrations with the 2 investigational doses.

The primary and secondary objectives are expected to provide initial benefit/risk profiles for the 2 investigational dulaglutide doses versus placebo. The exploratory objectives are included to guide dose selection and trial design for Phase 3 development (if the feasibility of further development is confirmed). For this purpose, the choice of Bayesian-based methods is considered suitable since the sample size is not large enough to allow the use of frequentist approaches. The treatment period duration of 18 weeks will allow patients to be treated with their randomized dose (for example, 3.0 mg or 4.5 mg) for at least 12 weeks, which is considered sufficient time to assess the effect of dulaglutide on HbA1c due to the short time needed to achieve maximum glucose-lowering effect (approximately 2 weeks after initiation [Weinstock et al. 2015]).

Taken together, the evidence provided supports the design and objectives of Study GBGJ, which aims to further explore the safety and efficacy of once weekly dulaglutide doses higher than 1.5 mg, and to guide further development of an additional dose with an improved glycemic efficacy versus the highest approved dulaglutide dose, with an acceptable safety profile.

## 5.5. Justification for Doses

The rationale for dulaglutide dose selection in this study was based on PK/pharmacodynamic (PD) model projections centered on identifying 1 or more doses higher than 1.5 mg that may yield up to or greater than 0.2% additional HbA1c reduction and up to or greater than 1.0 kg additional weight loss at the Week 18 endpoint, with an acceptable safety and tolerability profile compared to placebo and the 1.5 mg dose. The chosen higher dulaglutide doses (3.0 mg and 4.5 mg) were selected considering adequate separation in PK exposure range between the doses to enable evaluation of their efficacy and adverse effect profiles. Based on predicted plasma exposures in patients with T2D receiving the highest investigational dulaglutide dose of 4.5 mg, the margins of safety (ie, plasma exposure multiples at the no-observed-adverse-effect level [NOAEL]) in chronic toxicology studies in monkeys and rats were 162-fold and 55-fold, respectively.

The 2 titration algorithms for the investigational doses were designed based on PK/PD modeling, with the goal of alleviating GI AEs. The current predicted daily incidence of nausea and vomiting, together with observed data showing onset of such events diminishing by 4 to 6 weeks of treatment, suggest that utilizing a 4- to 6-week titration phase to reach the targeted dose will reduce the risk of new events with further uptitration by inducing tachyphylaxis. The titration algorithms will be initiated using 1 of the approved doses of dulaglutide (0.75 mg and 1.5 mg), because these doses do not require titration at initiation (see [Figure GBGJ.1](#) and also Section 5.4 for further details).

Study GBGJ is expected to inform the design of Phase 3 studies to further develop at least 1 higher dulaglutide dose by improving understanding of the effects of the 2 investigational dulaglutide doses on patient safety and tolerability, such as nausea and vomiting and the effect of an optimized dose-titration approach on these outcomes.

## 6. Study Population

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

### 6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at study entry (Visit 1), or at other visits, only when indicated:

- [1] are men or nonpregnant women aged  $\geq 18$  years;
- [2] have had T2D for  $\geq 6$  months according to the World Health Organization (WHO) classification ([Appendix 5](#));
- [3] have HbA1c of 7.0% to 10.0%, inclusive, as assessed by the central laboratory;
- [4] have been treated with stable doses of metformin for at least 3 months prior to Visit 1 and between Visit 1 and Visit 3; the metformin dose will be considered stable for this period if all prescribed daily doses were in the range between the minimum required dose ( $\geq 1500$  mg/day) and the maximum approved dose per country-specific label; lower doses will be allowed only with documented GI intolerability in the required dose range;
- [5] have had stable body weight for at least 3 months prior to Visit 1; body weight will be considered stable if it has not changed more than 5% in the past 3 months;
- [6] agree not to 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;
- [7] have a body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>;
- [8] in the investigator's opinion, are well-motivated, capable, and willing to:
  - [a] self-inject treatment as required for this protocol or come into the clinic for injections, up to 3 injections per week on the same day and within 30 minutes (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);
  - [b] perform fingerstick PG monitoring at least once daily and up to 6 times per day once weekly (per Schedule of Activities [[Section 2](#)]) throughout the trial;
  - [c] maintain a study diary as required for this protocol;

- [9] women of childbearing potential participating must agree to remain abstinent (if this is their preferred and usual lifestyle), use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception (see [Appendix 6](#)) starting at screening and continuing until 4 weeks after the last dose of the randomized therapy to allow for the plasma concentration to fall to  $\leq 365$  ng/mL level (average concentration [ $C_{ave}$ ] at the NOAEL from Study WIL-353116).
- [a] Women of childbearing potential participating must test negative for pregnancy as indicated by negative serum pregnancy test at screening (Visit 1) followed by a negative urine pregnancy test within 24 hours prior to exposure (Visit 3).
- [b] The patient may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide) ([Appendix 6](#)). It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.
- [c] Women must not be breastfeeding.
- [10] women not of childbearing potential may participate and include those who are:
- [a] infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or
- [b] postmenopausal – defined as either
- i. A woman  $\geq 50$  years of age with an intact uterus, not on hormone therapy who has had either
    - a) cessation of menses for at least 1 year, or
    - b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone  $>40$  mIU/mL (central laboratory, see Schedule of Activities [Section 2]); or
  - ii. A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
  - iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.
- [11] no male contraception is required except in compliance with specific local government study requirements;

- [12] have given written consent to participate in this study in accordance with local regulations and the Ethics Review Board (ERB) governing the study site

## 6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at study entry (Visit 1), or at other visits, only when indicated:

- [13] have type 1 diabetes (T1D);
- [14] have used any glucose-lowering medication other than metformin 3 months prior to study entry or during screening/lead-in period or have used any GLP-1 RAs at any time in the past. Short-term use of insulin for acute conditions is allowed ( $\leq 14$  days);
- [15] have been treated with any other excluded medication (Table GBGJ.3) within 3 months prior to screening (Visit 1) and/or between study entry and randomization (Visit 3); excluded glucocorticoids must not have been used for  $>14$  days within 1 month prior to Visit 1 or between Visits 1 and 3;
- [16] have a condition that is a contraindication for use of the GLP-1 RA class or metformin (per country-specific labels) at Visit 1 or develop such condition between Visit 1 and Visit 3;
- [17] have a history of  $\geq 1$  episode of ketoacidosis or hyperosmolar state/coma;
- [18] have had  $\geq 1$  episode of severe hypoglycemia and/or  $\geq 1$  episode of hypoglycemia unawareness within the 6 months;
- [19] have had any of the following CV conditions: acute myocardial infarction (MI), New York Heart Association Class III or Class IV heart failure, or cerebrovascular accident (stroke);
- [20] have a known clinically significant gastric emptying abnormality (eg, severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (eg, Lap-Band®);
- [21] have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine aminotransferase (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;
- [22] have had chronic or acute pancreatitis any time prior to study entry;
- [23] have an estimated glomerular filtration rate (eGFR)  $<45$  mL/min/1.73m<sup>2</sup>, calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) equation, as determined by the central laboratory at Visit 1 and confirmed at Visit 2; if any country-specific label for countries involved in this trial requires discontinuation of metformin for eGFR cut-off  $\geq 45$  mL/min/1.73 m<sup>2</sup>, then that requirement must be followed in that country;

- [24] have a personal or family history of medullary thyroid carcinoma (MTC) or personal history of multiple endocrine neoplasia syndrome type 2;
- [25] have serum calcitonin  $\geq 20$  pg/mL, as determined by the central laboratory at study entry;
- [26] have evidence of significant, active autoimmune abnormality (eg, lupus, rheumatoid arthritis);
- [27] have active or untreated malignancy, or have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years;
- [28] any serious disease or other condition (eg, known drug or alcohol abuse) which, in the opinion of the investigator, would pose a significant risk to the patient or interfere with the interpretation of safety, efficacy, or PD data;
- [29] have any hematologic condition that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle-cell disease);
- [30] 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);
- [31] 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;
- [32] are Lilly employees;
- [33] 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;
- [34] have previously completed or withdrawn from this study or any other study investigating dulaglutide

### 6.3. Lifestyle Restrictions

Per the Schedule of Activities (Section 2), qualified medical staff will provide diabetes management counseling, which will include instructions on diet and 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 healthy meal plan (with consistent meal size and time of day) throughout the course of the study. Dietary counseling may be reviewed throughout the study, as needed.

Study participants should be instructed not to donate blood or blood products during the study.

### 6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) must not be rescreened.

## 7. Treatments

### 7.1. Treatments Administered

In this study patients will receive treatment with 1 of the 3 doses of dulaglutide (4.5 mg, 3.0 mg, and 1.5 mg) or with placebo, each administered once weekly as subcutaneous injection(s) in patients with T2D who are already treated with a stable dose of metformin. Prefilled syringes (PFS) in 1 of 2 strengths (dulaglutide 0.75 mg; dulaglutide 1.5 mg) will be used to administer randomized dulaglutide doses and the interim doses required by the titration algorithms during the titration phase for the investigational dulaglutide doses only.

[Table GBGJ.2](#) shows the randomized treatments for the entire treatment period (titration phase and maintenance phase).

For doses requiring multiple injections, the entire dose (all injections for that week) should be administered within 30 minutes.

**Table GBGJ.2. Study Treatments**

Treatment Arm	Titration Phase Dose <sup>a</sup>					Maintenance Phase Dose <sup>b</sup>
	Titration Algorithm	Total dose/ Administered as	6-week Titration Phase			12-week Dosing
			Week 0 and Week 1	Week 2 and Week 3	Week 4 and Week 5	Week 6 through Week 17
4.5 mg Dulaglutide	1	Total dose	1.5 mg QW	1.5 mg QW	3.0 mg QW	4.5 mg QW
		Administered as	1 × 1.5 mg PFS	1 × 1.5 mg PFS	2 × 1.5 mg PFS	3 × 1.5 mg PFS
	2	Total dose	0.75 mg QW	1.5 mg QW	1.5 mg QW	4.5 mg QW
		Administered as	1 × 0.75 mg PFS	1 × 1.5 mg PFS	2 × 0.75 mg PFS	3 × 1.5 mg PFS
3.0 mg Dulaglutide	1	Total dose	1.5 mg QW	1.5 mg QW	3.0 mg QW	3.0 mg QW
		Administered as	1 × 1.5 mg PFS	1 × 1.5 mg PFS	2 × 1.5 mg PFS	2 × 1.5 mg PFS + 1 × Placebo PFS
	2	Total dose	0.75 mg QW	1.5 mg QW	1.5 mg QW	3.0 mg QW
		Administered as	1 × 0.75 mg PFS	1 × 1.5 mg PFS	2 × 0.75 mg PFS	2 × 1.5 mg PFS + 1 × Placebo PFS
1.5 mg Dulaglutide	—	Total dose	1.5 mg QW	1.5 mg QW	1.5 mg QW	1.5 mg QW
		Administered as	1 × 1.5 mg PFS	1 × 1.5 mg PFS	2 × 0.75 mg PFS	1 × 1.5 mg PFS + 2 × Placebo PFS
Placebo	—	Total dose	Placebo	Placebo	Placebo	Placebo
		Administered as	1 × Placebo PFS	1 × Placebo PFS	2 × Placebo PFS	3 × Placebo PFS

Abbreviations: PFS = prefilled syringe; QW = once weekly.

- <sup>a</sup> Patients will administer 1 injection per week at the assigned dose for the first 4 weeks of the titration phase (Weeks 0, 1, 2, and 3), and 2 injections per week for the final 2 weeks of the titration phase (Weeks 4 and 5), totaling the assigned dose.
- <sup>b</sup> During the maintenance phase, patients (Weeks 6 through 17) will administer 3 injections per week (different combinations of dulaglutide and placebo totaling the assigned dose).

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

- explaining the correct use of the study drug to the patient or patient representative
- explaining the correct use of metformin to the patient, including any contraindications and appropriate dosing per country-specific labeling
- verifying that treatment instructions described above are followed properly
- maintaining accurate records of study drug dispensing and collection
- Patients should return all unused study drug to the site according to the Schedule of Activities (Section 2). The patients should be instructed to discard all used PFSs in a closeable, puncture-resistant container, and dispose according to local regulations. Sites may be authorized to destroy used and unused PFSs locally per applicable local or national requirements.

### **7.1.1. Packaging and Labeling**

The sponsor will provide dulaglutide and injectable placebo in PFSs, which will be dispensed via an interactive web-response system (IWRS). Each PFS (0.75 mg dulaglutide in 0.5 mL OR 1.5 mg dulaglutide in 0.5 mL OR placebo in 0.5 mL) will be packaged in cartons to be dispensed. Titration cartons will contain 2 PFSs, and cartons for the maintenance phase will contain 3 PFSs. Injections are to be administered as described in [Table GBGJ.2](#) and Sections [7.2.1](#) and [7.2.2](#).

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

## **7.2. Method of Treatment Assignment**

Patients who meet all criteria for enrollment will be randomized to 1 of the study treatment arms at Visit 3. Assignment to treatment arms will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign cartons containing double-blind study drug to each patient. Site personnel will confirm that they have located the correct cartons by entering a confirmation number found on the label into the IWRS.

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

### **7.2.1. Selection and Timing of Doses**

Patients will be allocated to 1 of the 3 dulaglutide doses (4.5 mg, 3.0 mg, or 1.5 mg) or placebo, each administered once weekly as subcutaneous injection(s). Rationale for the choice of the 2 investigational doses (4.5 mg and 3.0 mg) is provided in Section [5.5](#). The dulaglutide 1.5 mg dose was chosen as the active comparator since this is the highest dose approved by regulatory agencies. The randomization strategy is described in Section [7.2](#).

During the titration phase (end of Visit 3 to Visit 6 [Weeks 0 to 5]), patients assigned to investigational-dose dulaglutide (3.0 mg or 4.5 mg) will begin treatment using Algorithm 1 or Algorithm 2 (Table GBGJ.2). Patients assigned to dulaglutide 1.5 mg or placebo will begin administering treatment as assigned at Visit 3, without titration. During the maintenance phase (end of Visit 6 to Visit 12 [Weeks 6 to 17]), all patients will administer study drug at their final assigned dose. The assigned doses during the titration and maintenance periods may not be dextitratid. Patients with poor tolerability of the study treatments will be allowed to discontinue dosing temporarily (Section 8.1.2). Patients who discontinue study treatment temporarily and are then unable to tolerate it upon rechallenge will be discontinued from study drug and will be initiated on glycemic rescue therapy (Section 8.1.1).

It is recommended that patients inject the study drug at approximately the same time of day on the same day each week. For doses requiring multiple injections, the entire dose (all injections for that week) should be administered on the same day, within 30 minutes. The day and time of all dose administrations are to be recorded in diaries by the patients. If 1 or more injections are not given on the scheduled day, the missed injection(s) should be given as soon as possible after the scheduled day if there are at least 3 days (72 hours) until the next dose. If fewer than 3 days remain before the next scheduled dose, the missed injection(s) should be skipped and the next dose given at the regularly scheduled day and time.

### **7.2.2. Injecting Study Drug**

All patients will inject study drug subcutaneously in the abdomen or thigh using the injection supplies provided; a caregiver may administer the injection(s) in the patient's upper arm. A new PFS will be used for each injection. For each individual dose, all injections should be administered at the same region. Different doses can be injected in different regions (rotation is encouraged).

### **7.3. Blinding**

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will have access to 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 actions 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 will continue on the assigned therapy through the end of the study, if medically appropriate. Study site personnel and the sponsor will document any unblinding events.

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 clinical research physician (CRP) prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

#### **7.4. Dosage Modification**

No adjustment in study drug doses (dulaglutide or placebo) will be allowed. Dosing of required concomitant metformin is discussed in Section 7.7.1.1.

##### **7.4.1. Special Treatment Considerations**

###### **7.4.1.1. Standards of Medical Care**

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 (American Diabetes Association 2016) 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 events of 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 (for example, severe thirst, dry mouth, frequent micturition, or dry skin) and hypoglycemia (for example, 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.

###### **7.4.1.2. Management of Increased Hypoglycemia Risk**

Dulaglutide and metformin are non-secretagogues; therefore, clinically relevant increases in the risk of hypoglycemia are not expected in this trial (Trulicity USPI [WWW]).

In this study, increased risk of hypoglycemia is defined as having a single episode of severe hypoglycemia or having more than 1 episode of documented symptomatic hypoglycemia within a 1-week period at any time during the treatment period.

In cases where a patient experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the patient has been fully compliant with the assigned therapeutic regimen and also that there is no evidence of other possible causes of hypoglycemia (for example, omission of meal, unexpected increase in exercise).

Patients fulfilling the definition of increased risk of hypoglycemia should first decrease the metformin dose, followed by discontinuation of metformin, if needed. If the patient continues to experience hypoglycemic events after the discontinuation of metformin, the investigator should discontinue the patient from study drug. No adjustment of the dulaglutide dose should be made.

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

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

- a) average FPG >240 mg/dL (>13.3 mmol/L) over any 2-week period or longer during the first 6 weeks postrandomization; or
- b) average FPG >200 mg/dL (>11.1 mmol/L) over any 2-week period or longer after the first 6 weeks postrandomization.

Investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that he/she does not have an acute condition causing severe hyperglycemia. The investigator will decide in consultation with the patient on an appropriate glucose-lowering intervention (rescue intervention) after considering relevant clinical criteria. Other GLP-1 RAs or DPP-4 inhibitors must not be included in the rescue intervention (see [Table GBGJ.3](#) for allowed medications). Patients who receive a new intervention for hyperglycemia management should also continue administering study drug for the remaining period in the trial.

### 7.5. Preparation/Handling/Storage/Accountability

The study site must store the PFS cartons in a locked and secure environment. The PFSs 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 containing the required number of dulaglutide and/or placebo PFSs at clinic visits per the Schedule of Activities (Section 2). They will receive insulated bags with cooling gel packs for use in transporting the PFS cartons from the site to home. Investigational products in each participating country will be labeled according to the country's regulatory requirements.

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.

### 7.6. Treatment Compliance

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

- Information about the 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 electronic case report form (eCRF);
- Study drug accountability will be checked at every visit. For that purpose, patients will be instructed to return the study drug carton(s) at the next visit. They will also be instructed to return any unused study drug at the next study visit;
- In all treatment arms, treatment compliance for once weekly study drug for prespecified intervals (for titration phase and every 4 weeks thereafter) is defined as taking at least

75% of the required injections of study drug as assessed by site personnel; this information will be entered in the eCRF.

Other aspects of compliance will also be assessed at each visit, including the patient's adherence to the visit schedule, compliance with the concomitant metformin requirements and other medication guidances (Section 7.7), completion of study diaries, results of SMPG, and any other parameters the investigator considers necessary. Patients considered to be poorly compliant with their medications and/or study procedures (for example, missed visits or specific diagnostic tests) will receive additional training and instructions, as required (see Section 7.6).

### **7.7. Concomitant Therapy**

Patients will be 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 treatments (Section 6.2).

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. This may not be possible when initiated for treatment of medical emergencies, in which case the patient will inform the investigator or a designated site staff member as soon as possible. Any additional medication initiated during the course of the study (including over-the-counter [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 required concomitant glucose-lowering agents (ie, metformin), the dosage will also be documented and collected.

Non-study 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.

[Table GBGJ.3](#) provides a summary of criteria for use of concomitant medications that may interfere with planned assessments during the study.

**Table GBGJ.3. Criteria for Use of Concomitant Medications that May Interfere with Efficacy and Safety Assessments in Study GBGJ**

Drug Class	Use During Screening/Lead-In	Conditions for Use after Randomization		
		Acute therapy <sup>a</sup>	Rescue therapy	During Safety Follow-Up Period
Drugs with approved weight loss indication <sup>b</sup>	Excluded	N	N/A	Y
Systemic glucocorticoid therapy <sup>c</sup>	Excluded except for acute therapy <sup>a</sup>	Y	N/A	Y
<b>Antihyperglycemia medications</b>				
Other GLP-1 RAs	Excluded	N	N	N
DPP-4 inhibitors	Excluded	N	N	N
SGLT2 inhibitors	Excluded	N	Y	Y
Insulins and insulin mixtures	Excluded except for acute therapy <sup>a</sup>	Y	Y	Y
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors	Excluded	N	Y	Y
Sulphonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y
Metformin <sup>d</sup>	Required	N/A	Y <sup>e</sup>	Y

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = no; N/A = not applicable; SGLT2 = sodium-glucose co-transporter 2; Y = yes.

<sup>a</sup> Acute therapy = treatment for up to 14 days.

<sup>b</sup> Includes Saxenda® (liraglutide 3.0 mg), Xenical® (orlistat), Meridia® (sibutramine), Sanorex® (mazindol), Apidex® (phentermine), BELVIQ® (lorcaserin), Qsymia® (phentermine/topiramate combination), Contrave® (naltrexone/bupropion), or similar other body weight loss medications including over-the-counter medications (eg, alli®) within 3 months prior to Visit 1 or any time during the trial.

<sup>c</sup> From 1 month prior to Visit 1 or between Visits 1 and 3; does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

<sup>d</sup> Switching metformin manufacturers is allowed as long as the dosage is the same. Changing to a metformin formulation with a different action profile (ie, from short-acting to long-acting metformin) is not permitted.

<sup>e</sup> For rescue therapy, metformin dose can be increased if the dose is below maximum approved dose per country-specific label.

### 7.7.1. Antihyperglycemia Medications

The only glucose-lowering agent allowed 3 months prior to study entry and during the study is the required concomitant metformin. In addition, short-term insulin use (up to 14 days) for management of medical emergencies is allowed prior to study entry and during the study. Rescue therapy with other glucose-lowering agents, including insulin, may be medically indicated in certain situations after randomization (Table GBGJ.3). These situations are described in Section 7.4.1.3 (severe, persistent hyperglycemia) and in Section 8.1.1 (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 and DPP-4 inhibitors. 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 entry or during the screening or lead-in/stabilization periods, other than metformin, will not be eligible for further participation in the trial.

If any new glucose-lowering medication is initiated after randomization at Visit 3 and prior to safety follow-up period, other than study drug, 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 lasts longer than 14 days will exclude the patient from the per-protocol (PP) population for analyses.

#### **7.7.1.1. Required Concomitant Antihyperglycemia Medication: Metformin**

The key requirements for the use of metformin, the required OAM in Study GBGJ, are provided in Section 6.1 and Section 6.2.

Patients in this study must be treated with metformin for at least 3 months prior to Visit 1; the minimum required dose during this time is 1500 mg/day; 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. The prescreening dose and formulation (short-acting or long-acting) should be maintained during the screening and lead-in periods, through randomization at Visit 3.

Metformin dose adjustment or discontinuation is allowed after randomization (during the treatment period) 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 7.4.1.2).

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

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

Guidance for treatment during the safety follow-up period is provided in Section 5.1 (Study Period III: Safety Follow-Up, Visit 801).

Where appropriate, 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 US and Puerto Rico, a prescription card will be available for patients to obtain metformin, with a prescription.

#### **7.7.2. Medications that Promote Weight Loss**

Prescription or OTC medications that promote weight loss are exclusionary if used within the 3 months prior to Visit 1 (study entry), or between study entry and randomization at Visit 3

(see Section 6.2). These medications are also not allowed at any time during the treatment period. If started after randomization, these medications should be immediately withdrawn. In addition, patients should not receive an intensive 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 6.3).

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).

### **7.7.3. Systemic Glucocorticoids**

Chronic systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) is exclusionary if used >14 consecutive days during the 1-month period before study entry (Visit 1) or between study entry (Visit 1) and randomization at Visit 3. Patients who require >14 consecutive days of therapy with these medications after randomization will be excluded from the PP population for analyses.

### **7.7.4. 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 (BP). If initiation, discontinuation, or dose adjustment of any BP-lowering agent is medically required at any time during the study, the type and dose of medication must be documented in the eCRF.

## **7.8. Treatment after the End of the Study**

### **7.8.1. Continued Access**

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

## 8. Discontinuation Criteria

### 8.1. Discontinuation from Study Treatment

#### 8.1.1. *Permanent Discontinuation from Study Treatment*

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

- if a patient is inadvertently enrolled and it is determined that continued treatment with study drug would not be medically appropriate (see Section 8.1.3)
- if a patient is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- if a patient is diagnosed by the investigator with acute or chronic pancreatitis
- if a patient is diagnosed with C-cell hyperplasia or MTC after randomization
- if a patient develops an eGFR  $<30$  mL/min/1.73m<sup>2</sup> as calculated by CKD-EPI
- if the patient or the patient's designee, for example, legal guardian, requests that the patient be withdrawn from study drug
- if the investigator or sponsor decides that the patient should be withdrawn from study drug; if the investigator decides to permanently discontinue study treatment because of an SAE or a clinically significant laboratory value, Lilly or its designee should be alerted immediately
- if the sponsor decides that a treatment arm and patients in that arm should be withdrawn from study drug

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)  $>8 \times$  upper limit of normal (ULN)
- ALT or AST  $>5 \times$  ULN for more than 2 weeks
- ALT or AST  $>3 \times$  ULN and total bilirubin level  $>2 \times$  ULN or prothrombin time  $>1.5 \times$  ULN
- ALT or AST  $>3 \times$  ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $>5\%$ )
- Alkaline phosphatase  $>3 \times$  ULN
- Alkaline phosphatase  $>2.5 \times$  ULN and total bilirubin  $>2 \times$  ULN

- Alkaline phosphatase  $>2.5 \times$  ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $>5\%$ )

Patients who stop the study drug permanently will receive another glucose-lowering intervention (rescue) and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements.

### **8.1.2. Temporary Interruption of Study Treatment**

In certain situations after randomization, the 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 9.2 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.

### **8.1.3. Discontinuation of Inadvertently Enrolled Patients**

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP and the investigator to determine if the patient may continue in the study. 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. Any inadvertently enrolled patient in whom continuous administration of study drug may result in possible or definite safety risk should be discontinued from study drug (see Section 8.1.1).

## **8.2. 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. Patient discontinuation from the study early may be warranted in the following situations for ethical or legal reasons:

- If a patient is diagnosed with T1D
- If a female patient becomes pregnant
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

Patients may also discontinue from the study due to:

- Sponsor or investigator decision when participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

- Patient decision when 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 (Section 2).

During the ET visit, the patient will be prescribed an appropriate glucose-lowering regimen and glucose self-monitoring plan.

### **8.3. 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.

## 9. Study Assessments and Procedures

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

[Appendix 2](#) lists the laboratory tests that will be performed for this study.

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

### 9.1. Efficacy Assessments

#### 9.1.1. Primary Efficacy Assessments

The primary efficacy measure is change in HbA1c from baseline at 18 weeks.

#### 9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be evaluated at 18 weeks:

- proportion of patients achieving HbA1c target  $<7.0\%$
- change in body weight from baseline
- change in fasting serum glucose (central laboratory) from baseline

#### 9.1.3. Exploratory Efficacy Assessments

The following exploratory efficacy measures will be evaluated at 18 weeks:

- proportion of patients achieving HbA1c target  $\leq 6.5\%$
- change in 6-point SMPG profile from baseline
- change in fasting plasma glucagon from baseline
- change in HOMA-IR and HOMA-%B from baseline

#### 9.1.4. 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.

#### 9.1.5. Body Weight, Height, and Body Mass Index

Body weight will be measured at prespecified time points (see Schedule of Activities, Section 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.

## 9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish 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 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 will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

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

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

### 9.2.1. *Serious Adverse Events*

An SAE is any AE from this study that results in 1 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 occurring 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.

#### **9.2.1.1. Suspected Unexpected Serious Adverse Reactions**

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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 guidance.

#### **9.2.2. Adverse Events of Special Interest**

##### **9.2.2.1. Hypoglycemia and Hyperglycemia**

Patients will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (Visit 801 or ET visit). For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect in the study diary appropriate information for each episode of hypoglycemia according to the Schedule of Activities (Section 2). Site personnel will enter this information into the eCRF at each visit.

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  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).
- **Asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG  $\leq 70$  mg/dL ( $\leq 3.9$  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  $\leq 70$  mg/dL [ $\leq 3.9$  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.

For additional analysis, hypoglycemia defined as glucose  $< 54$  mg/dL ( $< 3.0$  mmol/L) will also be considered.

Cases of relative hypoglycemia are 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  $> 70$  mg/dL ( $> 3.9$  mmol/L) is collected.

If a hypoglycemic event meets the criteria of severe, it needs to be recorded as serious on the AE 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. Management of increased risk of hypoglycemia is described in Section [7.4.1.2](#).

Severe, persistent hyperglycemia will be collected during the trial to assess the risk of extreme imbalance in glycemic control. Events of interest related to hyperglycemia include rescue therapy for severe, persistent hyperglycemia, per criteria specified in Section [7.4.1.3](#).

### 9.2.2.2. 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:

- 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);
- serum amylase (total and/or pancreatic) and/or lipase  $\geq 3 \times$  ULN
- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with investigational product, but will continue in the study on another glucose-lowering regimen (see Sections 7.7.1 and 8.1.1 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 pancreatitis, each patient will have measurements of pancreatic amylase and lipase at screening, baseline, Visit 6 (Week 6), Visit 12 (Week 18), and the last study visit (Visit 801 [Week 22] or ET visit), to assess any potential effects of dulaglutide on the exocrine pancreas (refer to the Schedule of Activities, Section 2). Further diagnostic assessment per Lilly algorithm for assessment of asymptomatic pancreatic hyperenzymemia will be required whenever lipase and/or pancreatic amylase are  $\geq 3 \times$  ULN at any time during the study. If this situation occurs at Visit 801 (Week 22), the patient will be required to undergo this additional work-up, and the data will be collected in the clinical trial database.

All suspected cases of acute or chronic pancreatitis, as well as cases of confirmed lipase or pancreatic amylase values  $\geq 3 \times$  ULN, will be adjudicated by an independent committee of expert physicians. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic

disease. Relevant data from patients with acute or chronic pancreatitis, those with severe or serious abdominal pain, and those that undergo additional assessments due to confirmed hyperenzymemia will be entered into a specifically designed eCRF page by study site or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

#### **9.2.2.3. 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 6.2). The assessment of thyroid safety during the trial will include reporting of thyroid treatment-emergent AEs (TEAEs) and measurements of calcitonin according to the Schedule of Activities (Section 2) at screening, baseline, and Visit 12 (Week 18) or ET visit. The purpose of calcitonin measurements is to assess the potential of dulaglutide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Patients who develop serum calcitonin increases  $\geq 50\%$  of the mean of the baseline and screening values AND an absolute value  $\geq 20$  pg/mL and  $< 35$  pg/mL at Visit 12 (Week 18) will be asked to repeat the measurement within 1 month. If this repeat value is increasing ( $\geq 10\%$  increase), the patient will be encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude a serious adverse effect on the gland.

Patients with an increase in serum calcitonin  $\geq 50\%$  of the mean of the baseline and screening values AND an absolute value  $\geq 35$  pg/mL at Visit 12 (Week 18) will be recommended to immediately undergo additional endocrine 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.

#### **9.2.2.4. 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 an eCRF created for this purpose. At the time of AE occurrence, a sample will be collected for measurement of dulaglutide anti-drug antibodies (ADA). Study drug should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug (Section 8.1.2). 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, see Section 8.1.1 for procedures required in this situation.

#### **9.2.2.5. Supraventricular Arrhythmias and Cardiac Conduction Disorders**

All events of treatment-emergent supraventricular arrhythmias and cardiac conduction disorders will be fully evaluated. Patients who develop any event from these groups of disorders should undergo an ECG which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will

be recorded as an AE. Events that meet criteria for serious conditions as described in Section 9.2.1 must be reported as SAEs. Study drug should be temporarily discontinued in any patient with signs and symptoms of serious cardiac arrhythmias or conduction disorders. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator.

### **9.2.3. 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.

## **9.3. Treatment of Overdose**

Study drug overdose (more than the specified number of injections, whether for placebo or dulaglutide treatment) will be reported as an AE. In the event of overdose, refer to the IB and or Product Label.

## **9.4. Safety**

### **9.4.1. CV Safety**

#### **9.4.1.1. 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 interventions (such as coronary artery bypass graft or percutaneous coronary intervention); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

#### **9.4.1.2. Electrocardiograms**

To assess the effect of higher doses on cardiac electrophysiology, ECGs will be collected according to the Schedule of Activities (Section 2) and centrally overread. Electrocardiograms should be recorded in triplicate according to 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.

#### **9.4.1.3. Vital Signs**

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

#### **9.4.2. Laboratory Tests**

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

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

#### **9.4.3. 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. An AC will review prespecified safety reports in an unblinded fashion. In addition, the study team will review safety reports in a blinded fashion according to the schedule provided in the Trial-Level Safety Review plan. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly CRP will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

In addition, specific safety measures are included in the protocol to ensure appropriate monitoring of pancreatic, thyroid, and liver safety. Laboratory findings that trigger pancreatic and thyroid safety monitoring per Lilly standards are provided in Sections [9.2.2.2](#) and [9.2.2.3](#), respectively. Details of liver safety monitoring are provided in [Appendix 4](#). If a study patient experiences elevated ALT  $\geq 3 \times$  ULN, alkaline phosphatase  $\geq 2 \times$  ULN, or elevated total bilirubin  $\geq 2 \times$  ULN, clinical and laboratory monitoring should be initiated by the investigator per Lilly Hepatic Safety Monitoring Algorithm. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See [Appendix 4](#).

## 9.5. Pharmacokinetics

Blood samples for determining plasma concentrations of dulaglutide, associated with time from dose, will be obtained at selected visits from all patients in accordance with the Study Schedule and at ET (see Schedule of Activities [Section 2]). However, only samples from patients assigned to treatment with dulaglutide will be analyzed for drug concentrations.

Timing of PK blood draws have been optimized for sparse sampling using a standard PK optimal sampling approach. Pharmacokinetic samples will be drawn to include a range of sampling time windows (predose, and 1-24 hours, 24-96 hours, and 120-168 hours postdose) spread over several clinic visits. For the ET visit, a sample may be drawn at any time during the visit. The study has been designed so that, where possible, each immunogenicity sample will be accompanied by a PK sample in the same visit. At visits where ECG measurements are taken, these should be accompanied by a time-matched PK sample within 30 minutes (before or after), during the same visit.

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 4 mL each will be collected to determine the plasma concentrations of dulaglutide.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling and all study drug doses must be clearly recorded.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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

## 9.6. Pharmacodynamics

Pharmacodynamic parameters will include safety and efficacy endpoints as described in Section 4. Analysis methods are described in Section 10.3.5.

## 9.7. Pharmacogenomics

### 9.7.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to dulaglutide and to investigate genetic variants thought to play a role in T2D and related complications. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All 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 retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of dulaglutide or when dulaglutide is widely 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, and candidate gene studies, and epigenetic analyses. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

## **9.8. Biomarkers and Antibodies**

### **9.8.1. Samples for Immunogenicity Research**

Samples from patients in each treatment arm will be tested for the development of treatment-emergent dulaglutide ADA, defined as 4-fold increase in titer from baseline. A blood sample will be collected at specific study visits according to the Schedule of Activities (Section 2).

Treatment-emergent positive dulaglutide ADA samples will be evaluated for their ability to neutralize the activity of assigned treatment (dulaglutide-neutralizing antibodies). Positive dulaglutide ADA samples may also be tested for cross-reactivity with native GLP-1, and if positive, then for neutralizing antibodies against native GLP-1.

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

### **9.8.2. Biomarkers**

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

Serum and plasma samples (ethylenediaminetetraacetic acid [EDTA] and remaining P800 plasma from glucagon collection) for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

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

All samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigative site personnel.

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

### **9.9. Health Economics**

Not applicable.

## 10. Statistical Considerations

### 10.1. Sample Size Determination

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

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

### 10.2. Populations for Analyses

Table GBGJ.4 defines the populations to be used for analyses.

**Table GBGJ.4. Populations for Analyses**

Population	Description
Entered	All participants who sign informed consent
Intent-to-treat (ITT)	All participants who are randomized and take at least 1 dose of study medication for an assigned treatment arm
All randomized population	All patients who are randomized
Per protocol	All ITT patients who meet all of the following criteria: <ul style="list-style-type: none"> <li>• Have no important protocol deviation that could impact the assessment of the primary endpoint*</li> <li>• At least 75% compliant with study drug administration</li> <li>• Complete the treatment period (18 weeks)</li> <li>• Have a value of the primary efficacy measure (HbA1c) at 18 weeks</li> </ul>
Completer set	All ITT patients who complete 18 weeks of study drug treatment without rescue therapy

Abbreviation: HbA1c = hemoglobin A1c.

\*Full list will defined in the Statistical Analysis Plan.

### 10.3. Statistical Analyses

#### 10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the 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

clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise specified, listings will include all randomized patients. Efficacy and safety analyses will be conducted in the intent-to-treat (ITT) population. The primary efficacy measure (change from baseline in HbA1c) will also be evaluated in the PP population and Completer sets. In all efficacy and hypoglycemia analyses, all data after rescue therapy will be censored. Analyses of safety parameters, except for hypoglycemia events, will be conducted in the ITT population including the post-rescue therapy data.

Countries with fewer than 10 randomized patients will be pooled for statistical analyses. Pooled country will be employed for all formal statistical model-based analyses.

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

The baseline visit will be Visit 3. For all variables, including HbA1c, if baseline data are not available or are missing, the last nonmissing measurement taken prior to this visit will be used for the baseline measurement. The measurement for the primary analysis is defined as the change from baseline in HbA1c to Week 18 (Visit 12).

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

A mixed-model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. In this model, restricted maximum likelihood will be used to obtain model estimates with Kenward-Roger option to estimate denominator degrees of freedom. The corresponding baseline value will be used as a covariate, and the stratification factor (HbA1c <8% or ≥8%), pooled country, treatment, visit, and treatment-by-visit interaction will be fixed effects. For HbA1c change from baseline analysis, stratification factor will be removed from the aforementioned model. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the following covariance structures will be tested in order:

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

The first covariance structure that converges will be used.

For continuous laboratory measurements for safety, an analysis of variance (ANOVA) on ranks will be used with treatment as a fixed effect.

For all continuous measures, summary statistics will include number of patients, mean, SD, median, minimum, and maximum for both the actual and change from baseline measurements at each scheduled visit for each treatment. Least-squares mean (LS mean) and standard errors (SEs) derived from the model will also be displayed for the change from baseline measurements at each scheduled visit for each treatment. Treatment comparisons will be displayed showing the treatment difference LS mean and the 95% CIs between each dose and placebo, and between each investigational dose and 1.5 mg at the same visit, along with the corresponding p-values.

Summary statistics for categorical measures will include number of subjects and percentages. The percentage of patients achieving target HbA1c <7.0% at Week 18 will be analyzed using a longitudinal logistic regression with repeated measurements with treatment, visit, treatment-by-visit interaction, and baseline HbA1c-by-visit interaction as fixed effects and baseline HbA1c as a covariate. For the analysis of other categorical measures, Fisher's exact test will be used for treatment comparisons, unless 80% of cells have an expected value of at least 5, in which case the Chi-square test will be used unless otherwise stated.

No adjustments for multiplicity will be performed.

### **10.3.2. Treatment Group Comparability**

#### **10.3.2.1. 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, and/or discontinuing from the study early will be presented for each treatment. The reasons for discontinuation from the study will be summarized by treatment group. A summary of discontinuations will also be presented by visit.

#### **10.3.2.2. Patient Characteristics**

Demographic and baseline characteristics will be summarized by treatment. For continuous measures, summary statistics will include sample size, mean, median, maximum, minimum, and SDs along with ANOVA's p-value to test overall treatment effect. For categorical measures, summary statistics will include sample size, frequency, and percent.

#### **10.3.2.3. Concomitant Therapy**

The prespecified concomitant medications of interest will be summarized by treatment.

#### **10.3.2.4. Treatment Compliance**

Treatment compliance is defined as taking at least 75% of required injections for the prespecified time intervals (see Section 7.6). Overall compliance is defined as being at least 75% compliant with investigational product across the treatment period. Compliance will be summarized by each treatment and time interval, and overall. Listings will also be produced.

### **10.3.3. Efficacy Analyses**

#### **10.3.3.1. Primary Analyses**

The primary analysis for the primary endpoint, change from baseline in HbA1c at 18 weeks, will employ MMRM described in Section 10.3.1 in ITT population by censoring all post rescue data.

#### **10.3.3.2. Secondary Analyses**

##### **10.3.3.2.1. Secondary Analyses for Primary Endpoint**

A Bayesian integrated 2-component prediction (ITP) model (Fu and Manner 2010) will be applied as a supportive analysis for the primary endpoint, change from baseline in HbA1c at 18 weeks, in ITT population by censoring all post-rescue data. Probabilities based on posterior distributions of the parameter of interest will be generated from this model. Non-informative priors will be used in this model. In addition, the informative priors from the posterior for placebo and posterior for dulaglutide 1.5 mg obtained from Studies GBCF and H9X-MC-GBDE (GBDE) will be evaluated in this model to check the robustness of the analysis. The primary analysis model, MMRM, will be repeated using the PP and Completers populations for the primary endpoint only to check the sensitivity of the analysis. If the conclusions differ from that of the ITT population, the data and analyses may be further explored using selected pattern mixture models for missing data (Kenward and Rosenkranz 2011). As a sensitivity analysis, the primary endpoint will be analyzed with MMRM and Bayesian ITP model in the ITT population including post-rescue therapy data.

##### **10.3.3.2.2. Analyses for Secondary Efficacy Endpoints**

The ITT population without post-rescue data is the analysis population for secondary efficacy endpoints. The MMRM described in Section 10.3.1 will be used for the secondary continuous efficacy endpoints. For percentages of patients achieving HbA1c target <7.0%, repeated measures logistic regression with generalized linear mixed model described in Section 10.3.1 will be fitted.

A Bayesian ITP model will be fitted to analyze body weight change from baseline as a supportive analysis.

##### **10.3.3.3. Tertiary/Exploratory Efficacy Endpoints**

The analysis of patients reaching HbA1c target  $\leq 6.5\%$  will use the same model as that for HbA1c target <7.0% described in Section 10.3.3.2.2.

Longitudinal continuous variables such as fasting glucagon will be analyzed using MMRM described in Section 10.3.1. If the normality assumption is violated, appropriate transformation is needed prior to analysis.

Non-longitudinal continuous variables such as 6-point SMPG, HOMA-IR, and HOMA-%B will be analyzed using last observation carried forward (LOCF) by fitting a linear model with pooled country, treatment, baseline HbA1c strata as fixed effect, and corresponding baseline value as a covariate. Data transformation may be applied if data are not normally distributed.

### **10.3.4. Safety Analyses**

The safety analyses will include AEs, SAEs, and TEAEs, defined as postbaseline events that are new events or preexisting conditions that worsened in severity after randomization, hypoglycemic and hyperglycemic episodes, and laboratory analytes. Unless otherwise specified, the ITT population will be used for analyses of safety measures.

#### **10.3.4.1. Study Drug Exposure**

Exposure will be calculated for each patient and summarized by each treatment group.

#### **10.3.4.2. Adverse Events**

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms.

Summary statistics will be provided for overall AE, 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. Adverse events will be analyzed as described in Section [10.3.1](#).

Listings of patients experiencing SAEs, allergic and hypersensitivity reactions, ADA as well as those discontinuing the study, or study medication due to AEs, will be generated.

#### **10.3.4.3. Hypoglycemic Episodes**

Section [9.2.2.1](#) 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. Hypoglycemia will be analyzed as documented symptomatic, asymptomatic, probable, severe, or nocturnal and for all events combined as total hypoglycemia. Other categories, including the categories above defined with different glucose thresholds, may also be included in these analyses when deemed appropriate.

The incidence will be analyzed using the categorical methods described in Section [10.3.1](#) and rate of hypoglycemic episodes will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution for hypoglycemic episodes. Incidence and rates will be summarized for each treatment arm and entire treatment period.

#### **10.3.4.4. Severe, Persistent Hyperglycemia**

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

#### **10.3.4.5. Pancreas Safety**

Listings and summaries of adjudicated pancreatic events will be provided.

#### **10.3.4.6. Cardiovascular Safety**

Listings and summaries of adjudicated CV events will be provided. Summaries and listings of supraventricular arrhythmias and cardiac conduction disorders will be provided.

**10.3.4.7. Thyroid Safety**

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

**10.3.4.8. Renal Safety**

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

**10.3.4.9. Gastrointestinal Safety**

Because GI AEs, including nausea, vomiting, and diarrhea, are among the most common events reported in patients treated with dulaglutide, summaries and analyses for incidence, time to onset, duration, and severity of nausea and vomiting will be provided for each treatment during the 18-week treatment period and during the first 6 weeks (titration phase), overall and by visit, to compare the effects of the 4 different dose escalations (2 algorithms for each of the 2 investigational doses) and effects of the 2 titration algorithms on GI tolerability, as well as the overall effects of randomized therapies. The planned reports will be further described in the statistical analysis plan (SAP).

**10.3.4.10. Allergic/Hypersensitivity Reactions**

Summaries and listings of allergic and other hypersensitivity AEs including injection site reaction will be provided.

**10.3.4.11. Immunogenicity**

Summaries and listings of dulaglutide ADA will be generated.

**10.3.4.12. Laboratory Analyses**

Laboratory measurements will be listed by patient. Additional listings will be presented for laboratory measurements that are outside the normal range and for measurements outside certain prespecified clinically relevant thresholds.

Laboratory safety measurements will be summarized. For continuous (numeric) laboratory analytes, the change from baseline to endpoint (Week 18) will be analyzed as detailed in Section [10.3.1](#).

For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using Chi-square tests or Fisher's exact test.

Shift tables of the change from baseline value to the most extreme postbaseline value, and from baseline to Week 18 for selected analytes using clinically meaningful thresholds will be summarized separately using generalized McNemar's test for within-treatment comparison and using likelihood ratio test for between-treatment comparisons.

**10.3.4.13. Vital Signs**

Vital signs will be listed for all randomized patients.

Descriptive statistics for the actual measurements and changes from baseline for SBP and DBP, and PR will be presented by treatment and visit.

Vital signs will be analyzed using a similar MMRM-based model as that described in Section 10.3.1 for continuous variable analysis.

#### **10.3.4.14. Electrocardiograms**

Descriptive statistics for the absolute measurements, outliers, and changes from baseline for selected ECG parameters defined in the SAP, including QT corrected for heart rate using Fridericia's formula (QTcF) will be presented by treatment and visit. These parameters will be analyzed using a similar MMRM-based model as that described in Section 10.3.1 for continuous variable analysis.

#### **10.3.5. Pharmacokinetic/Pharmacodynamic Analyses**

Population PK analyses will be conducted using dosing data and dulaglutide concentrations obtained from all patients via commonly accepted pharmacostatistical methods (for example, nonlinear mixed-effects modeling), and covariate screening.

The relationship between dulaglutide doses and/or concentrations and key safety measures (such as QT intervals, BP and HR, nausea, vomiting), and efficacy measures (such as fasting glucose, HbA1c, and weight) will be assessed in PK/PD analyses. Endpoints may include but are not necessarily limited to those listed above.

In addition, if positive antibody titers to dulaglutide are observed, the relationship between dulaglutide PK concentrations and antibody formations will be evaluated for impact on dulaglutide clearance and, if applicable, drug effect(s).

#### **10.3.6. Subgroup Analyses**

Subgroup analyses of treatment interaction for important factors, including age, race, gender, country, duration of diabetes, baseline HbA1c (<8%, ≥8%), and BMI may be conducted for the primary endpoint of HbA1c.

These will be conducted using the MMRM with treatment, visit, subgroup, treatment-by-visit, treatment-by-subgroup, visit-by-subgroup, and treatment-by-visit-by-subgroup as fixed effects, and baseline as covariate. If the MMRM fails to converge, the corresponding analysis of covariance (ANCOVA) or ANOVA model (LOCF) will be used.

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

Other exploratory subgroup analyses may be performed as deemed appropriate.

#### **10.3.7. Interim Analyses**

There will be at least 3 interim safety analyses for this study. The purpose of these analyses will be to monitor the safety and tolerability of the 2 investigational dulaglutide doses. An additional interim efficacy/safety analysis may be conducted for sponsor planning purposes. An AC will be formed to review the interim analyses in an unblinded fashion. The first interim safety analysis will occur after approximately 15 patients have completed 8 weeks of treatment. The AC will continue to evaluate safety when approximately 30 and 60 patients have exposure to therapy for

at least 8 weeks (interim safety analyses 2, and 3, respectively). The efficacy/safety interim analysis will be conducted after approximately 120 patients have completed the 18-week therapy. The AC proceedings will be described in a separate AC charter. Any change to the proceedings will be included in the AC charter and will not require a protocol amendment.

Only the AC and Statistical Analysis Center will be authorized to evaluate unblinded interim analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are specified in the unblinding plan section of the statistical analysis plan (SAP).

#### **10.3.7.1. PK/PD Prelock Data Access**

A limited number of preidentified individuals will require access to the unblinded PK and PD (safety and efficacy) data, as specified in the unblinding plan, prior to final database lock. This is necessary in order to initiate population PK/PD model development for final analyses.

Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the study data lock occurs.

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## 12. Appendices

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## Appendix 1. Abbreviations and Definitions

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Term	Definition
<b>AC</b>	Assessment Committee
<b>ADA</b>	anti-drug antibodies
<b>AE</b>	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.
<b>ALT</b>	alanine aminotransferase
<b>ANCOVA</b>	analysis of covariance
<b>ANOVA</b>	analysis of variance
<b>AST</b>	aspartate aminotransferase
<b>blinding/masking</b>	<p>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not.</p> <p>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.</p>
<b>BMI</b>	body mass index
<b>BP</b>	blood pressure
<b>bpm</b>	beats per minute
<b>CI</b>	confidence interval
<b>CKD-EPI</b>	Chronic Kidney Disease-Epidemiology
<b>Complaint</b>	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.
<b>CRP</b>	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.
<b>CSR</b>	clinical study report

<b>CT</b>	computed tomography
<b>CV</b>	cardiovascular
<b>DBP</b>	diastolic blood pressure
<b>DPP-4</b>	dipeptidyl peptidase-4
<b>ECG</b>	electrocardiogram
<b>eCRF</b>	electronic case report form
<b>eGFR</b>	estimated glomerular filtration rate
<b>Enroll</b>	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.
<b>Enter</b>	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>ERB</b>	Ethics Review Board
<b>ET</b>	early termination
<b>FPG</b>	fasting plasma glucose
<b>GCP</b>	good clinical practice
<b>GI</b>	gastrointestinal
<b>GLP-1</b>	glucagon-like peptide-1
<b>GLP-1 RA</b>	glucagon-like peptide-1 receptor agonist
<b>HbA1c</b>	hemoglobin A1c
<b>HOMA</b>	Homeostasis Model Assessment
<b>HOMA-%B</b>	$\beta$ -cell function as measured by the HOMA2 method
<b>HOMA-IR</b>	insulin resistance as measured by the HOMA2 method
<b>HR</b>	heart rate
<b>IB</b>	Investigator's Brochure
<b>ICF</b>	informed consent form
<b>ICH</b>	International Conference on Harmonisation
<b>interim analysis</b>	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

<b>investigational product</b>	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.
<b>ITP</b>	integrated 2-component prediction
<b>ITT</b>	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (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.
<b>IWRS</b>	interactive web-response system
<b>LOCF</b>	last observation carried forward
<b>LS mean</b>	least-squares mean
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>MI</b>	myocardial infarction
<b>MMRM</b>	mixed-model repeated measures
<b>MRI</b>	magnetic resonance imaging
<b>MTC</b>	medullary thyroid carcinoma
<b>NAFLD</b>	nonalcoholic fatty liver disease
<b>NOAEL</b>	no adverse effect level
<b>OAM</b>	oral antihyperglycemia medications
<b>OTC</b>	over-the-counter
<b>PD</b>	pharmacodynamic
<b>PFS</b>	prefilled syringe
<b>PG</b>	plasma glucose
<b>PK</b>	pharmacokinetics
<b>PP</b>	per-protocol set: 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.
<b>PR</b>	pulse rate
<b>QTc</b>	corrected QT interval

<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>SBP</b>	systolic blood pressure
<b>Screen</b>	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.
<b>SD</b>	standard deviation
<b>SE</b>	standard error
<b>SmPC</b>	Summary of Product Characteristics
<b>SMPG</b>	self-monitored plasma glucose
<b>SUSARs</b>	suspected unexpected serious adverse reactions
<b>T1D</b>	type 1 diabetes
<b>T2D</b>	type 2 diabetes
<b>TEAE</b>	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
<b>ULN</b>	upper limit of normal
<b>US</b>	United States
<b>USPI</b>	United States Package Insert
<b>WHO</b>	World Health Organization

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## Appendix 2. Clinical Laboratory Tests

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### Clinical Laboratory Tests<sup>a</sup>

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#### Hematology

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

#### Urinalysis

Specific gravity  
 pH  
 Protein  
 Glucose  
 Ketones  
 Blood  
 Urine leukocyte esterase  
 Creatinine

#### Albumin/creatinine ratio (urine)<sup>b</sup>

#### HbA1c

#### Endocrine

Fasting plasma glucagon<sup>c</sup>  
 Fasting serum insulin  
 Calcitonin  
 Follicle-stimulating hormone  
 C-peptide

#### Samples for PK analysis

#### Stored Samples

Pharmacogenomics sample  
 Non-pharmacogenomic biomarker sample  
 (serum, plasma EDTA/P800<sup>c</sup>)

#### Clinical Chemistry

##### Serum Concentrations of:

Sodium  
 Potassium  
 Total bilirubin  
 Direct bilirubin  
 Alkaline phosphatase  
 Alanine aminotransferase (ALT)  
 Aspartate aminotransferase (AST)  
 Blood urea nitrogen (BUN)  
 Creatinine  
 Creatine kinase (creatine phosphokinase; CPK<sup>d</sup>)  
 Uric acid  
 Calcium  
 Albumin  
 Glucose<sup>e</sup>

##### eGFR (calculated by CKD-EPI equation)<sup>f</sup>

##### Pancreas (Exocrine)

Serum pancreatic amylase  
 Serum lipase

##### Lipid Panel (fasting)

Total cholesterol  
 LDL<sup>g</sup>  
 HDL  
 VLDL  
 Triglycerides

##### Glucose (fasting)

##### Pregnancy test serum and urine<sup>h</sup>

#### Immunogenicity

Dulaglutide anti-drug antibody  
 Dulaglutide neutralizing antibody  
 Native GLP-1 crossreactive antibody  
 Native GLP-1 neutralizing antibody

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**Clinical Laboratory Tests**

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; CK-MB = creatine kinase-MB; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; PK = pharmacokinetics; RBC = red blood cells; VLDL = very low density lipoprotein cholesterol; WBC = white blood cells.

- a All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.
- b Urinary albumin and creatinine are measured; the ratio is calculated.
- c Remaining P800 plasma from glucagon collection for non-pharmacogenomic biomarker sample.
- d CK-MB is to be assayed if the creatine kinase result is >1000 IU/L.
- e For those visits when fasting glucose is required, glucose will not be included in the chemistry panel.
- f CKD-EPI equation described in Levey et al. 2009.
- g This value will be calculated. If triglycerides >400 ng/mL, then direct LDL will be assayed.
- h Serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing potential; urine pregnancy test will be performed at the site at Visit 3 for women of childbearing potential. Additional pregnancy tests may be performed at the investigator's discretion during the study.

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**Appendix 3. Study Governance Considerations**

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

### ***Appendix 3.1.1. Informed Consent***

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (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.

### ***Appendix 3.1.2. Ethical Review***

The investigator or an appropriate local representative must give assurance that the ethical review board (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 Good Clinical Practice (GCP).

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

- the current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- relevant curricula vitae

### ***Appendix 3.1.3. 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.

**Appendix 3.1.4. 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.

**Appendix 3.1.5. 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.

**Appendix 3.1.6. Final Report Signature**

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his 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.

**Appendix 3.2. Data Quality Assurance**

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

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give 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.

#### ***Appendix 3.2.1. Data Capture System***

An electronic data capture system will be used in this study. The sites will maintain 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 data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient will include diaries and dosing records.

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

### **Appendix 3.3. Study and Site Closure**

#### ***Appendix 3.3.1. Discontinuation of Study Sites***

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

#### ***Appendix 3.3.2. Discontinuation of the Study***

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

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## Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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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, clinical research physician.

### Hepatic Monitoring Tests

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#### Hepatic Hematology<sup>a</sup>

Hemoglobin  
Hematocrit  
RBC  
WBC  
Neutrophils, segmented  
Lymphocytes  
Monocytes  
Eosinophils  
Basophils  
Platelets

#### Hepatic Chemistry<sup>a</sup>

Total bilirubin  
Direct bilirubin  
Alkaline phosphatase  
ALT  
AST  
GGT  
CPK

#### Haptoglobin<sup>a</sup>

#### Hepatic Coagulation<sup>a</sup>

Prothrombin Time  
Prothrombin Time, INR

#### Hepatic Serologies<sup>a,b</sup>

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<sup>a</sup>

#### Alkaline Phosphatase Isoenzymes<sup>a</sup>

#### Anti-smooth muscle antibody (or anti-actin antibody)<sup>a</sup>

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

<sup>a</sup> Assayed by Lilly-designated or local laboratory.

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

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**Appendix 5. Protocol GBGJ World Health Organization Classification of Diabetes and Diagnostic Criteria**

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**Type 1 Diabetes:** Type 1 diabetes 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:** Type 2 diabetes, 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).

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## **Appendix 6. Classification of Contraceptive Methods**

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### **Highly Effective Methods of Contraception:**

- Combined oral contraceptive pill and mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence
- Vasectomy – for men in clinical trials

### **Effective methods of contraception (must use combination of 2 methods)**

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

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## **Appendix 7. Protocol GBGJ World Health Organization Standardized Protocols for the Measurement of Height and Weight**

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The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2008) (Available at: [http://www.who.int/chp/steps/Part3\\_Section3.pdf](http://www.who.int/chp/steps/Part3_Section3.pdf)), accessed: August 16, 2016.

### **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).

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## **Appendix 8. Protocol Amendment H9X-MC-GBGJ (a) Summary: A Phase 2, Double-Blind, Placebo-Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy**

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### **Overview**

Protocol H9X-MC-GBGJ [A Phase 2, Double-Blind, Placebo-Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy] has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- **Section 4 Objectives, Section 9.2.2.5 Supraventricular Arrhythmias and Cardiac Conduction Disorders, and 10.3.4.6. Cardiovascular Safety:** Based on a request from the US Food and Drug Administration (FDA) on 21 October 2016, supraventricular arrhythmias and cardiac conduction disorders were added as adverse events of special interest.
- **Section 8.1.1 Permanent Discontinuation from Study Treatment:** A criterion was added to allow for discontinuation of a treatment arm if decided by sponsor. This is to ensure the safety of patients at investigational doses of dulaglutide.
- Minor editorial changes were made throughout the protocol to improve clarity and/or correct typographical errors.

## Revised Protocol Sections

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

### Global Changes

- Page headers: H9X-MC-GBGJ (a) Clinical Protocol
- The terms “**HOMA\_B%**” and “**HOMA\_IR%**” have been changed to “**HOMA-%B**” and “**HOMA-IR**” throughout.

### 1. Synopsis

#### Treatment Arms and Duration:

At Visit 3, patients will be randomized in a 1:1:1:1 ratio to weekly injections of dulaglutide 4.5 mg, 3.0 mg, or 1.5 mg, or placebo, in combination with stable doses of metformin. Within each of the investigational dulaglutide dose (3.0 mg and 4.5 mg) arms, patients will be randomly assigned in a 1:1 ratio to 1 of the dulaglutide dose titration algorithms (Algorithm 1 ~~and~~ or Algorithm 2). Study participants will be treated for 18 weeks after randomization in a double-blind manner, followed by a 4-week safety evaluation.

### 4. Objectives

**Table GBGJ.1. Objectives and Endpoints**

Objectives	Endpoints
<p><b>Tertiary/Exploratory</b></p> <p><u>Safety</u></p> <ul style="list-style-type: none"> <li>• To compare the investigational dose dulaglutide arms (4.5 mg and 3.0 mg) to the placebo arm for additional safety measures at 18 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Selected gastrointestinal tolerability AEs (nausea, vomiting, and diarrhea)</li> <li>• Pancreatic safety assessed by incidence of cases of adjudicated pancreatitis</li> <li>• CV safety assessed by the incidence of adjudicated deaths and nonfatal major CV events</li> <li>• Thyroid-related safety assessed by the incidence of cases of thyroid neoplasms</li> <li>• Vital signs (PR, BP)</li> <li>• ECG (HR, QTcF, <u>supraventricular arrhythmias and cardiac conduction abnormalities</u>)</li> <li>• Immune system-related safety, including the incidence of dulaglutide anti-drug antibodies (ADA) and the incidence of allergic and hypersensitivity reactions</li> </ul>

**Objectives and Endpoints (continued)**

Objectives	Endpoints
Tertiary/Exploratory (concluded)	<ul style="list-style-type: none"> <li>• Thyroid-related safety assessed by the incidence of cases of thyroid neoplasms</li> <li>• Vital signs (PR, BP)</li> <li>• ECG parameters (HR, QTcF, <u>supraventricular arrhythmias and cardiac conduction abnormalities</u>)</li> <li>• Immune system-related safety, including the incidence of dulaglutide ADA and the incidence of allergic and hypersensitivity reactions</li> <li>• Injection site reactions</li> <li>• Incidence of rescue therapy initiation due to severe, persistent hyperglycemia</li> </ul>

**5.1. Overall Design****Randomization (Visit 3)**

At Visit 3, patients will perform study procedures that are required prior to randomization. Patients who continue to be eligible will then be randomized in a 1:1:1:1 ratio to 1 of the treatment arms: (1) dulaglutide 4.5 mg, (2) dulaglutide 3.0 mg, (3) dulaglutide 1.5 mg, or (4) placebo. Within each of the investigational dulaglutide dose (3.0 mg and 4.5 mg) arms, patients will be randomly assigned in a 1:1 ratio to 1 of the titration algorithms (Algorithm 1 ~~and or~~ Algorithm 2). Immediately after randomization, the patient will inject the first dose of study drug at the study site. The Visit 3 pharmacokinetics (PK) sample must be collected 1-24 hours after the patient has injected study drug for the first time.

**6.2. Exclusion Criteria**

[15] have been treated with any other excluded medication (Table GBGJ.3) within 3 months prior to screening (Visit 1) and/or between study entry and randomization (Visit 3); excluded glucocorticoids must not have been used for  $\geq 14$  days within 1 month prior to Visit 1 or between Visits 1 and 3;

**8.1.1. Permanent Discontinuation from Study Treatment**

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

- if a patient is inadvertently enrolled and it is determined that continued treatment with study drug would not be medically appropriate (see Section 8.1.3)
- if a patient is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- if a patient is diagnosed by the investigator with acute or chronic pancreatitis
- if a patient is diagnosed with C-cell hyperplasia or MTC after randomization

- if a patient develops an eGFR <30 mL/min/1.73m<sup>2</sup> as calculated by CKD-EPI
- if the patient or the patient's designee, for example, legal guardian, requests that the patient be withdrawn from study drug
- if the investigator or sponsor decides that the patient should be withdrawn from study drug; if the investigator decides to permanently discontinue study treatment because of an SAE or a clinically significant laboratory value, Lilly or its designee should be alerted immediately
- if the sponsor decides that a treatment arm and patients in that arm should be withdrawn from study drug

#### **9.2.2.5. Supraventricular Arrhythmias and Cardiac Conduction Disorders**

All events of treatment-emergent supraventricular arrhythmias and cardiac conduction disorders will be fully evaluated. Patients who develop any event from these groups of disorders should undergo an ECG which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 9.2.1 must be reported as SAEs. Study drug should be temporarily discontinued in any patient with signs and symptoms of serious cardiac arrhythmias or conduction disorders. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator.

#### **9.4.1.3. Vital Signs**

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

### 10.3.4. Safety Analyses

#### ~~10.3.4.5. — Special Safety Topics~~

##### ~~10.3.4.5.1. 10.3.4.5. Pancreas Safety~~

Listings and summaries of adjudicated pancreatic events will be provided.

##### ~~10.3.4.5.2. 10.3.4.6. Cardiovascular Safety~~

Listings and summaries of adjudicated CV events will be provided. Summaries and listings of supraventricular arrhythmias and cardiac conduction disorders will be provided.

##### ~~10.3.4.5.3. 10.3.4.7. Thyroid Safety~~

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

##### ~~10.3.4.5.4. 10.3.4.8. Renal Safety~~

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

##### ~~10.3.4.5.5. 10.3.4.9. Gastrointestinal Safety~~

Because GI AEs, including nausea, vomiting, and diarrhea, are among the most common events reported in patients treated with dulaglutide, summaries and analyses for incidence, time to onset, duration, and severity of nausea and vomiting will be provided for each treatment during the 18-week treatment period and during the first 6 weeks (titration phase), overall and by visit, to compare the effects of the 4 different dose escalations (2 algorithms for each of the 2 investigational doses) and effects of the 2 titration algorithms on GI tolerability, as well as the overall effects of randomized therapies. The planned reports will be further described in the statistical analysis plan (SAP).

##### ~~10.3.4.5.6. 10.3.4.10. Allergic/Hypersensitivity Reactions~~

Summaries and listings of allergic and other hypersensitivity AEs including injection site reaction will be provided.

##### ~~10.3.4.6. 10.3.4.11. Immunogenicity~~

Summaries and listings of dulaglutide ADA will be generated.

##### ~~10.3.4.7. 10.3.4.12. Laboratory Analyses~~

Laboratory measurements will be listed by patient. Additional listings will be presented for laboratory measurements that are outside the normal range and for measurements outside certain prespecified clinically relevant thresholds.

##### ~~10.3.4.8. 10.3.4.13. Vital Signs~~

Vital signs will be listed for all randomized patients.

##### ~~10.3.4.9. 10.3.4.14. Electrocardiograms~~

Descriptive statistics for the absolute measurements, outliers, and changes from baseline for selected ECG parameters defined in the SAP, including QT corrected for heart rate using

Fridericia's formula (QTcF) will be presented by treatment and visit. These parameters will be analyzed using a similar MMRM-based model as that described in Section 10.3.1 for continuous variable analysis.

Leo Document ID = 0c4771e4-5f04-410d-ba2c-aa0e2ac98b02

Approver: PPD  
Approval Date & Time: 04-Nov-2016 21:07:21 GMT  
Signature meaning: Approved

Approver: PPD  
Approval Date & Time: 07-Nov-2016 13:52:15 GMT  
Signature meaning: Approved