Protocol H9X-MC-GBGL

A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus

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(AWARD-11: Assessment of Weekly AdministRation of LY2189265 in Diabetes-11)

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Dulaglutide (LY2189265)

Study H9X-MC-GBGL is a Phase 3, randomized, double-blind trial designed to assess the efficacy and safety of once weekly investigational dulaglutide doses (4.5 mg or 3.0 mg) compared to dulaglutide 1.5 mg in patients with type 2 diabetes mellitus on metformin monotherapy.

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

Approval Date: 05-Feb-2018 GMT

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1. Synopsis

Title of Study: A Randomized, Double-Blind, Parallel-Arm Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus

Rationale:

Study H9X-MC-GBGL (GBGL) is a Phase 3 trial designed to assess the safety and efficacy of once weekly dulaglutide 3.0 mg and 4.5 mg in comparison to dulaglutide 1.5 mg (the highest dose approved by regulatory agencies). The overall goal of the Phase 3 program is to gain regulatory approval for inclusion of at least 1 higher dose in the Trulicity label for treatment of patients with type 2 diabetes mellitus (T2D) who require additional glucose-lowering to obtain their glycemic target. The additional dosing option(s) will be administered using the same device as that used for currently approved doses of 0.75 mg and 1.5 mg (single-dose pen [SDP]).

Objectives/Endpoints:

Objectives	Endpoints
Primary To demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg for change from baseline in HbA1c at 36 weeks in patients with inadequately controlled T2D on concomitant metformin therapy.	• The change in HbA1c from baseline
Secondary *Efficacy:* To demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg for secondary efficacy parameters at 36 weeks (controlled for Type 1 error).	• The change in body weight from baseline • Proportion of patients achieving HbA1c target <7.0% (53 mmol/mol) • The change in fasting serum glucose (FSG) from baseline
Safety: To compare each investigational dulaglutide arm (4.5 mg, 3.0 mg) to the 1.5 mg arm for selected safety parameters through 36 and 52 weeks (unless noted otherwise)	• Incidence of treatment-emergent adverse events (TEAEs) and discontinuation of study drug due to adverse events (AEs) • Adjudicated and confirmed cardiovascular and pancreatic AEs • Incidence of thyroid neoplasm AEs • Incidence of treatment-emergent (TE) dulaglutide anti-drug antibodies (ADA) and systemic hypersensitivity reactions • Change from baseline in pulse rate (PR) • Electrocardiogram (ECG) parameters • Occurrence of hypoglycemic episodes

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Objectives	Endpoints
Pharmacokinetics (PK) and Pharmacodynamics (PD) To characterize dulaglutide PK and the dose and/or exposure-response relationships for key efficacy (eg, HbA1c and weight), and safety (eg, heart rate) endpoints.	- PK parameters (eg, maximum concentration [Cmax], area under the curve [AUC]) at steady state - Pharmacodynamic evaluations may include changes from baseline in HbA1c, body weight, and heart rate at Weeks 36 and 52

Abbreviations: HbA1c = hemoglobin A1c; T2D = type 2 diabetes mellitus.

Summary of Study Design:

Study GBGL is a Phase 3, multicenter, randomized, double-blind, parallel-arm study with 3 study periods (Lead-In, Treatment, and Safety Follow-Up) in patients with T2D with inadequate glycemic control on metformin only; the study will have 52-week treatment duration, with primary endpoint at 36 weeks.

Treatment Arms and Duration:

At Visit 3 patients will be randomized in a 1:1:1 ratio to weekly injections of dulaglutide 4.5 mg, 3.0 mg, or 1.5 mg, in combination with stable doses of metformin. Patients will be titrated through sequential 4-week treatment segments beginning with 0.75 mg once weekly followed by 1.5 mg once weekly. At Week 8, patients randomized to the dulaglutide 1.5 mg group will continue on this dose for the remainder of the Treatment Period. Patients randomized to the dulaglutide 3.0 mg group will be escalated to 3.0 mg once weekly at Week 8 and will continue on this dose for the remainder of the Treatment Period. Patients assigned to the dulaglutide 4.5 mg group will be escalated to 3.0 mg once weekly at Week 8 for 4 weeks, followed by escalation to their final dose of 4.5 mg once weekly at Week 12. Study participants will be treated for 52 weeks, with the primary objectives assessed at Week 36. A 4-week Safety Follow-Up Period will follow the completion of the Treatment Period.

Number of Patients:

A sample size of approximately 1800 patients assuming 15% dropout rate will be enrolled (randomized) in order to obtain approximately 510 completers per arm at 36 weeks. This sample size provides at least 80% power for demonstrating superiority of at least 1 dulaglutide higher dose to dulaglutide 1.5 mg in glycated hemoglobin (HbA1c) change from baseline at Week 36. This assumes a true treatment difference in HbA1c of -0.22% with a standard deviation (SD) of 1.1%.

Statistical Analysis:

Efficacy Analyses:

There will be 2 primary estimands to compare the investigational dulaglutide arms (4.5 mg and 3.0 mg) with dulaglutide 1.5 mg in terms of the primary measure of HbA1c change from baseline to 36 weeks. One primary estimand will be an efficacy estimand (*de jure* effect) which will use the data collected before initiation of any rescue medication or premature treatment discontinuation to demonstrate the effect of treatment and avoid confounding effects of other antihyperglycemic agents; the other primary estimand will be a treatment-regimen estimand (*de facto* effect) which will include data collected after initiation of other antihyperglycemic therapy and/or after premature treatment discontinuation. The efficacy estimand measures the benefit of treatment when taken as

directed, and the treatment-regimen estimand measures the benefit of treatment as actually taken (that is, irrespective of adherence to investigational product or introduction of other antihyperglycemic therapy). Both estimands will use the same primary analysis model and each will be tested at the full significance level of 0.05. The treatment-regimen estimand is included as primary at the request of the US Food and Drug Administration (FDA). The efficacy estimand will be considered primary for all other purposes. The primary analysis model for HbA1c will be a mixed-model for repeated measures (MMRM) using restricted maximum likelihood, with pooled country, treatment, visit, and treatment-by-visit as fixed effects, and baseline HbA1c as a covariate. An unstructured covariance structure will be used to model the within-patient errors. The primary analysis model will be repeated using all available data from the Per Protocol and Completers populations to check the robustness of the analyses.

Multiple imputation for missing data within the same treatment arm will be conducted based on data from retrieved dropouts. Retrieved dropouts are defined as patients who had their HbA1c value at the Week 36 visit assessed after early discontinuation of study drug and/or initiation of rescue medication. An analysis of covariance (ANCOVA) model for the treatment-regimen estimand will be fit to the complete datasets, containing the same covariates as the primary analysis, by removing the visit-related terms.

Analyses of other continuous secondary efficacy measures will be performed using MMRM in the Intent-to-Treat (ITT) Population. For percentages of patients achieving target HbA1c <7.0%, longitudinal logistic regression with repeated measures will be conducted.

The primary and key secondary analyses will follow a graphical approach for multiple comparisons to strongly control the overall Type 1 error rate in the trial at a 2-sided alpha of 0.05.

Safety Analyses:

Summary statistics will be provided for incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and study discontinuation due to adverse events (AEs) or death during the Treatment Period. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

For continuous laboratory analytes, the change from baseline to endpoint will be analyzed using an analysis of variance (ANOVA) on the rank-transformed data, with treatment as a fixed effect. Last observation carried forward (LOCF) will be used to impute missing postbaseline values. For qualitative laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using Fisher's exact test.

Treatment differences in incidence of hypoglycemic episodes will be assessed by Fisher's exact test. Treatment differences in rates of hypoglycemic episodes may be assessed by a likelihood-based approach for repeated measures with negative binomial distribution if data warrant; otherwise, the Wilcoxon rank-sum test will be used.

2. Schedule of Activities

	Screening and Lead-In		Treatment Period										Safety Follow-Up
Visit	1	2	3	4	5	6	7	8	9	10	11	ET[a]	801
Week of Treatment	-2	-1	1	4	8	12	18	26	36	44	52		56
Allowable Deviation (Days)[b]	±3	±3		±3	±3	±3	±7	±7	±7	±7	±7		±7
Informed consent	X												
Randomization[c]			X										
Clinical Assessments													
Medical History (General)	X												
CV risk factor history		X											
Gallbladder disease history		X											
Physical	X												
Height	X												
Weight	X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs (3 sitting BP and PR measurements)[d]	X		X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X					X[e]	X		X[e]		X[e]	X[e]	X[e]
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Review/record hypoglycemic events			X	X	X	X	X	X	X	X	X	X	X
Remind patients about 6-point SMPG		X						X		X			
Record 6-point SMPG values[f]			X						X		X	X[g]	
Patient summary											X	X	X
Patient Education and Management													
Dispense study diary, instruct in use		X	X			X	X		X	X	X		
Review study diary			X	X	X	X	X	X	X	X	X	X	X
Return study diary			X			X	X		X	X	X	X	X
Diabetes management education[h]		X											
Dispense PG meter/supplies		X	X	X	X	X	X	X	X	X	X		
PG meter, SMPG training[h]		X	X										
Review SMPG values			X	X	X	X	X	X	X	X	X	X	X
Injection training[h]		X	X										
Dispense study drugs and/or injection supplies			X	X	X	X	X	X	X	X			

Schedule of Activities

	Screening and Lead-In		Treatment Period										Safety Follow-Up
Visit	1	2	3	4	5	6	7	8	9	10	11	ET[a]	801
Week of Treatment	-2	-1	1	4	8	12	18	26	36	44	52	ET	56
Allowable Deviation (Days)[b]	±3	±3		±3	±3	±3	±7	±7	±7	±7	±7		±7
Patient Education and Management (concluded)													
Observe patient inject study drug[i]			X										
Patient returns study drugs and/or injection supplies				X	X	X	X	X	X	X	X	X	
Assess study drug compliance				X	X	X	X	X	X	X	X	X	
Laboratory Tests													
Serum pregnancy test[k]	X												
Urine pregnancy test[l]			X			X		X			X		
Follicle-stimulating hormone test[m]	X												
Chemistry panel	X								X		X	X	X
Lipid panel (fasting)[n]			X						X		X	X	
Urinalysis	X								X		X	X	
Albumin/creatinine ratio (urine)[o]	X								X		X	X	
eGFR (CKD-EPI)[p]	X								X		X	X	X
Cystatin C			X						X		X	X	
Hematology	X								X		X	X	
Immunogenicity			X	X		X			X		X	X	X
Pancreatic amylase, lipase	X		X						X		X	X	X
Calcitonin	X					X			X		X	X	
HbA1c	X		X		X	X		X	X		X	X	X
Glucose (fasting)[n]			X		X	X		X	X		X	X	X
Serum insulin (fasting)[n]			X						X		X	X	
C-peptide			X						X		X	X	
Plasma glucagon (fasting)[n,q]			X						X		X	X	
Pharmacogenetic (stored sample)			X[r]										
Nonpharmacogenetic biomarker (plasma and serum) (stored sample)			X						X		X	X	
PK Samples													
PK samples[s]				X		X			X		X	X	X

Schedule of Activities

	Screening and Lead-In		Treatment Period										Safety Follow-Up
Visit	1	2	3	4	5	6	7	8	9	10	11	ET[a]	801
Week of Treatment	-2	-1	1	4	8	12	18	26	36	44	52	ET	56
Allowable Deviation (Days)[b]	±3	±3		±3	±3	±3	±7	±7	±7	±7	±7		±7
PRO Questionnaires (Health Economics)													
Diabetes Injection Device Experience Questionnaire (DID-EQ)						X						X[t]	
EQ-5D-5L			X						X		X	X	
Impact of Weight on Self-Perceptions Questionnaire (IW-SP)			X						X		X	X	
Ability to Perform Physical Activities of Daily Living Questionnaire (APPADL)			X						X		X	X	

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

a   Patients who are unable or unwilling to continue in the study for any reason will perform an ET 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 performed as an ET visit. Visit 801 (Safety Follow-Up Visit) should be performed 4 weeks after the ET visit as the final study visit.

b   The visit date is determined in relation to the date of the randomization visit (± the allowed visit window).

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

d   Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required. The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 3 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart.

e   Electrocardiograms occurring on visits with PK collection should be collected at least 30 minutes prior to obtaining the sample for PK measurement.

f   6-point SMPG consists of measurements before and 2 hours after each of 3 main meals within the same day. These SMPG profiles will be collected by the patient within 1 week prior to the assigned visits. If 6-point SMPG is not performed, then data from 4-point SMPG can be used.

g   If performed prior to visit; if 6-point SMPG is not performed, then data from 4-point SMPG can be used.

h   All training should be repeated as needed to ensure patient compliance.

i   Patients should administer their first dose of study drug at the end of this visit, after other study procedures and randomization.

j   Study drug compliance will be reviewed at every visit between Visit 4 and Visit 11.

k   A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.

Schedule of Activities

l   A urine pregnancy test will be performed at Visit 3, with the result available prior to randomization and first injection of study drug, and at additional visits as shown in the schedule, for women of childbearing potential only. Additional pregnancy tests may be performed at the investigator's discretion or if required per local regulations and/or institutional guidelines during the study.

m   Follicle-stimulating hormone test will be collected 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 (unless specified otherwise by local regulatory requirements). After Visit 1, additional tests may be performed at the investigator's discretion during the study.

n   For Visit 3, Visit 5, Visit 6, Visit 8, Visit 9, Visit 11, 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).

o   Urinary albumin and creatinine will be measured and the ratio will be calculated.

p   The CKD-EPI equation will be used by the central laboratory to compute and report eGFR. Values that are <30 mL/min/1.73 m^2 at Visit 1 will be required to be retested at Visit 2. If the highest of the 2 values is lower than <30 mL/min/1.73 m^2 (or lower than the cutoff value for discontinuation of metformin per country-specific label), the patient will be discontinued from the trial prior to randomization. After randomization (Visit 3), values that would require clinical action per protocol or country-specific label must be first confirmed on a retest before any treatment adjustment is implemented.

q   Samples should be collected in P800 tube. Aliquot samples, 1 for glucagon and the remainder for nonpharmacogenetic biomarker.

r   The pharmacogenetic sample should be collected at Visit 3, or at the earliest visit after obtaining local approval.

s   The PK sample should be collected within 30 min after the ECG is obtained on the visits where this procedure is also performed (Visits 6, 9, 11, ET, and 801). At Visit 4, the PK sample can be collected at any time during the clinic visit. The date and time of administration of all dulaglutide doses, and in particular the last dulaglutide dose administered prior to each PK sample, together with the date and time of the PK sample, must be clearly recorded.

t DID-EQ will be administered at the ET visit only if ET occurs at or before Week 12 (before Visit 6).

3. Introduction

3.1. Study Rationale

Dulaglutide (Trulicity®) 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 type 2 diabetes (T2D). Treatment of patients with T2D with dulaglutide results in significant reductions in glycated hemoglobin (HbA1c) with low risk of hypoglycemia, and reductions in body weight. 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 the European Union in 2014 (Trulicity US Package Insert [USPI], Summary of Product Characteristics [SmPC]).

While therapy with currently approved doses of dulaglutide enabled the majority of patients included in the Phase 3 program to attain their glycemic targets (sometimes with use of other concomitant medications for T2D), 30%-50% of patients receiving approved therapies today, including dulaglutide, are not reaching glycemic control goals (Stark Casagrande et al. 2013; Jendle et al. 2016). Therefore, there remains an important medical need to provide enhanced efficacy of pharmaceutical agents while also preserving an overall acceptable benefit/risk profile.

3.2. Background

Pharmacokinetic (PK)/pharmacodynamics (PD) modeling from original Phase 1-2 dulaglutide studies suggested a dose-dependent incremental benefit with dulaglutide versus currently approved doses on HbA1c and body weight reduction. Phase 2 Study H9X-MC-GBGJ (GBGJ) was recently conducted to assess the safety and efficacy of once weekly dulaglutide 3.0 mg and 4.5 mg in comparison to placebo in 317 patients with T2D treated with metformin monotherapy, with exploratory comparisons to dulaglutide 1.5 mg (the highest dose approved by regulatory agencies). Data from Study GBGJ provided evidence for incremental efficacy of these higher doses of dulaglutide versus 1.5 mg once weekly on glycemic control and body weight reduction, particularly at higher baseline HbA1c levels, with an acceptable tolerability and safety profile at both higher doses. The trial results also suggested stepwise titration of dulaglutide dose was associated with acceptable tolerability of the 2 higher doses.

Further study of higher doses of dulaglutide also was assessed in context with prior dose-finding studies. The currently approved dulaglutide doses (0.75 mg and 1.5 mg once weekly) were selected in the Phase 2/3 Study H9X-MC-GBCF (GBCF), which initially included doses up to 3.0 mg once weekly (Skrivanek et al. 2014). The purpose of the first stage of Study GBCF was to identify an optimal dose using prespecified measures of efficacy (HbA1c and weight) and safety (diastolic blood pressure [DBP] and heart rate [HR]). Following a number of interim data reviews, the Data Monitoring Committee (DMC) recommended discontinuing the dulaglutide 3.0 mg dose because of higher incidence in pancreatic enzyme values above upper limit of normal (ULN) (with or without abdominal pain or suspected pancreatitis), increases in HR, and higher incidence of gastrointestinal (GI) adverse events (AEs) (Skrivanek et al. 2014).

Since original dose selection and subsequent approval of dulaglutide, additional data have provided a better understanding of the clinical significance of the findings which prompted the DMC to terminate the 3.0 mg dose in Study GBCF. Elevations in pancreatic enzymes associated with GLP-1 RA treatment have not been associated with adverse clinical outcomes based on the results of adjudication (Nauck et al. 2017; Steinberg et al. 2017a; Steinberg et al. 2017b), and the risk of adjudicated pancreatitis and investigator-reported pancreatitis in patients treated with dulaglutide was similar to the risk observed with nonincretin comparators in dulaglutide registration trials (Nauck et al. 2017). Heart rate elevations are now recognized to be a class effect common to all GLP-1 RAs (Lorenz et al. 2017). Despite increases in HR, completed cardiovascular (CV) outcome trials for GLP-1 RAs have shown either neutral to favorable effects on the risk of major CV events compared to placebo in patients with T2D and high CV risk (Pfeffer et al. 2015; Marso et al. 2016a; Marso et al. 2016b; Holman et al. 2017). Finally, it is now understood that a slow, stepwise dose titration of weekly GLP-1 RAs upon initiation can attenuate the occurrence and severity of GIAEs at higher doses, providing for greater glucose-lowering effects and more robust body weight reduction (Nauck et al. 2016).

Thus, based on the limited amount of efficacy data available for higher dulaglutide doses, the promising results of Phase 2 Study GBGJ, and considering the updated understanding of the benefit/risk profile of GLP-1 RAs as a class, a re-evaluation of the optimal weekly dose of dulaglutide for glycemic control was deemed warranted. The purpose of this Phase 3 study (H9X-MC-GBGL [GBGL]) is to assess the safety and efficacy of once weekly dulaglutide 3.0 mg and 4.5 mg in comparison to dulaglutide 1.5 mg. The overall goal of the Phase 3 program is to gain regulatory approval for inclusion of at least 1 higher doses in the Trulicity label for treatment of patients with T2D who require additional glucose lowering to obtain glycemic targets, to be administered using the same device as that used for currently approved doses of 0.75 mg and 1.5 mg (single-dose pen [SDP]).

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 Investigator's Brochure (IB).

In addition, detailed information about the known and expected benefits and risks of dulaglutide may be found in the Trulicity USPI (2017 [WWW]) and SmPC (2017 [WWW]).

4. Objectives and Endpoints

Table GBGL.1 presents the objectives and endpoints of the study.

Table GBGL.1.   Objectives and Endpoints

Objectives	Endpoints
Primary To demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg for change from baseline in HbA1c at 36 weeks in patients with inadequately controlled T2D on concomitant metformin therapy.	• The change in HbA1c from baseline
Secondary *Efficacy:* To demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg for secondary efficacy parameters at 36 weeks (controlled for Type 1 error). *Safety:* To compare each investigational dulaglutide arm (4.5 mg, 3.0 mg) to the 1.5 mg arm for selected safety parameters through 36 and 52 weeks (unless noted otherwise) *Pharmacokinetics (PK) and Pharmacodynamics (PD):* To characterize dulaglutide PK and the dose and/or exposure-response relationships for key efficacy (eg, HbA1c and weight), and safety (eg, heart rate [HR]) endpoints.	• The change in body weight from baseline • Proportion of patients achieving HbA1c target <7.0% (53 mmol/mol) • The change in fasting serum glucose (FSG) from baseline • Incidence of treatment-emergent adverse events (TEAEs) and discontinuation of study drug due to adverse events (AEs) • Adjudicated and confirmed cardiovascular and pancreatic AEs • Incidence of thyroid neoplasm AEs • Incidence of treatment-emergent (TE) dulaglutide anti-drug antibodies (ADA) and systemic hypersensitivity reactions • Change from baseline in pulse rate (PR) • Electrocardiogram (ECG) parameters • Occurrence of hypoglycemic episodes • PK parameters (eg, maximum concentration [Cmax], area under the curve [AUC]) at steady state • Pharmacodynamic evaluations may include changes from baseline in HbA1c, body weight, and heart rate at Weeks 36 and 52
Tertiary/Exploratory To compare once weekly dulaglutide 4.5 mg and 3.0 mg to the 1.5 mg arm as measured by the primary and secondary outcome measures at 52 weeks.	• The change in HbA1c from baseline • The change in body weight from baseline • Proportion of patients achieving HbA1c target

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Objectives	Endpoints
To compare once weekly dulaglutide 4.5 mg and 3.0 mg to the 1.5 mg arm for exploratory measures through 36 and 52 weeks (unless noted otherwise).	<7.0% (53 mmol/mol) • The change in FSG from baseline • Proportion of patients achieving HbA1c target ≤6.5% (48 mmol/mol) • Change from baseline in 6-point self-monitored plasma glucose (SMPG) profile • Proportion of patients achieving ≥5% body weight loss • Proportion of patients achieving ≥10% body weight loss • Proportion of patients meeting the composite endpoint of HbA1c <7.0% (53 mmol/mol), no weight gain, and no documented symptomatic or severe hypoglycemia • Proportion of patients meeting the composite endpoint of HbA1c <7.0% (53 mmol/mol), body weight loss ≥5%, and no documented symptomatic or severe hypoglycemia • Changes from baseline in fasting plasma glucagon, HOMA2-%B, HOMA2-IR, and C-peptide • Changes from baseline in serum cystatin C and cystatin C-based assessment of eGFR • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia • Changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate pressure product (RPP) • Changes from baseline in serum lipid parameters (total cholesterol, high density lipoproteins [HDL], low density, lipoproteins [LDL], very low density lipoproteins [VLDL], and triglycerides) • Diabetes Injection Device Experience Questionnaire (DID-EQ) scores at Week 12 • Changes from baseline in EQ-5D-5L scores • Changes from baseline in Impact of Weight on Self-Perception Questionnaire (IW-SP) scores • Changes from baseline in Ability to Perform Physical Activities of Daily Living (APPADL) scores

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Abbreviations: eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin A1c; HOMA2-%B =
 β-cell function as measured by the Homeostasis Model Assessment-2 method; HOMA2-IR = insulin resistance
 as measured by the HOMA2 method; T2D = type 2 diabetes.

5. Study Design

5.1. Overall Design

Study H9X-MC-GBGL (GBGL) is a 52-week, Phase 3, double-blind, multicenter, parallel-arm study. The study is designed to assess the efficacy and safety of once weekly dulaglutide 3.0 mg and 4.5 mg in comparison to once weekly dulaglutide 1.5 mg following a primary 36-week treatment period and at the end of the 52-week Treatment Period. The primary objective of this trial is to demonstrate that once weekly dulaglutide 4.5 mg and/or 3.0 mg is superior to dulaglutide 1.5 mg as measured by change from baseline in HbA1c at Week 36 in patients with T2D who are inadequately controlled on concomitant metformin therapy (see Section 4). Secondary objectives (controlled for Type 1 error) are to demonstrate superiority of at least 1 of the higher dulaglutide doses to dulaglutide 1.5 mg at Week 36 on changes in body weight, proportions of patients achieving HbA1c <7.0% (53 mmol/mol), and changes in fasting serum glucose (FSG) from baseline at Week 36.

The study will consist of 3 periods: an approximately 2-week Lead-In Period followed by a 52-week Treatment Period (primary efficacy endpoint at Week 36) and a 4-week Safety Follow-Up Period.

Figure GBGL.1 illustrates the study design.
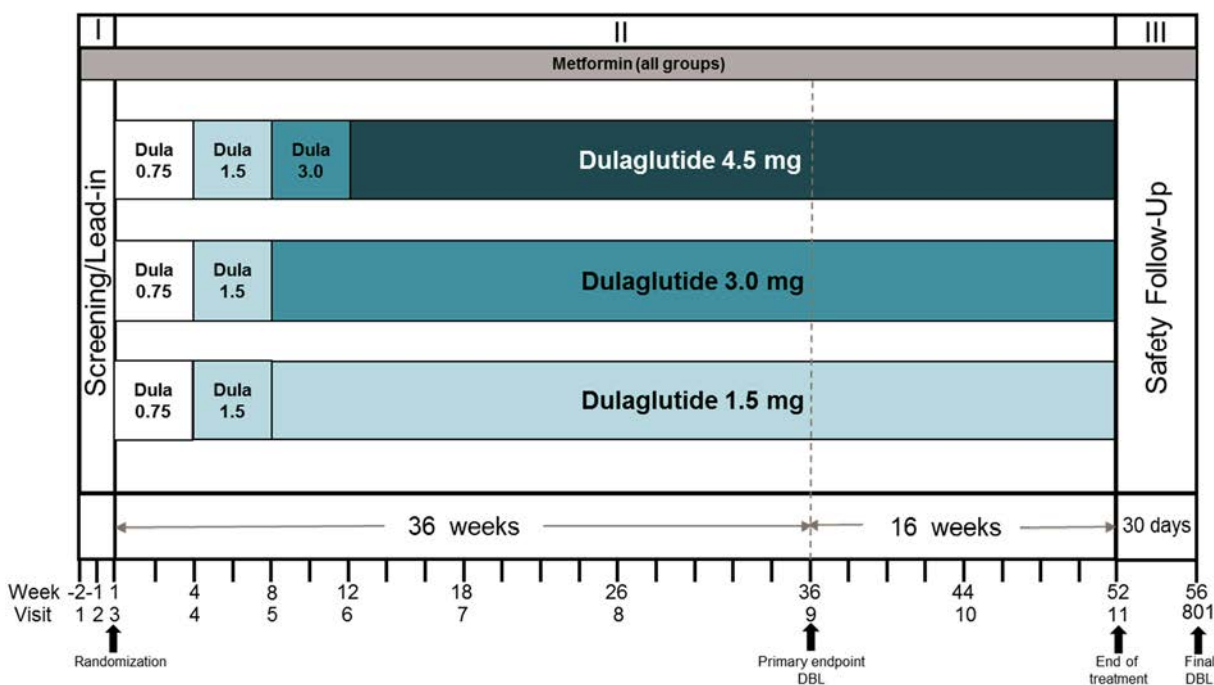
Abbreviations: DBL = database lock; dula = once weekly dulaglutide.
Note: all dulaglutide doses are once weekly.

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

Study Period I (Screening and Lead-In):

Screening (Visit 1)

The purpose of screening procedures at Visit 1 is to establish initial eligibility 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 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). If patients develop a condition that is a contraindication for the use of metformin or initiate other agents that are prohibited 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.

Study Period II (Treatment Period):

Randomization (Visit 3)

At Visit 3, patients will perform all required baseline study procedures (including the collection of all baseline laboratory measures) prior to randomization and prior to taking the first dose of study drug. Patients who continue to be eligible will then be randomized in a 1:1:1 ratio to 1 of the treatment arms: (1) dulaglutide 4.5 mg, (2) dulaglutide 3.0 mg, or (3) dulaglutide 1.5 mg. Immediately after randomization, the patient will inject the first dose of study drug at the study site, according to the dose escalation regimen described below. The date and time of the first dose of study drug should be recorded on the electronic case report form (eCRF).

Following randomization, patients will participate in a 52-week Treatment Period.

Postrandomization Treatment Period (end of Visit 3 to Visit 11)

Beginning at randomization, all patients will receive dulaglutide 0.75 mg once weekly for 4 weeks (Weeks 1-4), followed by dulaglutide 1.5 mg once weekly for 4 weeks (Weeks 5-8). At Week 8 the dosing will diverge based on the randomized treatment arm:

- Dulaglutide 1.5 mg arm: Patients will continue to receive dulaglutide 1.5 mg once weekly for the remainder of the treatment period.
- Dulaglutide 3.0 mg arm: Patients will receive dulaglutide 3.0 mg once weekly for the remainder of the treatment period.
- Dulaglutide 4.5 mg arm: Patients will receive dulaglutide 3.0 mg once weekly for 4 weeks (Weeks 9-12), and then escalate to dulaglutide 4.5 mg once weekly for the remainder of the treatment period.

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Study Period III (Safety Follow-Up Period):

Safety Follow-Up (Visit 801) Visits: All patients who complete the treatment period are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after their last visit. Patients discontinuing the study early and performing an early termination (ET) visit will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit. During the Safety Follow-Up Period, patients will not receive study drug. Patients will be treated with another glucose-lowering intervention decided upon by the investigator. Glucagon-like peptide-1 RAs (eg, exenatide, liraglutide, or commercial Trulicity) and dipeptidyl peptidase-4 (DPP-4) inhibitors are not allowed during this period. Initiation of new antihyperglycemic therapy for the Safety Follow-Up Period will not be classified as "rescue therapy" (Section 7.7.1.2). All antihyperglycemic medications will be entered on the eCRF specified for this purpose. Patients are also required to return any remaining study diaries to the study site at the end of this period.

Study Procedures

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

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-monitored plasma glucose (SMPG) measurements (consisting of fasting, prelunch, predinner, and bedtime plasma glucose [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. Data from the 6-point profiles will be entered into the eCRF as shown on the Schedule of Activities (Section 2). In the event that a 6-point SMPG profile is not collected as required, then data from the 4-point SMPG collected during the week preceding the required visit may be entered in the eCRF instead.

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Section 7.7.5.3) will receive a new glucose-lowering intervention ("rescue therapy") as outlined Section 7.7.1.2 and will also continue to administer study drug. Patients who need hyperglycemic rescue therapy will continue in the trial until they complete all study visits.

Patients who permanently discontinue study drug prior to the Safety Follow-Up Period will also be required to continue in the trial and should receive a new glucose-lowering intervention (Section 7.7.1.2).

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Every attempt will be made to keep patients in the trial irrespective of their adherence to treatment with study drug. An ET visit will be conducted for patients who are to be discontinued from the study early (after completing Visit 3 [randomization] and before completing the entire 52-week treatment period). If the patient is discontinued during an unscheduled visit, that visit should be performed as the ET visit. If the patient is discontinued during a scheduled visit, that visit should be performed as the ET visit. In either case, ET visit procedures will be performed according to the Schedule of Activities (Section 2). Patients should be instructed to return any remaining used or unused study drug supplies and patient diaries to the study site at this visit. Study treatment will be terminated at this visit (if not already terminated). Patients will be asked to perform the Safety Follow-Up visit (Visit 801) approximately 30 days after the ET visit, so that the Safety Follow-Up visit will be their final visit. If the patient is not able to perform the Safety Follow-Up visit, then the ET visit will be the final study visit.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants
Approximately 3000 participants will be screened to achieve approximately 1800 randomized patients and approximately 1530 patients completing Week 36 (for an estimated total of 510 patients completing Week 36 per treatment group).

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

5.4. Scientific Rationale for Study Design
Study GBGL utilizes the parallel 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 study is designed to determine the comparative benefits and risks of once weekly dulaglutide 3.0 mg or 4.5 mg versus once weekly dulaglutide 1.5 mg in patients with T2D who cannot maintain glycemic control with metformin alone. To minimize the potential confounding effect of changes to concomitant metformin, patients will be expected to maintain metformin throughout the treatment period until the last dose of randomized treatment, other than for the situations described in Section 7.7.1.1.

The planned duration of treatment for the primary endpoint at 36 weeks is considered appropriate to assess the full effects and benefit/risk of higher doses of dulaglutide compared with the dulaglutide 1.5 mg dose on both glycemic control and body weight. While the full effect of randomized treatments on PG is expected after approximately 8-12 weeks of therapy and on HbA1c after approximately 12-24 weeks (Jendle et al. 2016), a minimum of 26-30 weeks are required to assure maximal effects of dulaglutide on the key secondary outcome of body weight (Davies et al. 2015; Ahrén et al. 2017). The full treatment duration of 52 weeks will allow for collection of additional exposure data to monitor efficacy and safety.

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 H9X-MC-GBCD (GBCD) and GBCF (Barrington et al. 2011; Skrivanek et al. 2014) and evidence for incremental increases in efficacy for both glycemic control and body weight reduction, with an acceptable safety and tolerability profile, from Study GBGJ. Further details and the rationale for the choice of the doses and dose escalation regimens are provided in Section 5.5.

Dulaglutide 1.5 mg is included as the active comparator because it is the maximum approved dose and will enable comparison of efficacy and safety data of higher investigational doses collected under similar conditions. A placebo comparator was not included because it was not considered necessary for addressing the primary or secondary objectives of the trial. Moreover, maintaining patients with inadequate glycemic control on metformin monotherapy, particularly those with relatively poor glycemic control at entry (HbA1c ≥9.0% [75 mmol/mol]), would not be consistent with current recommendations provided in a position statement of the American Diabetes Association and the European Association for the Study of Diabetes (Inzucchi et al. 2015).

5.5. Justification for Dose and Dose Escalation Regimen

The investigational dulaglutide doses (3.0 mg and 4.5 mg) were selected considering adequate separation in PK exposure range between the doses and 1.5 mg to enable evaluation of their efficacy and adverse effect profiles. Ratios of mean area under concentration-time curve (AUC) for 3.0 mg/4.5 mg doses to 1.5 mg dose are 2.26 and 3.10, respectively. The steady-state mean AUC and 90% confidence intervals (CIs) for the 1.5 mg, 3.0 mg, and 4.5 mg doses are 11,800 (5300, 21,300), 26,700 (15,300, 41,400), and 36,600 (21,100, 56,500) ng.h/mL, respectively. Therefore, the ratio of mean AUC for 4.5 mg to 3.0 mg is anticipated to be 1.37. 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.

Data from Phase 2 Study GBGJ provided evidence for incremental efficacy of dulaglutide 3.0 mg and 4.5 mg once weekly versus 1.5 mg once weekly on glycemic control and body weight reduction. After 18 weeks of treatment (analysis of on-treatment data without rescue), the estimated treatment differences in HbA1c reduction with 3.0 mg and 4.5 mg once weekly relative to 1.5 mg once weekly were -0.22% and -0.26%, respectively. Larger differences were observed in subgroups of patients with higher baseline HbA1c (ie, ≥8.5% [69 mmol/mol] vs. <8.5% [69 mmol/mol]). Dulaglutide 3.0 mg and 4.5 mg once weekly also provided for additional body weight reduction over the 1.5 mg dose that exceeded 1 kg at Week 18, with further weight reduction expected with longer durations of treatment. Although the effects of dulaglutide 4.5 mg were generally greater than the effects of the 3.0 mg dose on measures of glycemic control and body weight, a larger study is required to fully characterize the benefit/risk profile of each higher dulaglutide dose compared with the 1.5 mg dose over a longer duration of treatment.

The dose escalation regimens used for the investigational doses were designed based on evaluation of the algorithms tested in Phase 2 Study GBGJ. While overall tolerability as measured by study drug discontinuations due to AE was comparable between the algorithms, initiating dose escalation at 0.75 mg once weekly generally resulted in a lower overall incidence of GI events. Pharmacokinetic/PD exposure-response modeling of Study GBGJ data also predicted that the daily incidence of nausea and vomiting at higher dulaglutide doses would be lowest in algorithms starting at the lower 0.75 mg dose with a slower dose escalation over an 8-week period, allowing adequate time for tolerance to develop. Based on these findings, the starting dose for all patients in the current study will be 0.75 mg once weekly followed by 1.5 mg once weekly, with a 4-week interval for each dose. Patients will then either remain on 1.5 mg once weekly or escalate to their final assigned dose as shown in Figure GBGL.1 and Table GBGL.2.

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 where indicated).

Type of Patient and Disease Characteristics

[1] Patients with T2D for ≥6 months according to the World Health Organization (WHO) classification (Appendix 5) or other locally applicable diagnostic standards, treated with stable doses of metformin (as defined in [4] below) for at least 3 months.

Patient Characteristics

[2] men or nonpregnant women aged ≥18 years;

[3] have HbA1c ≥7.5% (58 mmol/mol) and ≤11.0% (97 mmol/mol), inclusive, as assessed by the central laboratory;

[4] 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 (≥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 or a documented estimated glomerular filtration rate (eGFR; measured by the Chronic Kidney Disease-Epidemiology Collaboration equation [CKD-EPI]) or other renal function measure which requires lower doses per country-specific labeling;

[5] stable body weight for at least 3 months prior to Visit 1 (not changed by more than 5% in the past 3 months);

[6] have a body mass index (BMI) ≥25 kg/m^2;

[7] 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 (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 finger stick PG monitoring at least once daily every day and up to 6 times one day per week at designated times throughout the trial (see Schedule of Activities [Section 2]);

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

[8] women of childbearing potential participating must agree to remain abstinent (complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship without sexual relationships with males (as part of 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. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

[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). 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.

[9] 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 ≥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 (or longer if required by local regulatory requirements) 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

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iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[10] no male contraception is required except in compliance with specific local government study requirements;

Informed Consent

[11] 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:

Medical Conditions

[12] have type 1 diabetes (T1D);

[13] have a history of ≥1 episode of ketoacidosis or hyperosmolar state/coma;

[14] have had ≥1 episode of severe hypoglycemia and/or ≥1 episode of hypoglycemia unawareness within the last 6 months;

[15] have had any of the following CV conditions within 2 months prior to Visit 1: acute myocardial infarction (MI), New York Heart Association Class III or Class IV heart failure, or cerebrovascular accident (stroke);

[16] 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®) or chronically take drugs that directly reduce gastrointestinal motility;

[17] 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;

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

[19] have an eGFR <30 mL/min/1.73 m^2 (or lower than the country-specific threshold for discontinuing metformin therapy per local label), calculated by CKD-EPI, as determined by the central laboratory at Visit 1 and confirmed at Visit 2;

[20] have a personal or family history of medullary thyroid carcinoma (MTC) or personal history of multiple endocrine neoplasia syndrome type 2;

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[21] have serum calcitonin ≥20 ng/L, as determined by the central laboratory at study entry;

[22] have evidence of significant, active autoimmune abnormality (eg, lupus, rheumatoid arthritis) that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 12 months;

[23] 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;

[24] 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;

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

[26] known proliferative retinopathy or maculopathy requiring acute treatment according to the opinion of the investigator;

Prior/Concomitant Therapy

[27] have used any GLP-1 RAs (including investigational agents with GLP-1 RA activity) or insulin at any time in the past, except for short-term (≤14 consecutive days) use of insulin for acute conditions;

[28] have used any other glucose-lowering medications other than metformin (including insulin) 3 months prior to study entry or during the Screening/Lead-In Periods;

[29] have been treated with any other excluded medication (Section 7.7) 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;

[30] 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;

[31] discontinuation of metformin therapy, or change in metformin dose or formulation, between Visit 1 and Visit 3;

[32] have been treated with prescription or OTC drugs that promote weight loss (Table GBGL.3) within 3 months prior to screening (Visit 1) and/or between study entry and randomization (Visit 3); or current (or within the last 3 months) participation in, or planned intent to initiate within timeframe of the study, an organized diet and/or exercise weight reduction program other than the lifestyle and dietary measures for diabetes treatment;

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Prior/Concurrent Clinical Trial Experience

> [33] are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study;

> [34] 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;

> [35] have previously completed or withdrawn from this study or any other study investigating dulaglutide;

Other Exclusions

> [36] 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;

> [37] are Lilly employees;

> [38] have any other conditions (including known drug or alcohol abuse or psychiatric disorder) or circumstances (including known or anticipated plans for relocation or extended travel) that may preclude the patient from following the protocol and completing the study.

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. Per Exclusion Criterion [32] (Section 6.2), patients should not initiate during the study an organized diet and/or exercise weight reduction program other than the lifestyle and dietary measures for diabetes treatment.

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
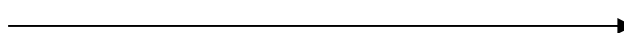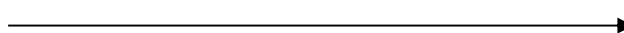
Patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment arms: dulaglutide 1.5 mg, dulaglutide 3.0 mg, or dulaglutide 4.5 mg, each administered once weekly as subcutaneous injection in patients with T2D who are already treated with a stable dose of metformin.

Table GBGL.2 shows the randomized treatments for the entire treatment period.

All patients in the study will initiate treatment with dulaglutide 0.75 mg once weekly for 4 weeks (Weeks 1 – 4) and will then receive dulaglutide 1.5 mg once weekly for 4 weeks (Weeks 5 – 8). Patients assigned to the dulaglutide 1.5 mg group will receive that dose once weekly from Weeks 9 through 52. Patients assigned to the dulaglutide 3.0 mg group will receive that dose once weekly from Weeks 9 through 52. Patients assigned to the dulaglutide 4.5 mg group will receive dulaglutide 3.0 mg once weekly for 4 weeks (Weeks 9 – 12) followed by dulaglutide 4.5 mg once weekly for the remainder of the treatment period (Weeks 13 – 52).

Single-dose pens will be used to administer randomized dulaglutide doses and the interim doses during dose escalation. No study drug treatment will be administered during the 4-week Safety Follow-Up Period.

Table GBGL.2.　　　　Study Treatments (Weeks 1-52)

Treatment Group	Treatment Period Interval			
	Weeks 1 – 4	Weeks 5 – 8	Weeks 9 - 12	Weeks 13 – 52
4.5 mg Dulaglutide	0.75 mg	1.5 mg	3.0 mg	4.5 mg →————————————→
3.0 mg Dulaglutide	0.75 mg	1.5 mg	3.0 mg →————————————→	
1.5 mg Dulaglutide	0.75 mg	1.5 mg	1.5 mg →————————————→	

Note: All doses will be administered once weekly using single-dose pens.

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

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- maintaining accurate records of study drug dispensing and collection, as well as records of interruptions in study drug administration

- 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 SDPs in a closeable, puncture-resistant container, and dispose according to local regulations. Sites may be authorized to destroy used and unused SDPs locally per applicable local or national requirements.

7.1.1. Packaging and Labeling

The sponsor will provide dulaglutide in SDPs, which will be dispensed via an interactive web-response system (IWRS). Each SDP will be packaged in cartons to be dispensed. Injections are to be administered as described in Section 7.2.2.

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

7.1.2. Medical Devices

The manufactured medical devices provided for use in the study will be SDPs containing dulaglutide 0.75 mg (0.5 mL at 1.5 mg/mL), dulaglutide 1.5 mg (0.5 mL at 3.0 mg/mL), dulaglutide 3.0 mg (0.5 mL at 6.0 mg/mL), and dulaglutide 4.5 mg (0.5 mL at 9.0 mg/mL).

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 ratio (dulaglutide 4.5 mg, dulaglutide 3.0 mg, dulaglutide 1.5 mg). Randomization will be stratified by HbA1c (<8.5% [69 mmol/mol], ≥8.5% [69 mmol/mol]).

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), each administered once weekly as subcutaneous injection. 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. Patients will be escalated to their final assigned dose using the regimens outlined in Table GBGL.2. The randomization strategy is described in Section 7.2.

The assigned doses will not be downtitrated. Patients with poor tolerability of the study treatments will be allowed to discontinue dosing temporarily (Section 8.1.2). Investigators should inform the Sponsor any time study drug is interrupted. If interruption occurs after Week 12, then study drug should be resumed as soon as it is safe to do so. If interruption occurs prior to Week 12 (that is, prior to when the final assigned dose may have been initiated), then the

investigator should consult with Lilly on the schedule and method for the resumption of study drug, and the approach will be documented. Patients who interrupt study treatment temporarily and are then unable to tolerate it upon rechallenge will be discontinued from study drug and should be initiated on new antihyperglycemic medication in accordance with Section 7.7.1.2; they should remain in the study and complete all study procedures.

After the administration of study drug in the clinic at Visit 3 (randomization), the patient should determine the most convenient day of the week and time of day for subsequent dosing throughout the study. Once determined, it is recommended that patients inject the study drug at approximately the same time of day on the same day each week. The date and time of all study drug administrations are to be recorded in diaries by the patients. If the injection is not given on the scheduled day, the missed injection 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 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 in the patient's upper arm. A new SDP will be used for each injection. Subsequent doses should be injected in different regions (eg, arm, abdomen, thigh; rotation is encouraged). If study drug is to always be injected in the same body region, patients should be advised to use a different injection site each week.

7.3. Blinding

This is a double-blind study. Investigators, site staff, clinical monitors and patients will remain blinded to the treatment assignments until the study is complete. To preserve the blinding of the study, the Sponsor will be blinded to treatment assignments until after the primary endpoint (Week 36) database lock. The primary endpoint database lock is planned to occur after all patients have completed or discontinued the study prior to Visit 9 (Week 36).

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.

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.

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.

7.4. Dosage Modification

No adjustment in study drug doses will be allowed. Further details about dose administration during the study are described in Section 7.2.1 and Section 8.1.2.

Dosing of required concomitant metformin is discussed in Section 7.7.1.1.

7.5. Preparation/Handling/Storage/Accountability

The study site must store the SDP cartons in a locked and secure environment. The SDPs must be refrigerated (not frozen) at 2°C to 8°C until use. Dry ice should not be used for cooling. Patients will be provided with cartons containing the required number of dulaglutide SDPs at clinic visits per the Schedule of Activities (Section 2). They will receive insulated bags with cooling gel packs for use in transporting the SDP 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 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 entered in the eCRF;
- Study drug accountability will be checked at every visit. For that purpose, patients will be instructed to return the study drug carton(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 each visit interval 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)

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will receive additional training and instructions, as required, but should not be discontinued from the study.

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. Certain categories of medications will be collected with more detailed information on specific eCRF pages:

- Antihyperglycemic medications used during the study. This includes:
    - Details on metformin use at screening and any subsequent changes to dose or formulation during the study, and
    - Any additional antihyperglycemic medications initiated during the study (eg, for hyperglycemic rescue, after permanent study drug discontinuation, or during the Safety Follow-Up Period)
- Antihypertensive medications (regardless of the specific indication for use)
- Glucocorticoid medications

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

Table GBGL.3 provides a summary of criteria for use of concomitant medications that may interfere with planned assessments during the study.

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

Drug Class	Use during Screening/Lead-In	Conditions for Use after Randomization	
		Acute Therapy[a]	Rescue Therapy or Post-IP Discontinuation Therapy
Drugs with approved weight loss indication[b]	Excluded	N	N/A
Systemic glucocorticoid therapy[c]	Excluded except for acute therapy[a]	Y	N/A
Antihyperglycemic medications			
Other GLP-1 RAs	Excluded	N	N
DPP-4 inhibitors	Excluded	N	N
SGLT2 inhibitors	Excluded	N	See Section 7.7.1.2
Insulins and insulin mixtures	Excluded except for acute therapy[a]	Y	See Section 7.7.1.2
Meglitinides	Excluded	N	See Section 7.7.1.2
Alpha-glucosidase inhibitors	Excluded	N	See Section 7.7.1.2
Sulfonylureas	Excluded	N	See Section 7.7.1.2
Thiazolidinediones	Excluded	N	See Section 7.7.1.2
Metformin[d]	Required	N/A	Y[e]

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

[a] Acute therapy = treatment for up to 14 days.

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

[c] 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.

[d] 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.

[e] Metformin prescreening dose and formulation (short-acting or long-acting) should be maintained throughout the study, except as specified in Section 7.7.1.1. Increasing the metformin dose should not be used as the sole intervention for antiglycemic rescue or after premature study drug discontinuation.

7.7.1. *Antihyperglycemic Medications*

The only glucose-lowering agent allowed 3 months prior to study entry and during the study (excluding the Safety Follow-Up Period) 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; otherwise, eligible patients must be insulin- and GLP-1 RA-naive. Patients who receive any glucose-lowering agents other than metformin within the 3 months prior to entry or during the screening or lead-in/stabilization periods will not be eligible for further participation in the trial.

7.7.1.1. Required Concomitant Antihyperglycemic Medication: Metformin

The key requirements for the use of metformin, the required oral antihyperglycemic medication (OAM) in the study, 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, or in cases where lower doses are recommended per country-specific labeling due to reduced renal function (for example, eGFR 30 to 45 mL/min/1.73 m^2). 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 7.7.5.2.

Dose reduction/discontinuation of metformin during the trial should be properly documented and recorded on the appropriate eCRF.

Guidance for treatment following the end of the study is provided in Section 7.8.1.

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.

7.7.1.2. Initiation of New Antihyperglycemic Medication during the Study

The introduction of new antihyperglycemic medication is expected during the study only in the following situations:

- As an antihyperglycemic intervention for severe, persistent hyperglycemia ("rescue therapy"), as defined in Section 7.7.5.3.
- In those patients who require permanent discontinuation of study drug, but remain in the study (Section 8.1.1).
- During the Safety Follow-Up Period (between Visit 11 [Week 52] or ET and Visit 801).

If a new antihyperglycemic medication is introduced during the Treatment Period (that is, prior to Visit 11), the patient should be treated with a locally approved glucose-lowering agent (except other GLP-1 RAs including commercial Trulicity and DPP-4 inhibitors) according to the following order of preference:

1. Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be initiated first, unless a contraindication is present;
2. If a contraindication to SGLT2 inhibitor is present, then a sulfonylurea or thiazolidinedione can be considered;
3. If glycemic control remains inadequate despite introduction of new antihyperglycemic medication (eg, after 3 months or within a timeframe determined by the investigator), then addition of basal insulin therapy should be considered; if insulin is prescribed as a rescue therapy for hyperglycemia or as a new antiglycemic intervention in patients requiring study drug discontinuation, it must be differentiated from short-term use of insulin therapy for medical emergencies when reported in the eCRF;
4. Initiation of insulin as first rescue intervention for hyperglycemia should be reserved for patients with severe, persistent hyperglycemia (Section 7.7.5.3) with an average FPG ≥300 mg/dL (16.6 mmol/L), in patients with symptoms of hyperglycemia, or in other clinical situations where the investigator believes more rapid glycemic control is warranted.

Initiation of other classes of antihyperglycemic medications (for example, meglitinides, alpha-glucosidase inhibitors) for hyperglycemic rescue or after premature discontinuation of study drug is discouraged. Since patients should already be taking maximally or near maximally tolerated doses of metformin, increases in metformin dose should not be used as the sole intervention for antiglycemic rescue or after premature study drug discontinuation.

While investigators are strongly encouraged to follow the above guidance for managing patients requiring the initiation of new antihyperglycemic medications during the Treatment Period, management of these patients is ultimately up to the judgment of the investigator and may be dependent on a number of patient- and disease-related factors, patient glycemic response, or other clinical factors. At a minimum, management of these patients should be consistent with local standards of care or current guidelines from the American Diabetes Association (2017) and the European Association for Study of Diabetes (Inzucchi et al. 2015).

The type of antihyperglycemic medication initiated during the Safety Follow-Up Period (at or after Visit 11) (excluding other GLP-1 RAs or DPP-4 inhibitors) can be at the discretion of the investigator and does not need to follow the order of preference outlined above.

Initiation of antihyperglycemic medication during the Safety Follow-Up Period (at or after Visit 11) or after premature discontinuation of study drug for any reason other than severe, persistent hyperglycemia will not be considered rescue therapy.

If any new glucose-lowering medication is initiated after randomization at Visit 3 and prior to Visit 11 (end of Treatment Period), other than study drug, rescue therapy, post study drug discontinuation, 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 consecutive days will exclude the patient from the Per-Protocol (PP) Population for analyses.

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 Population 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.

7.7.5. Special Treatment Considerations

7.7.5.1. 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 (2017) 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, and management of patients who permanently discontinue study drug prior to Visit 11 and continue in the study. For effective implementation of measures described here, it is important that patients, and their caregivers, if applicable, be well-educated about the signs and symptoms of hyperglycemia (eg, severe thirst, dry mouth, frequent micturition, or dry skin) and hypoglycemia (eg, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders). Patients should be instructed to contact the investigative site in the event of severe, persistent

hyperglycemia or severe hypoglycemia between study visits, or in the event that a patient intends to permanently discontinue study drug.

7.7.5.2. Management of Increased Hypoglycemia Risk

Dulaglutide and metformin are nonsecretagogues; 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 (eg, 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.

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

Investigators will be trained on the application of criteria for deciding when and how to intervene in patients who do not reach glycemic targets. An additional therapeutic intervention should be considered in patients who develop severe, persistent hyperglycemia after randomization based on the following criteria:

a) During the first 8 weeks postrandomization (up to Visit 5): An average FPG above 270 mg/dL (15.0 mmol/L) over at least a 2-week period (at least 4 values/week must be available)

<div align="center">**OR**</div>

b) Between Week 8 and Week 18 (between Visits 5 and 7): An average FPG above 240 mg/dL (13.3 mmol/L) over at least a 2-week period (at least 4 values/week must be available)

<div align="center">**OR**</div>

c) Between Week 18 and Week 26 (between Visits 7 and 8): An average FPG above 200 mg/dL (11.1 mmol/L) over at least a 2-week period (at least 4 values/week must be available) or HbA1c above 8.0% (64 mmol/mol)

<div align="center">**OR**</div>

d) Beginning at Week 26 (Visits 8 through 11): HbA1c above 8.0% (64.0 mmol/mol) which is not at least 0.3% less than the HbA1c at the previous scheduled measurement

Persistent hyperglycemia considered of severe intensity by the investigator should be reported on the AE eCRF whenever any of the above criteria are met.

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In considering whether initiation of rescue therapy is warranted, 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. If confirmed, the investigator will initiate an appropriate glucose-lowering intervention (rescue intervention) according to the guidance outlined in Section 7.7.1, and it will be recorded on the eCRF specified for collecting antihyperglycemic medications. Other GLP-1 RAs (including commercial Trulicity) or DPP-4 inhibitors must not be used as the rescue intervention. Patients who receive rescue intervention for hyperglycemia management should also continue administering study drug for the remaining period in the trial.

7.7.5.4. Management of Patients Permanently Discontinuing Study Drug

Circumstances under which patients may be required to prematurely discontinue study drug are outlined in Section 8.1. Patients who stop the study drug permanently will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements and should receive another glucose-lowering intervention (Section 7.7.1). The new glucose-lowering intervention will be recorded on the eCRF specified for collecting antihyperglycemic medications.

To assure timely initiation of another antihyperglycemic medication after permanent discontinuation of study drug, patients should be advised to promptly notify the site when this situation occurs. The investigator should evaluate the need for additional antihyperglycemic medication at this time (as outlined in Section 7.7.1) and initiate the additional intervention accordingly. An unscheduled visit should be used as needed for more timely initiation if warranted based on the investigator's clinical judgment.

7.7.5.5. Management of Patients with GI Symptoms

Patients will be guided on dietary behaviors that may help mitigate nausea symptoms and vomiting; for example, eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, and stopping eating when they feel full. For patients experiencing intolerable GI symptoms, the investigator may temporarily discontinue (interrupt) study drug and then restart study drug as soon as it is safe to do so (Section 8.1.2). Investigators may consider the use of oral antiemetic or antidiarrheal medication as needed in patients who experience intolerable GI symptoms, per local country availability and individual patient needs. In cases where study drug is temporarily interrupted due to nausea or vomiting, use of oral antiemetic medication may be considered prior to restarting study drug to mitigate the reoccurrence of symptoms.

7.8. Treatment after the End of the Study

7.8.1. Continued Access

After completion of the study (defined as completion of Visit 801 or ET visit), an appropriate diabetes treatment regimen should be initiated by the investigator.

8.　Discontinuation Criteria

8.1.　Discontinuation from Study Treatment

8.1.1.　Permanent Discontinuation from Study Treatment

Following randomization, it is expected that patients will remain on study medication for the duration of the Treatment Period (through Visit 11). Patients will be required to permanently discontinue from study drug only 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 <15 mL/min/1.73 m^2 (confirmed on retest) 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 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or aspartate aminotransferase (AST) >8×ULN

- ALT or AST >5×ULN for more than 2 weeks

- ALT or AST >3×ULN and total bilirubin level >2×ULN or prothrombin time >1.5×ULN

- ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Alkaline phosphatase >3×ULN

- Alkaline phosphatase >2.5×ULN and total bilirubin >2×ULN

- Alkaline phosphatase >2.5×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 (Section 7.7.1) 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 (eg, 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. 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. See Section 7.2.1 for dosing details when resuming study drug after a temporary interruption. Investigators should inform the sponsor that study drug has been temporarily interrupted. The data related to temporary interruption of study treatment will be documented in source documents and entered on an 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 will 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.

8.2. Discontinuation from the Study

Every attempt will 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 in 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. Visit 801 (Safety Follow-Up Visit) should be performed approximately 4 weeks after the ET visit as the final study visit.

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

8.3. Lost to Follow-Up

Every attempt will be made to minimize the number of patients considered lost to follow-up at the end of the study. Patients will be informed about the importance of completing the study and providing updated contact information to the study site when necessary. 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. Attempts to contact the patient should be documented in the study source documents.

9. Study Assessments and Procedures

Section 2 presents the Schedule of Activities, with the study procedures and their timing (including number of days for allowable visit deviations [visit windows]).

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 Assessment
The primary efficacy measure is change from baseline in HbA1c at 36 weeks.

9.1.2. Secondary Efficacy Assessments
The following secondary efficacy measures (controlled for Type 1 error) will be evaluated at 36 weeks:

- change in body weight from baseline
- proportion of patients achieving HbA1c target <7.0% (53 mmol/mol)
- change in FSG (central laboratory) from baseline

9.1.3. Exploratory Efficacy Assessments
The primary (Section 9.1.1) and secondary efficacy measures (Section 9.1.2) will also be evaluated at 52 weeks as an exploratory efficacy assessment.

The following exploratory efficacy measures will be evaluated at 36 and 52 weeks (unless noted otherwise):

- proportion of patients achieving HbA1c target ≤6.5% (48 mmol/mol)
- proportion of patients achieving ≥5% body weight loss
- proportion of patients achieving ≥10% body weight loss
- change in 6-point SMPG profile from baseline
- proportion of patients meeting the composite endpoint of HbA1c <7.0% (53 mmol/mol), no weight gain, and no documented symptomatic hypoglycemia
- proportion of patients meeting the composite endpoint of HbA1c <7.0% (53 mmol/mol), body weight loss ≥5%, and no documented symptomatic hypoglycemia or severe hypoglycemia
- changes in systolic blood pressure (SBP) and DBP from baseline
- changes from baseline in serum lipid parameters (total cholesterol, high density lipoproteins [HDL], low density, lipoproteins [LDL], very low density lipoproteins [VLDL], and triglycerides)

- changes in insulin resistance as measured by the Homeostasis Model Assessment-2 (HOMA2) method (HOMA2-IR) (Caumo et al. 2006)
- β-cell function as measured by the HOMA2 method (HOMA2-%B), changes in fasting plasma glucagon, changes in fasting plasma glucagon adjusted for fasting glucose, changes in fasting insulin, and changes in C-peptide
- Diabetes Injection Device Experience Questionnaire (DID-EQ) scores at Week 12
- changes in EQ-5D-5L scores from baseline
- changes in Impact of Weight on Self-Perceptions Questionnaire (IW-SP) scores from baseline
- changes in Ability to Perform Physical Activities of Daily Living (APPADL) score from baseline

9.1.4. 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 and recorded on the eCRF to the nearest one-tenth kg (Appendix 7).

Body mass index will be computed from the patient's weight and height. Body mass index should be rounded to the nearest whole number for purposes of Inclusion Criterion [6] (Section 6.1).

9.1.5. 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.

9.2. 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.

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

The investigator answers yes/no when making this assessment.

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.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

Information on CV risk factors will be collected on an eCRF at Visit 2. In addition to monitoring of vital signs (PR, SBP, DBP) and 12-lead electrocardiograms (ECGs) throughout the study, data on any new CV event will be prospectively collected using a CV event eCRF.

Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise (Clinical Endpoint Committee [CEC]). The nonfatal CV AEs to be adjudicated are: 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.

9.2.2.2. Hypoglycemia and Hyperglycemia

Patients will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (ET visit or Visit 801). 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). If a hypoglycemic event occurs, the patient should record in the study diary the PG level measured during the episode and prior to administration of treatment (if taken), as well as associated symptoms and treatment administered. Site personnel will enter this information into the hypoglycemia 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

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Medicine plasma-equivalent glucose meters and strips) in accordance with the 2017 American Diabetes Association position statement on glycemic targets:

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of ≤70 mg/dL (≤3.9 mmol/L).

- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

- **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 <54 mg/dL (<3.0 mmol/L).

- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG <54 mg/dL (<3.0 mmol/L).

- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG <54 mg/dL (<3.0 mmol/L).

Severe hypoglycemia (Level 3):

- **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.

Other hypoglycemia categories:

- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

- **Relative hypoglycemia** is defined as any symptomatic event 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.

- **Probable symptomatic hypoglycemia** is defined as symptoms of hypoglycemia but PG measurement was not reported.

All reported cases of hypoglycemia will be reported on the hypoglycemia eCRF.

To avoid duplicate reporting, all consecutive PG values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

In each case of suspected or confirmed hypoglycemia, it is important that details for each event be recorded on the eCRF as completely and accurately as possible, including information on the date, time, PG value, symptoms, and the nature and outcome of any interventions. 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 7.7.1 and Section 8.1.1.

It is important that each case of suspected or confirmed hypoglycemia be properly categorized with respect to severity. **If a hypoglycemic event meets the criteria of severe, it also needs to be recorded on the AE eCRF as serious and reported to Lilly as an SAE**.

Severe, persistent hyperglycemia will be collected as an AE during the trial to assess the risk of extreme imbalance in glycemic control, as defined in Section 7.7.5.3. Details of antihyperglycemic medication initiated as rescue therapy for severe, persistent hyperglycemia per these criteria will be collected on the antihyperglycemic concomitant therapy eCRF.

9.2.2.3. 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 ≥3×ULN

- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with investigational product, but will continue in the study on another glucose-lowering regimen (see Section 7.7.1 and Section 8.1.1 for details on the introduction of new antihyperglycemic interventions). A review

of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each suspected 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.

Each patient will have measurements of p-amylase and lipase (assessed at the central laboratory) as shown on the Schedule of Activities (Section 2) to assess the effects of the investigational doses of dulaglutide on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck et al. 2017; Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3×ULN) is not mandated, but may be performed based on the investigator's clinical judgement and assessment of the patient's overall clinical condition. Only cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent CEC. 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 and those with severe or serious abdominal pain 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.

9.2.2.4. 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). Patients with a personal or family history of MTC or personal history of multiple endocrine neoplasia syndrome type 2, or who have serum calcitonin ≥20 ng/L at study entry as determined by the central laboratory will be excluded. The assessment of thyroid safety during the trial will include reporting of thyroid treatment-emergent (TE) AEs (TEAEs) and measurements of calcitonin according to the Schedule of Activities (Section 2).

Patients who develop serum calcitonin increases ≥50% of the screening value AND an absolute value ≥20 ng/L and <35 ng/L at a postrandomization visit will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase from the initial elevated value), the patient will be encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to rule out a serious adverse effect on the gland.

Patients with an increase in serum calcitonin ≥50% of the screening value AND an absolute value ≥35 ng/L at a postrandomization visit will be asked to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

For patients who require additional endocrine assessments due to increased calcitonin concentration per the criteria provided in this section or for thyroid-related TEAEs, data from the follow-up assessments will be collected on a specific eCRF.

9.2.2.5. Hypersensitivity Reactions

All hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data about these events, such as type of reaction and treatment received, will be collected on an eCRF created for this purpose. Injection site reactions will be collected on an eCRF separate from the hypersensitivity reaction eCRF. At the time of AE occurrence, samples will be collected for measurement of dulaglutide anti-drug antibodies (ADA) and dulaglutide concentration. Study drug should be temporarily interrupted in any individual suspected of having a severe or serious hypersensitivity 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.

9.2.2.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

All events of TE 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.

9.2.2.7. Acute Gallbladder Disease

Information on the patient's history of gallbladder disease (prior cholecystectomy, history of acute cholecystitis or cholelithiasis) will be recorded on an eCRF at Visit 2. All events of TE biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed.

9.2.2.8. Acute Renal Events

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

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, and a product complaint form should be completed.

9.3. Treatment of Overdose

Study drug overdose (more than the specified number of injections) 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. Electrocardiograms

Electrocardiograms will be collected according to the Schedule of Activities (Section 2) and centrally overread. Electrocardiograms should be recorded 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 relevant findings from ECGs obtained *before* the first dose of study drug that result in a diagnosis should be reported as a preexisting condition and medical history. Any clinically relevant 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.

9.4.1.2. Vital Signs

Sitting BP and 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 SBP should be used to collect all 3 measurements of both BP and PR at all study visits. For each parameter (PR, SBP, and DBP), 3 measurements will be taken for each patient at each visit 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.

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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).

Specific laboratory measures to be analyzed as exploratory endpoints are listed in Section 4.

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.

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

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. 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.

Specific safety measures are included in the protocol to ensure appropriate monitoring of pancreatic (Section 9.2.2.3), thyroid (Section 9.2.2.4), and liver safety (Section 9.4.3.1).

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (an advisory group for this study formed to protect the safety of the patients and the integrity of data; refer to Section 10.3.8) will be allowed to conduct additional analyses of the safety data.

9.4.3.1. Hepatic Safety Monitoring

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, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, alkaline phosphatase, and total bilirubin should continue until levels normalize or return to approximate baseline levels.

9.4.3.1.1. Hepatic Safety Data Collection

Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- elevation of serum ALT to $\geq 5 \times$ULN on 2 or more consecutive blood tests

- elevated serum total bilirubin to $\geq 2 \times$ULN (except for cases of known Gilbert's syndrome)

- elevation of serum alkaline phosphatase to ≥2×ULN on 2 or more consecutive blood tests

- patient discontinued from treatment due to a hepatic event or abnormality of liver tests

- hepatic event considered to be a SAE

9.5. Pharmacokinetics

Venous blood samples of approximately 4 mL 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 (Section 2). 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.

A PK sample can be collected at any time during those clinic visits at which an immunogenicity sample is to be taken, and at ET visits.

The study has been designed so that, where possible, each immunogenicity sample will be accompanied by a PK sample in the same visit (except for Visit 3 [baseline]). At visits where ECG measurements are also taken, these should be accompanied by a time-matched PK sample within 30 minutes after the ECG measurement, during the same visit.

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 at a facility selected by Lilly or its designee 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 impose shorter time limits. 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.

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 dulaglutide ADA. A blood sample will be collected at specific study visits according to the Schedule of Activities (Section 2), along with a simultaneous drug concentration sample.

Samples with dulaglutide ADA detected will be titered and evaluated for their ability to neutralize the activity of assigned treatment (dulaglutide-neutralizing antibodies). Samples with dulaglutide ADA detected will also be tested for cross-reactive-binding to native GLP-1, and if such is detected, 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 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 not be observed until later in the development of dulaglutide or after dulaglutide is commercially available.

9.9. Health Economics

9.9.1. Diabetes Injection Device Experience Questionnaire (DID-EQ)

The Diabetes Injection Device Experience Questionnaire is a newly developed questionnaire to specifically evaluate newer diabetes injection devices (Matza et al. 2016, Matza et al. 2017).

This questionnaire has been developed because all validated device questionnaires were developed specifically for evaluating devices for insulin injections; no validated device experience questionnaire was available that could be used to evaluate devices for injections of GLP-1 RAs.

The DID-EQ will be administered at Week 12 (Visit 6) only, or at the ET visit if early termination occurs prior to Visit 6.

9.9.2. EQ-5D-5L

Generic health-related quality of life will be assessed using the EQ-5D (EQ-5D; EuroQoL Group 2015). The EQ-5D is a standardized 5-item instrument for use as a measure of health outcomes. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as population health surveys. The EQ-5D comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no, slight, moderate, severe problems, extreme problems), for a total of 3251 possible health states. In addition, the EQ Visual Analog Scale (VAS) records the respondents' self-rated health status on a vertical graduated (0 to 100) VAS. In conjunction with the health state data it provides a composite picture of the respondents' health status.

The EQ-5D is used worldwide and is available in more than 170 languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D User Guide (EuroQoL Group 2015).

The EQ-5D-5L will be administered at Weeks 0, 36, and 52, and at ET (Visits 3, 9, 11, and ET).

9.9.3. Impact of Weight on Self-Perceptions Questionnaire (IW-SP)

Patients' self-perception related to their body weight will be assessed using the IW-SP (Hayes and DeLozier 2015). The IW-SP is a 3-item questionnaire that has demonstrated validity, reliability, and responsiveness in individuals with T2D and obesity, thereby making it an appropriate tool for the evaluation of weight-loss interventions targeted toward patients with T2D (Hayes and DeLozier 2015). Each item is rated on a 5-point scale ranging from "always" to "never." Total scores for the IW-SP are derived by summing the item scores and dividing by the

number of items. The score can also be transformed to a range from 0 to 100. Higher IW-SP scores correspond to better self-perception (Hayes and DeLozier 2015).

The IW-SP will be administered at Weeks 0, 36, and 52, and at ET (Visits 3, 9, 11, and ET).

9.9.4. Ability to Perform Physical Activities of Daily Living (APPADL)

The APPADL questionnaire contains 7 items that assess how difficult it is for patients to engage in various physical activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs (Hayes et al. 2011; Hayes et al. 2012). Items are scored on a 5-point numeric rating scale, where 5="not at all difficult" and 1="unable to do." A raw overall score is calculated by simply summing the scores of the 7 items, and a transformed overall score is obtained by linearly transforming the raw overall score to a 0 to 100 scale. A higher raw overall score and a lower transformed overall score are indicative of better ability to perform activities of daily living.

The APPADL will be administered at Weeks 0, 36, and 52, and at ET (Visits 3, 9, 11, and ET).

10.   Statistical Considerations

10.1. Sample Size Determination

Assuming a screen failure rate of 40%, approximately 3000 patients will need to be screened to attain approximately 1800 patients randomized to the 3 treatment groups (600 patients/groups) in a 1:1:1 ratio for dulaglutide 4.5 mg, 3.0 mg, and 1.5 mg. Assuming 15% dropout, this will result in approximately 510 patients per arm completing 36 weeks of treatment (the primary time point).

The aforementioned sample size provides ≥80% power to demonstrate superiority of at least 1 of the investigational dulaglutide doses (4.5 mg or 3.0 mg) to dulaglutide 1.5 mg with respect to the primary endpoint (change from baseline in HbA1c) at Week 36. This sample size is calculated based on the assumption that there is a treatment difference (for either investigational dose) in HbA1c change from baseline of approximately -0.22%, a standard deviation (SD) of 1.1%, and a 2-sided alpha of 0.05.

10.2. Populations for Analyses

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

Table GBGL.4.   **Populations for Analyses**

Population	Description
Entered	All participants who sign informed consent
All randomized	All patients who are randomized
Intent to treat (ITT)	All participants who are randomized and take at least 1 dose of study medication for an assigned treatment arm
Completers	All ITT patients who have an HbA1c measure at Visit 9 (Week 36) regardless of compliance with the protocol, rescue medication, or treatment discontinuation. However, data postrescue and/or posttreatment discontinuation will be excluded
Per protocol (PP)	All ITT patients who meet all of the following criteria: • Have no important protocol deviation that could impact the assessment of the primary endpoint • At least 75% compliant with study drug administration through Week 36 • Complete the treatment period through 36 weeks (Visit 9) • Have a value of the primary efficacy measure (HbA1c) at Visit 9 (Week 36) • Excluding data collected postrescue and/or posttreatment discontinuation

Abbreviation: HbA1c = hemoglobin A1c.

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

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

Efficacy and safety analyses will be conducted in the Intent to Treat (ITT) Population. There will be 2 primary estimands to compare treatment groups in terms of the primary measure of HbA1c change from baseline to Week 36.

One primary estimand will be an efficacy estimand (*de jure* effect) which will use the data collected before initiation of any rescue medication or premature treatment discontinuation to demonstrate the effect of treatment and avoid confounding effects of other antihyperglycemic agents (Little and Kang, 2014). The other primary estimand will be a treatment-regimen estimand (*de facto* effect) which will include data collected after initiation of other antihyperglycemic therapy and/or after premature treatment discontinuation.

The treatment-regimen (*de facto*) estimand is included as primary at the request of the US Food and Drug Administration (FDA). The efficacy (*de jure*) estimand will be considered primary for all other purposes, and will be applied to all efficacy outcomes unless otherwise specified to demonstrate effect of treatment and avoid confounding effects with other antihyperglycemic agents.

Both estimands will be tested at the full significance level of 0.05.

Analyses of safety parameters, except for hypoglycemia events, will be conducted in the ITT Population unless otherwise specified.

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

The baseline will be at the randomization visit (Visit 3). If baseline data are missing, the last nonmissing measurement taken prior to Visit 3 will be used.

Two analysis models will be used for the primary and key secondary continuous efficacy measures. The primary analysis will be mixed-model repeated measure (MMRM) analysis using restricted maximum likelihood (REML). The model will include factors for treatment, pooled country, visit, treatment-by-visit interaction and the baseline as a covariate. For analyses of body weight and FSG, the baseline HbA1c stratification (≥8.5% [69 mmol/mol] and <8.5%) will be added in this model as a fixed effect. An unstructured covariance structure will be used to model

the within-patient errors. If this model fails to converge, the following covariance structures will be tested in order:

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

The first covariance structure that converges will be used.

The secondary analysis for the primary and key secondary continuous endpoints will be analysis of covariance (ANCOVA). Missing endpoints will be imputed with the last (postbaseline) observation carried forward (LOCF) unless otherwise specified. The percentage of patients achieving target HbA1c <7.0% (53 mmol/mol) will be analyzed using a longitudinal logistic regression with repeated measurements.

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

For categorical measures, summary statistics will include sample size, frequency, and percentages. A Fisher's exact test will be used for treatment comparisons.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition
Frequency counts and percentages of all patients entered, randomized/enrolled, completing Weeks 36 and/or 52, and/or discontinuing from the study and/or study treatment early will be presented for each treatment. The reasons for discontinuation from the study will be summarized by treatment group. Patient disposition will be listed.

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 an analysis of variance (ANOVA) p-value to test overall treatment effect. For categorical measures, summary statistics will include sample size, frequency, and percent. Demographics will be summarized for the ITT, Completers, and PP populations.

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

Incidence of initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint.

10.3.2.4. Treatment Compliance

Treatment compliance is defined as taking at least 75% of required injections for the visit intervals (see Section 7.6). Overall compliance is defined as being at least 75% compliant with investigational product for at least 75% of visits across the Treatment Period. Compliance will be summarized by each treatment, and overall.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

There will be 2 primary estimands to compare each investigational dulaglutide dose and dulaglutide 1.5 mg in terms of the primary measure of HbA1c change from baseline to Week 36. See Section 10.3.1.

Both estimands will use the same primary analysis model by employing the MMRM described in Section 10.3.1 in the ITT Population, and each will be tested at the full significance level of 0.05. For each type of estimand, the 2 investigational doses will each be tested versus dulaglutide 1.5 mg simultaneously, controlling the 2-sided alpha of 0.05.

10.3.3.1.1. Secondary Analyses for Primary Endpoint

The primary analysis model, MMRM, will be repeated using the PP Population and the Completers Population to check the sensitivity of the analysis. If the conclusion differs from that of the primary analysis, the data and analyses may be further investigated.

10.3.3.1.2. Multiple Imputation for Missing Data

To investigate departure from the missing at random (MAR) assumption for the primary analysis (MMRM) and check the robustness of the conclusions drawn from the primary analysis, a pattern-mixture model (PMM) coupled with multiple imputation, recommended by National Research Council ([NRC]; 2010), will be performed.

All data including those collected after rescue and/or treatment discontinuation will be included in the analyses. The missing data will be imputed based on measurements from patients in the same treatment arm who discontinued treatment but still had their measurements taken at the primary endpoint visit (Week 36) if there are an adequate number of observations for imputation. An ANCOVA model will be fit to the complete datasets at Week 36, containing effects for treatment, pooled country, and the baseline as a covariate.

Inference based on PMM does not involve directly making the assumption of MAR. Instead, PMM involves making other types of (untestable) identifiability assumptions for the unobservable distributions. This assumption cannot be validated from the observed data. The PMM model depends on the probability mass function of possible missing data patterns, which would not be known a priori. The proposed multiple imputation may require posthoc changes after database lock to resolve any convergence issues.

10.3.3.2. Analyses for Secondary Efficacy Endpoints

The key secondary measures change from baseline to 36 weeks in body weight and FSG, will be analyzed using both models, the MMRM and the ANCOVA, described in Section 10.3.1.

For percentages of patients achieving target HbA1c of <7.0% (53 mmol/mol), longitudinal logistic regression with repeated measurements will be used. The model will include independent variables treatment, pooled country, visit, treatment-by-visit, and baseline HbA1c as a covariate.

Treatment-regimen estimands using an ANCOVA model coupled with a PMM may be conducted for each key secondary continuous endpoint.

10.3.3.3. Multiplicity Adjustments for the Primary and Key Secondary Endpoints Analyses

Superiority for the primary and secondary endpoints for each type of estimand will be assessed in a graphical approach (Bretz et al. 2009; Bretz et al. 2011) to control the overall Type 1 error rate. The tested hypotheses are superiority of each of the investigational dulaglutide doses versus dulaglutide 1.5 mg at Week 36 for the following measures: (1) change from baseline in HbA1c, (2) change from baseline in body weight, (3) percent to target HbA1c <7.0% (53 mmol/mol), and (4) change from baseline in FSG.

Each estimand will be tested at the full significance level of 0.05 (2-sided).

10.3.3.4. Tertiary/Exploratory Efficacy Endpoints

The analysis of patients reaching HbA1c target ≤6.5% and other binary outcomes will use the same model as that for HbA1c target <7.0% (53 mmol/mol) described in Section 10.3.3.2.

Longitudinal continuous variables will be analyzed using MMRM described in Section 10.3.1. The analysis will be conducted for on-treatment without rescue medication data. Log-normal-distributed data such as fasting glucagon may be analyzed using log scale.

Nonlongitudinal continuous variables such as 6-point SMPG, HOMA2-IR, and HOMA2-%B will be analyzed using LOCF by fitting a linear model with pooled country, treatment, baseline HbA1c strata as fixed effects, 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 endpoints will include incidence of AEs, adjudicated AEs, discontinuations due to 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 (SOC). Selected notable AEs of interest may be reported using high-level terms.

Summary statistics will be provided for overall AE, TEAEs, SAEs, study discontinuation due to AEs or death, and study drug discontinuation due to AEs. Counts and proportions of patients experiencing AEs will be reported for each treatment.

Summaries (if appropriate) of adverse events of special interest (AESI) defined in Section 9.2.2 will be generated.

10.3.4.3. Hypoglycemic Episodes

Section 9.2.2.2 contains definitions of categories of hypoglycemia. Summary reports on-treatment without rescue medication will include both incidence and rates of hypoglycemia. Hypoglycemia will be analyzed as documented symptomatic, asymptomatic, nocturnal documented symptomatic, or severe.

Hypoglycemic episodes will be analyzed using 2 hypoglycemic thresholds: Level 1 (glucose alert level, ≤ 70 mg/dL [3.9 mmol/L]) and Level 2 (clinically significant hypoglycemia level, <54 mg/dL [3.0 mmol/L]). 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 (events/patient/1 year) will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution for hypoglycemic episodes if data warrants. Otherwise, the rate will be analyzed using Wilcoxon rank-sum test. Incidence and rates will be summarized for each treatment arm and entire Treatment Period.

10.3.4.4. 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 may be provided for each treatment during the weeks of dose escalation, during the period on the final assigned dose, and overall, to compare the effects of the 3 different doses on GI tolerability, as well as the overall effects of randomized therapies.

10.3.4.5. Laboratory Analyses

Laboratory safety measurements will be summarized. For continuous (numeric) laboratory analytes, the change from baseline by visit will be summarized as detailed in Section 10.3.1. Change from baseline to endpoint (LOCF) will be analyzed using an ANOVA on the ranks with treatment as a fixed effect unless otherwise specified. For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using Fisher's exact test.

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Shift tables of the change from baseline value to the most extreme postbaseline value and from baseline to Week 52 for selected analytes using clinically meaningful thresholds will be summarized.

10.3.4.6. Vital Signs

Descriptive statistics for the actual measurements and changes from baseline for SBP and DBP, PR, and rate-pressure product (RPP; SBP×PR/1000) 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 analyses.

10.3.4.7. Electrocardiograms

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

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. If necessary, data from this study may be combined with data from previous study/studies for analysis, or prior population PK or PK/PD model information from previous studies may be utilized to initiate analysis.

The relationships between dulaglutide doses and/or concentrations and key safety measures (such as QT interval, PR interval, and HR), tolerability measure (such as nausea and vomiting), and efficacy measures (such as fasting glucose, HbA1c, and weight) will be assessed either graphically or through modeling. Endpoints may include but are not necessarily limited to those listed above.

In addition, if positive antibody titers to dulaglutide are observed, the impact of antibody formation on PK exposures, dulaglutide clearance, and if applicable, drug effect(s) will be evaluated.

10.3.6. Other Analyses

10.3.6.1. Health Economics

Continuous measures from the patient reported outcomes (PRO) instruments will be analyzed using the MMRM model specified in Section 10.3.1, using on-treatment without rescue data.

Categorical measures from the PRO instruments will be summarized for each treatment.

10.3.6.2. Subgroup Analyses

Subgroup analyses of treatment interaction with important factors, including age (<65 years, ≥65), race, gender, country, duration of diabetes, baseline HbA1c (<8.5% [69 mmol/mol], ≥8.5% [69 mmol/mol]), body weight, 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 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. Evaluation of Immunogenicity

The frequency and percentages of patients with preexisting (baseline) ADA and with TE ADA to dulaglutide will be tabulated. For patients with ADA detected at baseline, TE ADA are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. The frequency of neutralizing antibodies with specificity for dulaglutide and with specificity for native-sequence GLP-1 will also be tabulated in patients with TE ADA detected.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to dulaglutide may be assessed.

10.3.8. Interim Analyses

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

An independent DMC will have the responsibility to review unblinded interim analysis results in order to monitor the safety of the patients in the study up until the last patient completes the Week 36 visit (Visit 9). The detailed analysis and communication plan for the interim analyses will be defined in a separate DMC charter. An internal Statistical Analysis Center (SAC) external to the study team will perform the data analysis for the DMC. As no efficacy analyses are planned by the DMC, the Family-Wise Error Rate will not be affected by any of these interim analyses; hence, no alpha spending is necessary.

Only the DMC will be authorized to evaluate unblinded interim safety analyses. Study sites will receive information about interim results ONLY if deemed necessary for the safety of their patients.

The DMC will perform the first safety analysis after approximately 900 patients (50% of the planned sample size) have the opportunity to complete Visit 7 (Week 18) or approximately 7 months after the first patient is randomized (whichever comes first). A second safety review will be planned after approximately 900 patients have the opportunity to complete Visit 9 (Week 36), or approximately 12 months after the first patient is randomized (whichever comes first). The number and timing of the DMC interim analyses may be adjusted by the actual enrollment rate. This adjustment will not require a protocol amendment.

There may be 2 database locks for this study. A primary database lock may be conducted for all data accumulated through the time when all randomized patients have completed 36 weeks of treatment (Visit 9, primary objective endpoint). The final database lock will be conducted for all data accumulated through the time when all patients have completed the 4-week Safety Follow-Up Period (through Visit 801). For the primary database lock, all efficacy analyses will be conducted based on Week 36 (Visit 9). If a decision is made to only conduct the final database lock and not the primary lock, it will be documented without an amendment to the protocol.

A limited number of pre-identified individuals may gain access to unblinded data, as specified in the unblinding plan prior to the primary lock, in order to initiate the population PK/PD model development processes. Following the primary database lock, the Sponsor will be unblinded to analyze and report the data. Unblinded data and results will not be shared with the study sites in order to maintain blinding at the site while the study is still ongoing.

Unblinding details are specified in the unblinding plan.

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12. Appendices

Appendix 1.   Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APPADL	Ability to Perform Physical Activities of Daily Living
AST	aspartate aminotransferase
AUC	area under concentration-time curve
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not.
	A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CEC	Clinical Endpoint Committee
CI	confidence interval
CKD-EPI	Chronic Kidney Disease-Epidemiology
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.

CSR	clinical study report
CT	computed tomography
CV	cardiovascular
DBP	diastolic blood pressure
DID-EQ	Diabetes Injection Device Experience Questionnaire
DMC	Data Monitoring Committee
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethics Review Board
ESRD	end-stage renal disease
ET	early termination
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSG	fasting serum glucose
GCP	good clinical practice
GGT	gamma glutamyl-transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HOMA2	Homeostasis Model Assessment-2
HOMA2-%B	β-cell function as measured by the HOMA2 method

HOMA2-IR	insulin resistance as measured by the HOMA2 method
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the complete reporting database is created/locked for the primary endpoint.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IW-SP	Impact of Weight on Self-Perceptions Questionnaire
IWRS	interactive web-response system
LOCF	last observation carried forward
LS mean	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed-model repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
NOAEL	no adverse effect level
NRC	National Research Council
OAM	oral antihyperglycemic medication

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OTC	over-the-counter
PD	pharmacodynamic
PG	plasma glucose
PK	pharmacokinetics
PMM	pattern-mixture model
PP	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.
PR	pulse rate
PRO	patient reported outcome
QTcF	QT corrected for heart rate using Fridericia's formula
REML	restricted maximum likelihood
RPP	rate-pressure product
SAC	Statistical Analysis Center
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SDP	single-dose pen
SGLT2	sodium-glucose co-transporter 2
SmPC	Summary of Product Characteristics
SMPG	self-monitored plasma glucose
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
T1D	type 1 diabetes
T2D	type 2 diabetes mellitus
TE	treatment-emergent

TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
VAS	Visual Analog Scale
WHO	World Health Organization

Appendix 2.   Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Creatine kinase (creatine phosphokinase; CPK[d])
Platelets	Uric acid
	Calcium
Urinalysis	Albumin
Specific gravity	Glucose[e]
pH	
Protein	
Glucose	**eGFR (calculated by CKD-EPI equation)[f]**
Ketones	
Blood	**Pancreas (exocrine)**
Urine leukocyte esterase	Serum pancreatic amylase
Creatinine	Serum lipase
	Lipid Panel (fasting)
Albumin/creatinine ratio (urine)[b]	Total cholesterol
	LDL[g]
HbA1c	HDL
	VLDL
Endocrine	Triglycerides
Fasting plasma glucagon[c]	
Fasting serum insulin	**Glucose (fasting)**
Calcitonin	**Cystatin C**
Follicle-stimulating hormone	**Pregnancy test serum and urine[h]**
C-peptide	
Samples for PK analysis	**Immunogenicity**
	Dulaglutide anti-drug antibody
Stored Samples	Dulaglutide neutralizing antibody
Pharmacogenomics sample	Native GLP-1 cross-reactive antibody
Non-pharmacogenomic biomarker sample (serum, plasma EDTA/P800[c])	Native GLP-1 neutralizing antibody

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 will be measured; the ratio will be calculated.

[c] Remaining P800 plasma from glucagon collection for nonpharmacogenomic biomarker sample.

[d] CK-MB will 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 or if required per local regulations and/or
  institutional guidelines during the study.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1.   Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study.

- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

- that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.

- that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2.   Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3.   Ethical Review

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

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

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB), and updates during the course of the study

- ICF

- other relevant documents

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Appendix 3.1.4. **Regulatory Considerations**

This study will be conducted in accordance with the protocol and with the:

- 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 3.1.5. **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 3.1.6. **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

- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, 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

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- review and evaluate eCRF 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.

Appendix 3.4.   Publication Policy

The publication policy for Study H9X-MC-GBGL is described in the Clinical Trial Agreement.

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Appendix 4.   Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-Nuclear Antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-Smooth Muscle Antibody (or Anti-Actin Antibody)[a]

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.

[a] Assayed by Lilly-designated or local laboratory.

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

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

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Appendix 6.   Classification of Contraceptive Methods

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 (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle). Note: periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception
- 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 GBGL Standardized Protocols for the Measurement of Height and Weight

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2008) (Available at: http://www.who.int/chp/steps/Section%204%20Step%202%20Physical%20Measurements.pdf), accessed: January 24, 2018.

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 height 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 electronic scale capable of measuring weight in kilograms.
- All weights for a given patient should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Patients should be lightly clothed but not wearing shoes while their weight is measured.

Step 1 Ask the patient to remove their footwear, outerwear (coat, jacket, etc), and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the patient at every clinic visit when 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 arms by sides and then record weight in kilograms (kg) to the nearest one-tenth kg.

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