H9X-MC-GBDJ (d) REWIND Clinical Protocol

Protocol H9X-MC-GBDJ (d) (REWIND) The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)

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1. Protocol H9X-MC-GBDJ(d) (REWIND) The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)

Dulaglutide (LY2189265)

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel study to assess the effects of dulaglutide (LY2189265) on cardiovascular outcomes in patients with type 2 diabetes who are drug naïve or who are on a stable antidiabetic regimen.

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Protocol Signed and Approved by Lilly

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2. Synopsis

Study Rationale

Dulaglutide (LY2189265) is a glucagon-like peptide-1 (GLP-1) receptor agonist administered as a once-weekly subcutaneous injection to improve glycemic control in patients with type 2 diabetes mellitus. Dulaglutide has received regulatory approval in some countries and is under review in other countries.

Data from clinical trials have shown that dulaglutide reduces glycosylated hemoglobin (HbA1c), fasting and postprandial blood glucose, and body weight, and GLP-1 receptor agonists generally improve a variety of risk factors for cardiovascular (CV) disease. However, whether GLP-1 receptor agonists in general or dulaglutide in particular reduces CV outcomes is unknown. The purpose of this trial is therefore to assess the effect of once-weekly administration of dulaglutide compared to placebo on major adverse CV events when added to the existing antihyperglycemic regimen of patients with type 2 diabetes who are at high risk for CV events. Other serious outcomes will be assessed, including the effect of dulaglutide on thyroid C-cell function and the incidence of pancreatitis.

Name of Investigational Product: Dulaglutide (LY2189265)	
Title of Study: The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)	
Approximate Number of Planned Patients/Subjects: Entered: 16,000 Enrolled/Randomized: 9600 Completed: 9500	**Phase of Development:** 3
Length of Study: This is an event-driven study and will complete when approximately 1200 patients experience a primary endpoint event, adjudicated as such. The estimated follow-up duration will depend on the observed cardiovascular (CV) event rate. Planned first patient visit: June 2011 Planned last patient visit: Second Quarter 2019	

Objectives: The primary objective is to test the hypothesis that once-weekly injection of 1.5-mg dulaglutide reduces the occurrence of the composite primary endpoint of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke when added to the glucose-lowering regimen of patients with type 2 diabetes, compared to the addition of a once-weekly placebo injection.

The secondary efficacy objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the occurrence of:

- the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy, or anti-vascular endothelial growth factor (anti-VEGF) therapy; development of clinical proteinuria, a 30% decline in estimated glomerular filtration rate (eGFR), or need for chronic renal replacement therapy
- hospitalization for unstable angina
- each component of the composite primary endpoint
- all-cause mortality
- heart failure (HF) requiring hospitalization or an urgent HF visit

The prespecified safety objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the incidence of:

- acute pancreatitis
- serious gastrointestinal events
- any cancer (excluding basal or squamous cell skin cancer) and specific categories of
    - pancreatic cancer
    - medullary thyroid carcinoma (MTC) and C-cell hyperplasia
    - thyroid carcinomas
- severe hypoglycemia
- immune mediated reactions including serious allergic and hypersensitivity reactions
- serious hepatic events
- clinically significant supraventricular arrhythmias and cardiovascular conduction disorders
- serious renal events
- discontinuation of study drug for any reason

The additional objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the following:

- hemoglobin A1c (HbA1c) levels
- weight
- waist/hip ratio
- the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
- coronary, carotid, or peripheral revascularization, individually and compositely
- any hospitalization
- cognitive function as measured by the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST)
- erectile function using the International Index of Erectile Function Questionnaire (IIEF)
- any fracture
- development of cholelithiasis

Study Design: Phase 3, event-driven, multicenter, international, randomized, double-blind, placebo-controlled, parallel study to assess the effect of once-weekly 1.5-mg dulaglutide on CV outcomes when added to the existing antihyperglycemic regimen of patients with type 2 diabetes. The study will consist of a screening visit followed by a single-blind placebo run-in period. Afterwards, patients will be randomized to either dulaglutide or placebo and followed at approximately 6-month intervals. Patients will be followed until approximately 1200 patients experience a primary endpoint event, adjudicated as such.

The international steering committee (SC) will be responsible for the overall scientific conduct of the study and all scientific trial-related decisions. The SC will be chaired by the Principal Investigator and will include, as members, all National Leaders, one representative from Lilly, and one representative from the clinical research organization (CRO). An independent data-monitoring committee (IDMC) will be responsible for monitoring patient safety throughout the study and review of interim analyses. An independent clinical endpoint committee (CEC) will adjudicate all deaths and CV, pancreatic, and thyroid events. Lilly will assign the obligation of study operation management to a CRO.

Diagnosis and Main Criteria for Inclusion and Exclusions: Men or women with type 2 diabetes (HbA1c ≤9.5%) treated with various antihyperglycemic regimens who are at high risk for CV events (aged ≥50 years old with clinical vascular disease, ≥55 years and subclinical vascular disease, or ≥60 years and at least 2 or more CV risk factors)

Test Product, Dosage, and Mode of Administration: Dulaglutide, 1.5 mg administered subcutaneously once weekly

Planned Duration of Treatment: This is an event-driven study and patients will be followed until approximately 1200 patients experience a primary endpoint event, adjudicated as such. The estimated follow-up duration will depend on the observed CV event rate.

Screening period: 1-2 weeks
Run-in period: 3 weeks
Treatment period: Visits will continue until a sufficient number of primary endpoint events, adjudicated as such, have occurred. The estimated average follow-up duration is approximately 6.5 years.

Reference Therapy, Dose, and Mode of Administration: Placebo, administered subcutaneously once weekly

Criteria for Evaluation:

Primary efficacy measure: Time to first occurrence (after randomization) of the composite endpoint of death from CV causes, nonfatal MI, or nonfatal stroke.

Secondary efficacy measures include:

- time (after randomization) to:
  - first occurrence of the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy, or anti-VEGF therapy; development of clinical proteinuria, a 30% decline in eGFR or need for chronic renal replacement therapy
  - first hospitalization for unstable angina
  - first occurrence of each individual component of the composite primary endpoint
  - death
  - first occurrence of HF requiring hospitalization or an urgent HF visit

The prespecified safety measures include the incidence of:

- acute pancreatitis
- serious gastrointestinal events
- any cancer (excluding basal or squamous cell skin cancer) and specific categories of
  - pancreatic cancer
  - medullary thyroid carcinoma (MTC) and C-cell hyperplasia
  - thyroid carcinomas
- severe hypoglycemia
- immune mediated reactions including serious allergic and hypersensitivity reactions
- serious hepatic events
- clinically significant supraventricular arrhythmias and cardiovascular conduction disorders
- serious renal events
- discontinuation of study drug for any reason

Safety will be also assessed based on other data collected in the trial.

The additional measures include:

- change from baseline in:
  - HbA1c
  - weight
  - waist/hip ratio
  - cognitive function as measured by MoCA and DSST
  - erectile function as measured by the IIEF
- time to first occurrence (after randomization) of:
  - the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
  - coronary, carotid, or peripheral revascularization, individually and compositely
  - any hospitalization
- the incidence of:
  - any fracture
  - development of cholelithiasis

Statistical Methods:

The primary efficacy measure is the time to first occurrence of the composite endpoint of death due to CV causes, nonfatal MI, or nonfatal stroke (adjudicated as such). The primary analyses will be based on the intent-to-treat principle and will use time-to-event analyses via a Cox proportional hazards regression model. Estimates of hazard ratios and 95% confidence intervals will be calculated and treatment group comparisons will be based on the p-value from the Cox model. Dulaglutide will be considered different from placebo if the 2-sided p-value from the primary analysis (adjusted for interim looks) is <0.05. Kaplan-Meier estimates of the survival curve for each treatment will be generated. The incidence rate per 100 person-years of follow-up will be calculated for each treatment group.

Analyses of the secondary efficacy and select additional measures will be based on the time from randomization to the occurrence of the first event, with patients analyzed in the treatment group to which they were randomized (according to the intent-to-treat principle). Where applicable, analyses will be based upon adjudicated events. Patients who complete the study but do not experience an outcome will be censored on the last day of their follow-up. Patients who discontinue from the study will be censored on their discontinuation dates or their last contact dates, whichever is later. Patients who die during the study will be censored as of the date of death for all time-to-event analyses where death is not an outcome of interest. Patients who prematurely discontinue assigned treatment will be followed until the end of the study.

Demographic and baseline characteristics will be summarized by treatment group. Separate subgroup analyses of the primary endpoint will be performed based on patient demographics and baseline characteristics. Predefined key subgroups include gender, age group (age <65 years and age ≥65 years), prior CV event, body mass index below and at or above the median, duration of diabetes (0 to 5 years, 5 to 10 years, and 10 or more years), baseline HbA1c below and at or above the median, and geography. Consistency of treatment effects across subgroups will be assessed using an interaction term in the Cox regression model. As the number of these subgroup variables may be large, the probability of observing at least 1 statistically significant result just by chance is nontrivial. Thus, these analyses will be considered exploratory.

For other analyses, including analyses of prespecified safety measures, the number and proportion of patients will be calculated for binary data and summary statistics (mean, median, standard deviation, 10th and 90th percentiles) will be presented for continuous data. Summary statistics of change from baseline for HbA1c per year will be presented along with percentage of patients within ranges of clinical interest (for example, HbA1c <7.0%).

Safety data will be monitored on an ongoing basis. Clear evidence of net harm that is consistent over time and across subgroups would justify early stopping of the trial. One interim and 1 final analysis of the efficacy data will be performed. The interim analysis will occur when approximately 61% (730 events) of the expected number (1200) of primary endpoint events have accrued. The final analysis will occur when approximately 1200 patients have experienced a primary endpoint event if the trial is not stopped early.

The secondary analyses will follow a graphical statistical approach for multiple comparisons to strongly control the overall Type I error rate in the trial at a 2-sided α level of 0.05.

An IDMC will monitor unblinded study data on a regular basis to assess study progress, efficacy, and patient safety.

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4. Abbreviations and Definitions

Term	Definition
ACR	albumin/creatinine ratio
Adherence	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and 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.
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARD	absolute risk difference
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirements.
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignments. Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor(s), and in some cases, select sponsor personnel being unaware of the treatment assignments.
BP	blood pressure
case report form (CRF) and electronic case report form (eCRF)	Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CABG	coronary artery bypass grafting
CEC	independent clinical endpoint committee
clinical research physician (CRP)	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.

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.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRO	contract research organization
CV	cardiovascular
DBP	diastolic blood pressure
DPP-IV	dipeptidylpeptidase-IV
DSST	Digit Symbol Substitution Test
ECG	electrocardiogram
efficacy	efficacy is the ability of a treatment to achieve a beneficial intended result.
eGFR	estimated glomerular filtration rate
end of study (trial)	End of study (trial) is the date of the last visit (final visit) or last scheduled procedure shown in the Study Schedule for the last active subject in the study. The European Union has additional reporting requirements associated with the end of study. Consult regional SOPs for further information.
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EV	extended (follow-up) visit
FV	final visit
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
IDMC	independent data monitoring committee

IIEF	International Index of Erectile Function
institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
intention to treat (ITT)	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the allocated treatment regimen rather than the actual treatment received. 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 adherence to the planned course of treatment or protocol deviations or use of prohibited drugs.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is locked.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
ISAC	independent statistical analysis center
IVRS	interactive voice-response system
IWRS	interactive web-response system
LDL-C	low-density lipoprotein cholesterol
legal representative	An individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial.
LS	least squares
LV	left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed-effects model for repeated measures
MoCA	Montreal Cognitive Assessment
MTC	medullary thyroid carcinoma
NPH	neutral protamine Hagedorn
OAM	oral antihyperglycemic medication
patient	A study participant who has the disease or condition for which the investigational product is targeted.

PCI	percutaneous coronary interventions
per protocol set (PPS)	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.
Randomize	The act of assigning a patient to a treatment after completing the run-in period.
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
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. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SMBG	self-monitored blood glucose
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
TIA	transient ischemic attack
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after the first injection of study drug following randomization and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms [TESS]).
VEGF	vascular endothelial growth factor

The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)

5. Introduction

5.1. Background

Despite the identification of an increasing number of cardioprotective therapies, type 2 diabetes continues to be a strong, independent risk factor for serious cardiovascular (CV) outcomes. Indeed, more than two-thirds of people with type 2 diabetes die from CV causes (Panzram 1987; Standl et al. 1996). Therapeutic approaches that can reduce or eliminate this increased risk are therefore urgently needed. Approaches that also have favorable glycemic effects are of particular interest due to the proven benefits of glycemic control for retinal and renal disease (UKPDS 1998; ADVANCE 2008; ACCORD 2010) and the relationship between these outcomes and CV disease. Indeed, identification of glucose-lowering agents that also have cardioprotective properties would be a welcome addition to the menu of drugs used to treat diabetes.

Glucagon-like peptide-1 (GLP-1) is a hormone that is synthesized in the L cells of the distal ileum and released in response to a meal. It acts to increase pancreatic insulin secretion in response to glucose, suppress glucagon secretion, and suppress appetite through a central effect. Patients with type 2 diabetes have reduced secretion of GLP-1 in response to meals and this defect contributes to reduced insulin secretion, increased glucagon secretion, and hyperglycemia (Verspohl 2009). These abnormalities and perhaps the GLP-1 deficit itself may contribute to the 2- to 3-fold higher risk of fatal CV events in people with type 2 diabetes. Moreover, several studies have shown that providing GLP-1 or one of its receptor agonists can safely reduce glucose levels in people with type 2 diabetes, through various possible mechanisms including increased meal-stimulated insulin secretion, reduced glucagon secretion, reduced dietary intake, and weight loss (Verspohl 2009).

5.2. Study Rationale

Several observations suggest that GLP-1 and its receptor agonists may have beneficial CV effects. First, the GLP-1 receptor is widely expressed in the heart. Animal studies have shown that deletion of the GLP-1 receptor elevates left ventricular (LV) end diastolic pressure and causes increased LV thickness (Gros et al. 2003), suggesting that GLP-1 may prevent LV dysfunction. Indeed, in preliminary studies of patients with acute myocardial infarction (MI) and severe LV dysfunction, acute infusion of recombinant GLP-1 after angioplasty significantly improved LV ejection fraction (Nikolaidis et al. 2004) and reduced hospital mortality from 27% to 10%. In another study, GLP-1 improved ejection fraction in people with severe LV dysfunction after an MI (Ban et al. 2008). Moreover, preoperative infusion of GLP-1 before coronary artery bypass grafting reduced the use of inotropic infusions needed postoperatively to

maintain hemodynamic function (Sokos et al. 2007). Animal studies have shown that GLP-1 receptor agonists reduce infarct size (Addison and Aguilar 2010). These findings suggest that GLP-1 or its receptor agonists may prevent myocardial damage in response to an insult.

Second, GLP-1 and its receptor agonists increase insulin levels. Insulin is one of the body's key anabolic hormones, with well-studied effects on glucose and lipid homeostasis. In addition to maintaining normoglycemia, insulin inhibits adipose tissue lipolysis. Insufficient insulin effect, due to insufficient insulin secretion to compensate for the degree of insulin resistance, may increase free fatty acid flux, exacerbate insulin resistance, and increase atherogenic lipoproteins (Lewis et al. 2002). The higher free fatty acid flux may also reduce anaerobic energy production from glucose and increase the demand for oxygen in ischemic cardiac muscle (Apstein 2000; Stanley and Chandler 2002). Insufficient insulin effect may also promote inflammation, raise PAI-1 levels (Chaudhuri et al. 2004), and reduce myocardial ischemic preconditioning of myocardium and vasodilation in response to ischemia (Dandona 2002; Dandona et al. 2002). Improving insulin physiology with GLP-1 receptor agonists may reverse some of these defects. Indeed, the reduction in free fatty acids by GLP-1 in people with type 2 diabetes (Zander et al. 2002; Meier et al. 2006) may explain the acute myocardial effects noted above; it may also account for the observed reduction in atherogenic lipids (Horton et al. 2010).

Third, GLP-1 receptor agonists modestly reduce systolic blood pressure (SBP) (Okerson et al. 2010), either due to weight loss or a direct effect as suggested by a blood pressure-lowering effect of acute infusion of GLP-1 in patients with type 2 diabetes (Toft-Nielsen et al. 1999). Fourth, the strong link between obesity and CV disease suggests that GLP-1 receptor agonist-mediated weight loss may also reduce CV outcomes. Fifth, GLP-1 and its receptor agonists may improve endothelial function (Addison and Aguilar 2010). Finally, GLP-1 and its receptor agonists reduce glucagon levels, and there may be a relationship between glucagon (which is elevated in diabetes) and CV disease (Ferrannini et al. 2007).

5.3. Dulaglutide (LY2189265)

Dulaglutide, which contains two analogs of the endogenous hormone GLP-1, is administered as a once-weekly subcutaneous injection to improve glycemic control in patients with type 2 diabetes mellitus. Dulaglutide has received regulatory approval in some countries and is under review in other countries.

The biosynthetic dulaglutide molecule, produced using mammalian cell culture, consists of 2 identical disulfide-linked chains, each containing an N-terminal GLP-1 receptor agonist sequence covalently linked to a human IgG4 heavy chain by a small peptide linker. Dulaglutide has been modified to render the molecule more stable against dipeptidylpeptidase-IV (DPP-IV) inactivation, increase the solubility of the peptide, reduce immunogenic potential, and increase the duration of its pharmacological activity. The pharmacokinetic (PK) half-life of dulaglutide is approximately 5 days, with less than 50% accumulation at steady state, supporting once-weekly dosing. The maximum dulaglutide plasma concentration (C_{max}) was observed between 24 and 72 hours following subcutaneous administration.

In clinical trials completed to date, dulaglutide has exhibited the expected GLP-1 receptor agonist pharmacological effect on insulin secretion resulting in significant reductions in glycosylated hemoglobin (HbA1c). Dulaglutide administration in patients with type 2 diabetes has been associated with reductions in body weight. No episodes of severe hypoglycemia have been reported in completed studies. The most common adverse events (AEs) reported in patients administered dulaglutide are those related to the gastrointestinal organ class, including nausea and vomiting. Other AEs that have been rarely reported in trials of dulaglutide include pancreatitis and medullary thyroid cancer (MTC); whether or not these are due to exposure to the analog remains unknown. More detailed information about the known benefits and risks of dulaglutide may be found in the Investigator's Brochure (IB).

The purpose of this trial is to determine whether a once-weekly administration of dulaglutide compared to placebo reduces major adverse CV events, when added to the existing antihyperglycemic regimen of patients with type 2 diabetes who are at high risk for CV events. In addition, it will also assess the effect of the compound on other serious outcomes.

This study will be executed in compliance with the protocol, International Conference on Harmonization (ICH) guideline on good clinical practice (GCP), and applicable regulatory requirements.

6. Objectives

6.1. Primary Objective

The primary objective is to test the hypothesis that a once-weekly injection of 1.5-mg dulaglutide reduces the occurrence of the composite primary endpoint of death from cardiovascular (CV) causes, nonfatal myocardial infarction (MI), or nonfatal stroke when added to glucose-lowering regimen of patients with type 2 diabetes, compared to the addition of a once-weekly placebo injection.

6.2. Secondary Objectives

6.2.1. Efficacy Objectives

The secondary efficacy objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the occurrence of:

- the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy, or anti-vascular endothelial growth factor (anti-VEGF) therapy; development of clinical proteinuria, a 30% decline in estimated glomerular filtration rate (eGFR), or need for chronic renal replacement therapy
- hospitalization for unstable angina
- each component of the composite primary endpoint
- all-cause mortality
- heart failure (HF) requiring hospitalization or an urgent HF visit

6.2.2. Prespecified Safety Objectives (AEs of Special Interest)

The prespecified safety objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the incidence of:

- acute pancreatitis
- serious gastrointestinal events
- any cancer (excluding basal or squamous cell skin cancer) and specific categories of
    - pancreatic cancer
    - medullary thyroid carcinoma (MTC) and C-cell hyperplasia
    - thyroid carcinomas
- severe hypoglycemia
- immune mediated reactions including serious allergic and hypersensitivity reactions
- serious hepatic events

- clinically significant supraventricular arrhythmias and cardiovascular conduction disorders
- serious renal events
- discontinuation of study drug for any reason

6.3. Additional Objectives

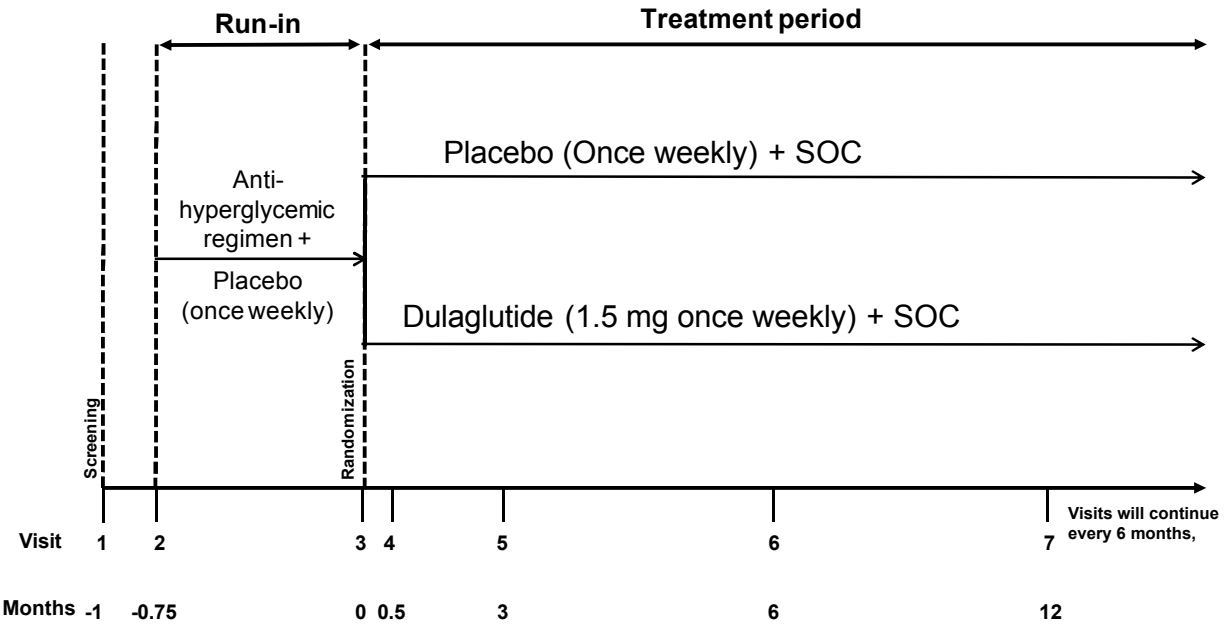
The additional objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the following:

- hemoglobin A1c (HbA1c) levels
- weight
- waist/hip ratio
- the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
- coronary, carotid, or peripheral revascularizations, individually and compositely
- any hospitalization
- cognitive function as measured by the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST)
- erectile function using the International Index of Erectile Function Questionnaire (IIEF)
- any fracture
- development of cholelithiasis

7. Investigational Plan

7.1. Summary of Study Design

The REWIND trial is a Phase 3, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group trial.



Study drug should be dispensed every 3 months. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available onsite, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug.

Abbreviation: SOC = standard of care for type 2 diabetes management.

Figure GBDJ.1. REWIND trial design.

This study will assess the effect of once-weekly dulaglutide compared to placebo on major adverse CV events in patients with type 2 diabetes when added to their existing antihyperglycemic regimen. Patients 50 years of age or older who have type 2 diabetes treated with various antihyperglycemic regimens; have an HbA1c value ≤9.5% at screening; and have either established CV disease, documented subclinical CV disease, or multiple CV risk factors will be eligible to participate in this trial. All eligible patients will participate in a single-blind placebo run-in period. Patients who are adherent to study drug during the run-in period will be randomized in a 1:1 ratio to either 1.5-mg dulaglutide or placebo, injected subcutaneously once weekly (Figure GBDJ.1). After randomization, patients will be followed for CV outcomes and other measures at 2 weeks, 3 months, 6 months, and then followed at approximately 6 months thereafter. Management of glycemic control will be at the discretion of the study investigator and informed by current guidelines and routine patient management (Section 9.5.2). Either the study investigator or the patient's usual physician(s) will manage other CV risk factors and comorbid conditions (depending on local arrangements). The primary analysis of this study

is an intent-to-treat analysis; therefore, every randomized patient will be followed until death or study end regardless of adherence to study drug.

Approximately 9600 patients will be enrolled at approximately 480 sites globally and randomized to 1 of 2 treatment groups: 1.5-mg dulaglutide or placebo. Patients will be followed until approximately 1200 patients experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after a minimum of 5.6 years and an average of approximately 6.5 years of follow-up on all patients, unless the trial is stopped early on the basis of an independent data monitoring committee (IDMC) safety review or the interim analysis.

Section 10 contains a discussion of specific study measures. Details regarding the study procedures at each visit are presented in the Study Schedule Attachment 1). A treatment duration of approximately 84 months (Visit 19) is planned but, if required, additional visits may occur beyond 84 months. These additional follow-up visits will occur in 6-month intervals (semiannually and annually). Activities for these visits will alternate between schedules for the Extended Follow-Up Visit a (EVa) for semiannual visits and the Extended Follow-Up Visit b (EVb) for annual visits (Attachment 1). Study drug dispensing will occur at every scheduled clinic visit (Attachment 1) except for Visit 4 and the Final Visit. Additional study drug-dispensing visits should occur at 3-month intervals between scheduled clinic visits (Attachment 2). At the investigator's discretion, and after confirming sufficient non-expiring study drug is available onsite, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug.

7.1.1. Screening (Visit 1)

After signing the informed consent form (ICF) and receiving a patient number from the interactive voice-response system (IVRS), patients will provide details of their medical history, undergo a physical examination, have vital sign and anthropomorphic measurements recorded, and provide samples for laboratory tests, as outlined in the Study Schedule (Attachment 1). A pregnancy test for women of childbearing potential and all laboratory tests, except calcitonin, will be performed locally. Calcitonin will be measured by the central laboratory. Preexisting conditions and concomitant medication information will be collected. Patients should continue on their antihyperglycemic regimen until study eligibility is confirmed.

Patients who are eligible (Sections 8.1 and 8.2) will proceed to Visit 2. If a patient is not eligible for the trial after the initial screen and is willing to participate, the patient may be re-screened on one occasion. The re-screen visit should be conducted 6 or more weeks after Visit 1. All other patients who do not meet eligibility criteria and do not wish to undergo re-screening will not participate further.

7.1.2. Run-In Period (Visit 2)

For eligible patients proceeding on to Visit 2, vital signs will be measured and lifestyle interventions (for example, diet and exercise) will be reviewed.

The single-blind placebo run-in period will commence at this visit. All patients will receive placebo and will be instructed on how to inject study drug. Patients may be observed injecting

the first dose of study medication (the entire solution in the prefilled syringe) under the supervision of the site personnel. Per the Study Schedule (Attachment 1), patients will be given sufficient study drug and will be instructed to inject study drug once-weekly subcutaneously, on the same day at approximately the same time each week (based on the patient preference), until the next study visit (Visit 3) and to return unused study drug at the next visit. Adherence to study drug will be emphasized. Patients should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering the study medication. Patients should be advised about the appropriate course of action in the event that study drug is not taken at the required time (see Section 9.5.1). Used syringes should be placed in the sharp items container provided to patients.

Patients will be instructed to remain on their antihyperglycemic therapy (Section 9.5.2.1) with the exception of patients taking a DPP-IV inhibitor or GLP-1 receptor agonist at screening, who must discontinue these therapies at the start of the run-in period.

7.1.3. Randomization (Visit 3)

Patients who are adherent to study drug during the run-in period and who still meet eligibility criteria will be randomized, while those not adherent to study drug during the run-in will not participate further.

For patients who remain eligible to be randomized, vital signs and waist and hip circumference will be measured, an electrocardiogram (ECG) will be recorded, and samples will be collected as outlined in the Study Schedule (Attachment 1). Laboratory samples that need to be drawn fasting should be drawn after an 8-hour fasting period. Patients will be administered the cognitive function tests (that is, MoCA and DSST); men will complete the erectile function questionnaire (that is, IIEF). Concomitant medications, preexisting conditions, AEs, injection instructions, and adherence to study drug and lifestyle interventions will be reviewed.

Patients will be instructed to remain on their antihyperglycemic therapy except where adjustments may be needed to minimize the risk of hypoglycemia (Section 9.5.2.1.1). If the screening HbA1c value is <7.0% and if the patient is taking insulin, a sulfonylurea or a meglitinide, the total daily dose of insulin may be reduced by 15%, the total daily dose of sulfonylurea may be reduced by 1 dose level, and the mealtime dose of meglitinide may be reduced by 1 dose level or discontinued.

Patients will be randomized to 1 of the following treatment arms:

1) placebo: once-weekly subcutaneous placebo injection

2) dulaglutide: once-weekly subcutaneous dulaglutide (1.5 mg) injection

Patients will be instructed to inject study drug, on the same day at approximately the same time, each week (that is, to continue on the same schedule used during the run-in period). Patients should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering the study medication. Patients should be advised about the appropriate course of action in the event that study drug is not taken at the required time (see

Section 9.5.1). Used syringes should be placed in the sharp items container provided to patients. Adherence to study drug will be emphasized.

Self-monitored blood glucose (SMBG) testing supplies will be dispensed, the measurement technique will be reviewed, and patients will be advised regarding the frequency of SMBG testing according to their other medications and the investigator's clinical judgment.

7.1.4. Treatment Period (Visit 4 and Beyond)

Visit 4 will occur 2 weeks, Visit 5 at 3 months, and Visit 6 at 6 months after randomization; subsequent study visits will occur approximately every 6 months thereafter until study closure. Study drug dispensing should occur approximately every 3 months after randomization. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug.

Study procedures are those outlined in the Study Schedule (Attachment 1).

At all post-randomization visits, concomitant medications, AEs, and adherence to study drug and lifestyle interventions will be reviewed. New endpoint events (for example, CV events) will be collected and recorded. Vital signs will be measured. Self-monitored blood glucose testing supplies will be dispensed. Injection instructions will be reviewed, if needed.

Electrocardiograms will be recorded and weight measurements will be obtained every 12 months and at the final visit. Height and waist and hip circumference will be measured every 24 months and at the final visit. Samples for laboratory tests will be collected as outlined in the Study Schedule (Attachment 1). Laboratory samples that need to be drawn fasting should be drawn after an 8-hour fasting period. Calcitonin will be measured by the central laboratory. All other laboratory tests will be performed locally, including additional pregnancy tests for women of childbearing potential. Patients will be administered the cognitive function tests (that is, MoCA and DSST) and men will complete the erectile function questionnaire (that is, IIEF) at Visits 3, 9, 15, and the final visit as scheduled (Attachment 1).

Management of glycemic control will be at the discretion of the study investigator and will be informed by current guidelines and/or local standards of medical care (Section 9.5.2). The investigator may increase or reduce the dose of existing glucose-lowering therapies, or add or remove other glucose-lowering therapies (with the exception of a GLP-1 receptor agonist or pramlintide) to maintain acceptable glycemia control and to reduce hypoglycemic episodes. Either the study investigator or the patient's usual physician(s) will manage other CV risk factors and comorbid conditions (depending on local arrangements).

Patients who are unable to tolerate study drug may discontinue the drug temporarily (Section 8.3.2). If study drug is temporarily discontinued, re-challenge should be attempted as soon as it is safe to do so and if this is deemed appropriate in the judgment of the investigator. In select circumstances, study drug may need to be permanently discontinued (Section 8.3.3). Regardless of whether or not participants continue to take study drug, they will continue to be followed for AEs and endpoints. The primary analysis of this study is an intent-to-treat analysis;

therefore, every randomized patient will be followed until death or study end, regardless of adherence to study drug. Thus, every attempt will be made to encourage all patients to come for their study visits regardless of study drug adherence.

7.1.4.1. Additional Study Drug Dispensing Visits

Study drug will be dispensed at Visit 2, at randomization (Visit 3), and should be dispensed every 3 months thereafter. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug. Study drug will be dispensed at clinic visits as per the Study Schedule (Attachment 1) and in between clinic visits (Attachment 2). Sites will access (starting February 2015) IWRS to assign study drug. Patients will be instructed to inject study drug subcutaneously once weekly on the same day at approximately the same time each week. Patients should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering the study medication. Patients should be advised about the appropriate course of action in the event that study drug is not taken at the required time (see Section 9.5.1). Unused prefilled syringes will be returned at each visit (that is, scheduled clinic visit or study drug dispensing visit) to assess study drug adherence and for drug accountability at all visits; the only exception to this will be that study drug dispensed at Visit 3 will be returned at Visit 5 (that is, unused study drug will not be returned at Visit 4). Used syringes should be placed in the sharp items container provided to patients. The sharp items container should be returned when full or sooner, if appropriate.

7.1.5. Final Visit

When the number of adjudicated primary endpoint events has occurred, a final visit will be conducted for each patient. Study procedures for the final visit will be performed as outlined in the Study Schedule whenever possible (Attachment 1). At a minimum, vital status must be ascertained for all randomized study participants. All study drug (unused and used syringes) must be returned for adherence and final drug accountability, along with the sharp items container. Investigators should make every effort to contact all patients who are lost to follow-up to ascertain health status by contacting them, their family members, and/or their personal physicians, or by searching national registers or death indices, where permissible by law.

7.1.6. Missed Study Visit(s)

Every attempt should be made to encourage all patients to attend all study visits regardless of study drug adherence. In the event a study visit (ie, a scheduled clinic visit or a study drug dispensing visit) is missed, the site should attempt to contact the patient and have the patient return for the missed study visit. Study visits should resume in accordance with the Study Schedule (Attachment 1 and Attachment 2).

In the event a patient on study drug is unable to return to the site for the next planned study visit, the site should confirm a sufficient supply of study drug is available at their site and notify the sponsor of their request to dispense a 6-month supply of study drug to the patient. The site should consider alternatives for conducting the potentially missed visit, including through

telephone contact, and attempt to collect and record as much visit information as possible according to the Study Schedule (Attachment 1).

7.2. Study Operations and Medical Oversight

The international steering committee (SC) will be responsible for the overall scientific conduct of the study and all scientific trial-related decisions, and will assist with local issues to support the implementation and good conduct of the study worldwide. The SC will be chaired by the principal investigator and will include as members all national leaders from participating countries, one representative from Lilly, and one representative from the CRO. The Lilly and CRO representatives will be nonvoting members. The operations committee is a subset of the SC led by the principal investigator. This committee is responsible for finalizing the trial design and for addressing trial specific issues as they arise and that may need consideration by the entire SC.

An IDMC will be responsible for monitoring patient safety throughout the study and review of interim analyses. The SC and the IDMC will monitor the proportion of patients who meet the primary endpoint and may recommend modifications to the protocol and the eligibility criteria. An independent clinical endpoint committee (CEC) will adjudicate CV events, pancreatitis events, thyroid evaluations that result in a biopsy or thyroidectomy, and all deaths.

Lilly will assign the obligation of study operation management to a contract research organization (CRO). CCI [redacted] Medical oversight will be the responsibility of Lilly and the CRO. The CRO will be responsible for addressing medical and study operational questions. All participating investigators and site staff will be provided the CRO contact information and instructed to direct all calls to the CRO as the primary point of contact. The CRO will triage calls and direct investigators and site staff as appropriate. The Lilly clinical research physician will be consulted as necessary. Throughout the study, the CRO will maintain call logs where all issues and resolutions will be documented when a site is assisted.

7.3. Discussion of Design and Control

The objective of this trial is to determine whether the addition of the once-weekly GLP-1 receptor agonist dulaglutide to the diabetes regimen of patients with type 2 diabetes and high CV risk reduces major adverse CV and other serious outcomes. This is a multicenter, international, randomized, double-blind, placebo-controlled trial that will recruit patients 50 years of age or older with type 2 diabetes treated with various antihyperglycemic regimens who have either known clinical or subclinical CV disease or multiple CV risk factors.

A single-blind placebo run-in period will test a prospective patient's behavior and willingness to inject study drug on a weekly basis, given that patients will be expected to inject study therapy once weekly for 5 or more years. In this intent-to-treat study, adherence will be critical to assessing the impact of study drug on the natural progression of this chronic illness. Failure to comply with treatment also may have a profound impact on study power. The run-in period should provide a useful assessment of overall adherence to study drug injections.

Approximately 9600 patients will be enrolled and randomized to 1 of 2 treatment groups: 1.5-mg dulaglutide or placebo. Patients will be followed until approximately 1200 patients experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after an average of approximately 6.5 years of follow-up on all patients, unless the trial is stopped early following an IDMC safety review or an interim analysis. Maximum duration of follow-up is dependent upon the primary endpoint event rate. Patients will be followed at approximately 6-month intervals. Management of glycemic control will be at the discretion of the study investigator and will be informed by current guidelines and/or local standards of medical care. The management of blood pressure, lipids, other CV risk factors and comorbid conditions will be at the discretion of the study investigator or the patient's usual physician(s), as informed by current guidelines and the patient's clinical state.

Superiority will be assessed by the reduction in risk of the primary composite endpoint of death from CV causes, nonfatal MI, or nonfatal stroke. This same primary efficacy endpoint was used in the ACCORD study (ACCORD 2008) and in many other studies in CV research (ADVANCE 2008; Duckworth et al. 2009). The CV event rate is assumed to be about 2% annually, based on recently completed trials in patients with type 2 diabetes (ACCORD 2008; ADVANCE 2008). Given this, in order to assess long-term clinical CV outcomes, patients are expected to be followed for between 5 and 8 years; however, the actual duration of the study will depend on the observed CV event rate and time to accrue the number of anticipated primary CV events (approximately 1200). As the primary analysis of this study is an intent-to-treat analysis, every randomized patient will be followed until death or study end. Every attempt will be made to encourage all patients to come for their study visits. The long duration of this trial will also enable a robust assessment of dulaglutide on other measures, including its effects on thyroid C-cell function, microvascular complications, and the incidence of pancreatitis.

8. Study Population

Before entering the study, informed consent must be signed by the study participant according to local rules and regulations. Entered patients who meet the inclusion criteria and do not meet any of the exclusion criteria will proceed to Visit 2. Patients who are adherent to study drug during the run-in period and who continue to be eligible, as assessed by inclusion and exclusion criteria, will be randomized (Visit 3). Patients who are not adherent to study drug during the run-in period will not participate further in the study.

8.1. Inclusion Criteria

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

[1] Men or women with type 2 diabetes based on:

a) a previous diagnosis of type 2 diabetes; or

b) newly detected type 2 diabetes based on the American Diabetes Association criteria (ADA 2011) as either two of the following criteria or one of the following criteria that is confirmed on a second day:

- fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), or
- 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) following a 75-gram oral glucose load, as described by the World Health Organization (WHO 2006), or
- HbA1c ≥6.5% (≥48 mmol/mol)

[2] HbA1c value of ≤9.5% (≤81 mmol/mol) at screening

[3] Are taking:

a) no glucose-lowering drugs; OR

b) 1 or 2 classes of oral glucose-lowering drugs; with or without basal insulin daily [as defined below in (d)]; if one of the oral glucose-lowering drugs is a DPP-IV inhibitor, the patient must be willing to stop the DPP-IV inhibitor after eligibility is confirmed; OR

c) 1 or 2 classes of oral glucose-lowering drugs with a GLP-1 receptor agonist; with or without basal insulin daily [as defined below in (d)]; the patient must be willing to stop the GLP-1 receptor agonist after eligibility is confirmed; OR

d) basal insulin daily defined as 1 to 2 injections per day of either glargine, detemir, neutral protamine Hagedorn (NPH), or another approved basal insulin.

[4] No change in the number or class of glucose-lowering drugs, no change in excess of doubling or halving the dose of these drugs, and if on insulin, no change in the dose of insulin in excess of 20% of the average daily dose, for at least 3 months before screening.

[5] If age ≥50 years and established clinical vascular disease defined as 1 or more of the following:

- a history of MI
- a history of ischemic stroke
- a history of coronary, carotid, or peripheral artery revascularization. If prior coronary artery bypass grafting (CABG), the CABG should have been performed >2 years prior to randomization. If prior carotid or peripheral artery revascularization, the revascularization should have been performed >2 months prior to randomization.
- hospitalization for unstable angina with ECG changes (new or worsening ST or T wave changes), or myocardial ischemia on imaging, or need for percutaneous coronary intervention (PCI);

OR

- If age ≥55 years and subclinical vascular disease defined as 1 or more of the following:
  - a history of myocardial ischemia by a stress test or with cardiac imaging, with or without history of exertional angina
  - >50% vascular stenosis with imaging of the coronary, carotid, or lower extremity arteries, with or without claudication history
  - ankle-brachial index <0.9
  - 2 consecutive values or a documented history of persistent eGFR<60 mL/minute/1.73m^2
  - a history of hypertension with documented LV hypertrophy on an ECG or echocardiogram
  - documented history of persistent microalbuminuria, or macroalbuminuria; or 2 consecutive urine samples demonstrating micro- or macroalbuminuria;

OR

- If age ≥60 years and at least 2 or more of the following risk factors for CV outcomes:
  - current tobacco use (any form of tobacco)
  - use of at least 1 approved lipid modifying therapy to treat hypercholesterolemia or a documented untreated low-density lipoprotein cholesterol (LDL-C) ≥3.4 mmol/L (130 mg/dL) within the past 6 months

- documented treated or untreated high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months
- use of at least 1 blood pressure medication to treat hypertension or untreated systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥95 mmHg
- measured waist-to-hip ratio >1.0 for men and >0.8 for women

[6] Body mass index ≥23 kg/m^2

[7] Adherence to study drug during the run-in period is 100%

[8] In the investigator's opinion, are well-motivated, capable, and willing to self-inject study treatment once weekly, as required for this protocol

[9] Have given written informed consent to participate in this study in accordance with local regulations and Ethical Review Board (ERB) governing the study site

8.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[10] Uncontrolled diabetes requiring immediate therapy (such as diabetic ketoacidosis) at screening or randomization, in the judgment of the physician.

[11] Have experienced a severe hypoglycemic episode within 1 year prior to randomization.

[12] Have experienced an acute coronary or cerebrovascular event within 2 months prior to randomization.

[13] Are currently planning a coronary, carotid, or peripheral artery revascularization.

[14] Have known chronic renal failure (defined as a known eGFR <15 mL/minute/1.73m^2) or are on chronic dialysis at screening.

[15] Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (such as bariatric) surgery.

[16] Have a past history of chronic, acute, or idiopathic pancreatitis or signs/symptoms of pancreatitis.

[17] Have severe hepatic dysfunction such as portal hypertension or cirrhosis, acute or chronic hepatitis, signs or symptoms of any other liver disease, or an alanine transaminase (ALT) level ≥3.0 times the upper limit of normal (ULN) for the reference range at screening.

[18] Have a) any self or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial or part of multiple endocrine neoplasia MEN 2A or 2B syndrome), or

b) any known self or family history of type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) in the absence of known C-cell hyperplasia. This includes patients with a family history of MEN 2A or 2B whose family history for the syndrome is RET negative. The only exception for this exclusion will be patients whose family members with MEN 2A or 2B have a known RET mutation and the potential patient for the study is negative for that RET mutation.

[19] Have a calcitonin value ≥20 pg/mL according to the central laboratory measurement at screening.

[20] Are previous organ transplant recipients or are awaiting an organ transplant (corneal transplants [keratoplasty] are allowed).

[21] Are taking a weight loss drug (over-the-counter or prescription) and are unwilling or unable to discontinue the drug at the time of screening or are taking pramlintide at the time of screening.

[22] History of, an active, or untreated malignancy, in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years prior to, or are receiving or planning to receive therapy for cancer, at screening.

[23] Females who are pregnant or have a positive pregnancy test at screening, or who have given birth within the past 90 days, or who are breastfeeding.

[24] Females of childbearing potential (that is, females who are between menarche and less than 1-year past the last menses with an intact uterus) who do not agree to use a reliable method of birth control during the study and for 1 month following the last dose of study drug. Menopause is the absence of menses for ≥1 year and/or surgically or chemically induced.

[25] Are medically unstable with life expectancy <1 year.

[26] Are unwilling to permit sites to contact their primary physician to communicate information about the study and the patient's data.

[27] In the judgment of the investigator, have any other condition likely to limit protocol compliance or reporting of AEs (for example, conditions such as alcoholism, mental illness, drug dependence, or not having access to a refrigerator to store study drug).

[28] Are currently enrolled in, or discontinued within the last 30 days from a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or intend to participate in another clinical trial while participating in this study.

[29] Have previously completed or withdrawn from any study investigating dulaglutide (LY2189265).

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

[31] Are Lilly employees or employees of the CRO involved in the study.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [10] may indicate severe insulin deficiency, which may require intense insulin therapy, or the presence of serious comorbidities.

Exclusion Criterion [11] may be an AE reflective of intensive glycemic management, or may have severe sequelae for the patient, and the impact of severe hypoglycemia on CV morbidity and mortality remains to be determined.

Exclusion Criteria [12] and [13] exclude patients with recent serious CV events who may be unstable and are at high risk of repeated events, which may confound interpretation of the results. Also, these patients may not be able to comply with the requirements of the protocol.

Exclusion Criterion [14] excludes patients with severe renal impairment because the effect of dulaglutide in patients with this condition has not been well characterized .

Exclusion Criterion [15] excludes patients with known clinically significant gastric emptying abnormalities or prior gastric bypass surgery as the effect of dulaglutide on these conditions is not known.

Exclusion Criterion [16] excludes patients with acute or chronic pancreatitis or signs/symptoms of pancreatitis because the effect of dulaglutide on these conditions is not known.

Exclusion Criterion [17] excludes patients with impaired hepatic function because the effect of dulaglutide in patients with this condition has not been well characterized.

Exclusion Criterion [18] excludes patients with a personal or family history of medullary C-cell cancer, other C-cell disorders, related endocrine conditions, or certain genetic risk factors to avoid confounding the outcome of the assessment of thyroid safety in individuals treated with dulaglutide.

Exclusion Criterion [19] excludes patients with a higher likelihood of having C-cell abnormalities, because their participation in the trial may confound the assessment of thyroid safety.

Exclusion Criterion [21] excludes patients who have taken drugs that could confound the efficacy and safety results observed for dulaglutide in this study.

Exclusion Criteria [20], [22], and [25] include clinical conditions that may prevent patients from completing the protocol or require use of medications that have not been studied in concomitant use with study treatment.

Exclusion Criteria [23] and [24] exclude female patients who are pregnant, breastfeeding, or of childbearing potential who refuse to use a reliable method of birth control, since effects of dulaglutide on human fetal development are unknown.

Exclusion Criterion [26] ensures open communication between the investigative site and the patient's primary physician to ensure continuity of care and receipt of appropriate standard for medical care.

Exclusion Criterion [27] allows investigators to exclude patients who meet all other inclusion and exclusion criteria, but may not be appropriate study candidates for other obvious reasons.

Exclusion Criterion [28] eliminates drugs that cannot be mapped to a standard drug dictionary, or for which little data are known to analyze the potential relationship of AEs or drug interactions.

Exclusion Criterion [29] prevents situations in which potential positive or negative outcomes may not be clearly attributable to dulaglutide, and excludes patients who have been randomized in studies with dulaglutide, in order to accurately represent the safety profile of the drug.

Exclusion Criteria [30] and [31] reduce the potential bias that may be introduced at the study site.

8.3. Discontinuations

8.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. In the rare case where a patient who does not meet enrollment criteria is inadvertently enrolled, the CRO should be contacted within 1 business day. The CRO will discuss with the Lilly clinical research physician who will engage the leadership of the SC, if needed.

A patient who does not meet enrollment criteria and is inadvertently enrolled in the study may continue in the study if the following 2 criteria are met:

a. In the opinion of the investigator and the CRO physician responsible for the study, there are no safety concerns which would prohibit continuance.

b. The CRO physician responsible for the study and the investigator determine it is acceptable for a patient to continue in the study with or without receiving investigational product.

If it is determined that, in considering patient safety, it is appropriate to continue study drug (documentation of this is necessary), the patient will continue on study drug and be monitored for all visits and testing for the duration of the study. If after discussion, it is determined that the

patient should not continue study drug due to safety concerns, study drug will be discontinued, but the patient will remain in the study to be evaluated for efficacy and safety endpoints and be monitored for all visits and testing for the duration of the study.

Patients will be discontinued from the study if the investigator or Lilly stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.

8.3.2. Temporary Discontinuation of Study Drug

After randomization, the investigator may need to temporarily discontinue study drug, for example, due to an AE or a clinically significant laboratory value. If study drug discontinuation is due to an AE, the event is to be followed according to the procedures in Section 10.2 of this protocol and documented. Investigators should inform the CRO that study drug has been temporarily discontinued. Every effort should be made by the investigator to maintain patients on study drug and to restart study drug promptly after any temporary discontinuation, as soon as it is safe to do so. The patient will remain in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and testing. The dates of study drug discontinuation and restart will be documented.

If a woman of childbearing potential becomes pregnant after randomization, study drug should be temporarily discontinued. The patient will remain in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and testing. Study drug may be resumed after the pregnancy but not until it is safe to do so.

8.3.3. Permanent Discontinuation of Study Drug

It may be necessary for a patient to permanently discontinue study drug. Investigators should contact the CRO prior to permanent study drug discontinuation. The date of study drug discontinuation will be documented.

Patients who permanently discontinue study drug prior to completing the study will remain in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and testing. If a patient is unwilling or unable to return for future study visits, the site should attempt to collect as much visit information as possible, including through telephone contact, contact with the family or the patient's primary physician, or by searching national registers or deaths indices where permissible by law.

If study drug discontinuation is due to an AE, the event is to be followed according to the procedures in Section 10.2 of this protocol and documented.

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

- 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, and the patient refuses to immediately discontinue from the other clinical trial or medical research.

- The patient's attending physician or the CRO physician requests that the patient permanently stops study drug.
- The patient was inadvertently randomized and, in the opinion of the investigator or the CRO physician, continuation of study drug is not advisable due to safety concerns.
- A patient requires chronic renal replacement therapy (that is, chronic dialysis or renal transplantation).
- A patient is diagnosed with acute or chronic pancreatitis (see Section 10.2.2.1 for criteria to diagnosis acute pancreatitis).
- If after randomization, a patient is observed to have an elevated calcitonin value as described in Section 10.2.2.3.3.1.
- If after randomization, a patient is diagnosed with C-cell hyperplasia or medullary thyroid carcinoma (MTC).
- If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study drug and the CRO must be notified within one business day.

8.3.4. Discontinuation of Study Sites

Study site participation may be discontinued if the SC, Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice. Every effort will be made to redirect the patients to another study site.

8.3.5. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice. The SC and the IDMC will review and comment on any decision regarding study discontinuation before the decision is finalized.

9. Treatment

9.1. Treatments Administered

This study involves a comparison of 1.5-mg dulaglutide administered subcutaneously once weekly with a subcutaneous, once-weekly injection of placebo when added to a patient's existing antihyperglycemic regimen. The investigator or his/her designee is responsible for explaining the correct use of the investigational agent to the patient, verifying that injection instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

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

9.2. Materials and Supplies

The sponsor will provide the study drug, sharp items containers, and blood glucose monitoring supplies.

Study drug (dulaglutide or placebo) will be provided as a clear liquid in prefilled syringes. The syringes should be kept refrigerated (not frozen) until use at 2ºC to 8ºC and should be left at room temperature for 10 to 15 minutes before injection. Dry ice should not be used for cooling study drug. Patients will be provided with a carton of prefilled syringes at Visit 2, at clinic visits, and at study drug dispensing visits as outlined in the Study Schedule (Attachment 1 and Attachment 2). Patients will be instructed to return any unused study drug at the next study visit. Used syringes should be disposed of in the sharp items container and the container should be returned to the site when full or sooner if needed.

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

Patients will be provided a commercially available blood glucose meter and test strips for use during the study. An adequate supply of blood glucose testing materials will be dispensed at each visit.

Study personnel will review that the patient is correctly administering the assigned study drug, storing the study drug according to the provided instructions, and is able to use a glucose meter.

9.3. Method of Assignment to Treatment

After the ICF is signed and dated, a patient is considered "entered" in the study and will be assigned a patient number by the IVRS. Entered patients who meet all eligibility criteria will proceed to Visit 2. At Visit 2, all patients will receive placebo for the single-blind run-in period. Patients who are adherent to study drug during the run-in period and who continue to meet all inclusion criteria and no exclusion criteria will proceed to Visit 3 for randomization. Patients

will be randomized to one of 2 treatment groups (1.5 mg dulaglutide or placebo) following a 1:1 ratio according to a computer-generated random sequence using an IVRS. Randomization will be stratified by site.

9.4. Rationale for Selection of Doses in the Study

Two doses of once-weekly dulaglutide (0.75- and 1.5-mg) administered subcutaneously were evaluated in Phase 3 registration studies. This trial will investigate the high dose of dulaglutide (1.5 mg) so as to detect both the CV benefits and risks of the dose with greater pharmacological activity.

9.5. Selection and Timing of Doses

9.5.1. Study Drug (Placebo and Dulaglutide)

Patients in the dulaglutide and placebo treatment groups will inject subcutaneously the entire solution in the prefilled syringe, once each week, in the skin fold of the left or right abdominal wall. Study drug should be injected at approximately the same time of the same day each week. A new prefilled syringe must be used for each injection. Used syringes should be discarded in the sharp items container.

If the weekly injection is not given on the scheduled day, the missed dose should be given as soon as possible after the scheduled day if there are at least 3 days (72 hours) until the next scheduled injection. If less than 3 days remain before the next scheduled injection, the missed dose should be skipped and the next regularly scheduled dose should be given at the usual time and day.

9.5.2. Special Treatment Considerations

9.5.2.1. Standards of Medical Care for Diabetes

Patients should remain on their antihyperglycemic regimen unless adjustments are needed to attain HbA1c goals, or due to frequent hypoglycemic episodes.

The investigator is responsible for managing the patient's diabetes. Maintenance of adequate glycemic control in study participants should not be compromised because of participation in the trial. Investigators and other study team members are expected to treat patients according to the standards of medical care for diabetes established nationally (in respective participating countries) or internationally.

It is important that investigative sites educate patients, and their caregivers if applicable, about the signs and symptoms of hyperglycemia and hypoglycemia. Patients should be instructed how to monitor their blood sugars and on the appropriate frequency of performing blood glucose testing based on the concomitant antihyperglycemic medication and clinical judgment.

9.5.2.1.1. Minimizing the Risk of Hypoglycemia

Investigative sites are to educate patients about the detection of hypoglycemia (for example, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep,

or transient neurological disorders), factors that may increase the risk of hypoglycemia (for example, dietary changes or physical activity), and treatment of hypoglycemia. If a patient experiences hypoglycemic episodes after randomization, the investigator may reduce the dose of or withdraw any concomitant antihyperglycemic medications at their discretion.

9.5.2.1.2. Management of Hyperglycemia

Investigative sites are to educate patients on the detection of hyperglycemia (for example, severe thirst, dry mouth, frequent micturition, dry skin) and factors that may increase the risk of hyperglycemia (for example, dietary changes).

Additional therapeutic intervention may be considered (with the exception of a GLP-1 receptor agonist or pramlintide) in patients who do not attain target HbA1c values and/or develop severe hyperglycemia, despite full compliance with the assigned study treatment regimen. These changes may be instituted 3 months after randomization to enable the effects of study drug on HbA1c to stabilize, unless sooner intervention is indicated, in the judgment of the investigator. Patients should continue to inject their allocated study drug and will remain in the study.

9.5.2.1.3. Management of Diabetes Complications and Cardiovascular Risk Factors

Either the study investigator or the participant's usual physician(s) will manage other CV risk factors and comorbid conditions (depending on local arrangements) according to local standards of care. Use of weight loss drugs (over-the-counter or prescription) will be prohibited.

9.6. Continued Access to Study Drug

Study treatment will be stopped after patients have finished the active treatment period or permanently discontinued study treatment early, after which an appropriate diabetes treatment regimen for the patient will be initiated by the investigator. The study sponsor will not provide the patients with an ongoing supply of study drug after the patients have stopped their study treatment. Other effective therapies are available that may be prescribed for patients with type 2 diabetes.

9.7. Blinding

The run-in period is single-blind and the treatment period is double-blind. To preserve the blinding of the study, a minimum number of Lilly IVRS/IWRS personnel or designated clinical trial material personnel will see the randomization table and treatment assignments before the study is complete. However, all personnel involved with the study, including the SC, all investigators, all Lilly personnel (excluding those referenced above) and all CRO personnel, and anyone other than those people charged with assuring the safety of the trial (such as, the IDMC) and drug will be blinded to all post-randomization data by treatment group.

Emergency unblinding for AEs may be performed through an IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS/IWRS.

The investigator should make every effort to contact the CRO physician prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, the CRO must be notified within 1 business day.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must permanently discontinue study drug (see Section 8.3.3), but should be continued in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and testing.

9.8. Concomitant Therapy

Concomitant therapies that are part of routine medical care are allowed and can be used during the study. GLP-1 receptor agonists, pramlintide, or weight loss drugs (over-the-counter or prescription) are not allowed. Concomitant medications will be recorded only for randomized patients.

Investigative staff will inform each patient that they must consult with the investigator or a designated site staff member upon taking any newly prescribed medications. Any additional medication initiated during the course of the study (including over-the-counter drugs such as paracetamol or aspirin) must be documented.

9.9. Treatment Adherence

The investigator will assess study drug compliance at each visit by reviewing study drug injection information provided by the patient.

Treatment adherence will be assessed for each visit interval. Study drug adherence will be calculated at each visit after randomization when study drug is dispensed and will be based on the percentage of syringes used. Specifically, it will be calculated as follows:

Study drug adherence for each visit = [(number of syringes dispensed – number of syringes returned) / (number of weeks between the 2 consecutive visits)]*100%.

A patient will be considered adherent for each visit interval if he/she uses at least 75% of the study drug syringes dispensed for that interval.

In addition, the overall adherence during the study will be calculated for each patient. This will be calculated by taking the number of visits the patient was adherent divided by the total number of visits for which information about adherence was known.

Any instances of overdose will be documented and summarized. Study drug overdose is defined as injection of study drug more than one time in any three calendar days

Documented overdose will be reported as a TEAE and will be summarized (Section 12.2.9.1).

Patients considered poorly adherent with study medication and/or the study procedures should receive additional training and instructions.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing are summarized in the REWIND Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

The primary efficacy measure is the time to first occurrence (after randomization) of the composite of death from CV causes, nonfatal MI, or nonfatal stroke.

An independent CEC will adjudicate all primary endpoint events. The CEC Charter will contain the final detailed event definitions used for adjudication; however, high-level definitions of each primary endpoint event are provided below.

1) **Death from CV Causes** will be defined as a death resulting from an acute MI, sudden cardiac death, death due to HF, death due to stroke, and death due to other CV causes. All cases in which the cause of death cannot be determined (that is, undetermined) will be included in deaths from CV causes.

2) **Myocardial Infarction (MI):** The term myocardial infarction will be used when there is evidence of myocardial necrosis (that is, changes in cardiac biomarkers or post mortem pathological findings) in a clinical setting consistent with myocardial ischemia. The endpoint of MI will include the following subtypes: spontaneous MI, percutaneous coronary intervention (PCI) related MI, coronary artery bypass grafting (CABG) related MI, and silent MI.

3) **Stroke** will be defined as an acute episode of neurological dysfunction caused by a focal or global brain, spinal cord, or retinal vascular injury. Strokes will be classified as ischemic, hemorrhagic, or undetermined. Stroke disability, as measured using the modified Rankin scale, will be assessed at approximately 30 days after the diagnosis.

   A transient ischemic attack (TIA) will be defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, *without* acute infarction. TIA events must also be reported by sites and will be adjudicated by the CEC to determine if any such events meet criteria for a stroke.

All potential or suspected primary endpoint events must be reported to the CRO as soon as (for example, within 2 business days) the site staff learns of the clinical event. Study sites should send the requested source documentation to the CEC in a timely fashion for adjudication of the event.

10.1.2. Secondary Efficacy Measures

Secondary efficacy measures include time (after randomization) to:

- first occurrence of the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy, or anti-VEGF therapy; development of clinical proteinuria, a 30% decline in estimated glomerular filtration rate (eGFR), or need for chronic renal replacement therapy
- first hospitalization for unstable angina
- first occurrence of each component of the composite primary endpoint
- death
- first occurrence of heart failure (HF) requiring hospitalization or an urgent HF visit

The independent CEC will adjudicate all deaths and hospitalizations for HF or unstable angina. The CEC Charter will contain the final detailed event definitions used for adjudication; however, high-level definitions for these endpoints are provided below.

1) **All Cause Mortality** will be defined as deaths from CV causes, deaths from non-CV causes (for example, pulmonary, renal, etc.) and deaths not attributable to a CV or non-CV cause (that is, undetermined).
2) **Heart failure (HF) requiring hospitalization** will be defined as new or worsening clinical symptoms and physical signs of HF that require hospitalization for additional/increased therapy. An **urgent HF visit** will be defined as an urgent, unscheduled office/practice or emergency department visit (requires clinical signs and symptoms of HF and need for additional/increased therapy).
3) **Hospitalization for unstable angina** will be defined as clinical symptoms of myocardial ischemia (new or worsening) that necessitates hospitalization and one of the following: new or worsening ST or T wave changes on ECG, evidence of myocardial ischemia on imaging, angiographic evidence of a lesion in a coronary artery responsible for symptoms, need for coronary revascularization procedure (PCI or CABG) during the hospitalization; AND no evidence of an acute MI.

All potential or suspected endpoint events must be reported to the CRO as soon as (for example, within 2 business days) the site staff learns of the clinical event. Study sites should send the requested source documentation to the CEC in a timely fashion for adjudication of the event.

For the composite microvascular endpoint, the following definitions will apply:

1) **Diabetic retinopathy requiring laser therapy** will be defined as use of laser therapy (photocoagulation) for the treatment of diabetic retinopathy.
2) **Vitrectomy** for the treatment of diabetic retinopathy will be defined as a surgical procedure to remove the vitreous gel from the inside of the eye, and silicone gas, oil or other fluid is injected to fill the space the vitreous once occupied.
3) **Anti-VEGF therapy** for the treatment of diabetic retinopathy will be defined as an intravitreal injection(s) of an anti-VEGF agent for the treatment of diabetic retinopathy.

4) **Clinical proteinuria (macroalbuminuria)** will be defined as an albumin-creatinine ratio (ACR) >300 mg/g (>33.9 mg/mmol).
5) **Renal replacement therapy (RRT)** will be defined as chronic hemodialysis or peritoneal dialysis used as maintenance therapy in patients with end stage renal disease (ESRD), or renal transplantation.
6) **A sustained 30% decline in eGFR** will be based on a 30% reduction from the baseline value (Visit 3) in 2 consecutive calculations of post-randomization eGFR, using the MDRD equation.

Events of laser therapy, vitrectomy, anti-VEGF therapy, or RRT will be prospectively collected. Identification of clinical proteinuria will be based on reported laboratory data (and/or calculated if needed) and eGFR will be calculated using reported laboratory (serum creatinine) and clinical data.

10.1.3. Additional Measures

Additional measures include:

- Change from baseline in:
  - hemoglobin A_{1c} levels
  - weight
  - waist/hip ratio
  - cognitive function as measured by the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST)
  - erectile function as measured by the International Index of Erectile Function Questionnaire (IIEF)
- Time to first occurrence of (after randomization):
  - composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
  - coronary, carotid, or peripheral revascularization, individually and compositely
  - any hospitalization
- Incidence of
  - any fracture
  - development of cholelithiasis

10.1.3.1. Cognitive Function

Cognitive function will be assessed using the MoCA and the DSST.

The MoCA is a cognitive screening test designed to detect mild cognitive impairment (Nasreddine et al. 2005). It assesses different cognitive domains: attention and concentration,

executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. It will take approximately 10 minutes to complete the test. The total possible score is 30 points; a score of 26 or above is considered normal.

The DSST is an attention-demanding psychomotor component of the Wechsler Adult Intelligence Scale (Kuo et al. 2007). This test objectively evaluates cognitive function, exploring attention and psychomotor speed. The patient will be given a symbol-digit code in which each of the digits 1 through 9 is paired with a different symbol. Below the code, a series of symbols selected from those in the code is presented in an irregular order. The patient will be instructed to draw the symbol that matches the number and to complete as many correct symbols as possible within a 120-second test period. The DSST score will be calculated as the number of correct symbol-number matches. The number of matches attempted will also be recorded.

10.1.3.2. Erectile Function

Erectile function will be assessed in male patients using the International Index of Erectile Function (IIEF), a 15-item questionnaire. This instrument evaluates 5 domains: erectile function, orgasmic function, sexual desire, overall satisfaction, and intercourse satisfaction (Rosen et al. 2002).

10.1.3.3. Revascularizations

The independent CEC will adjudicate coronary, carotid, and peripheral revascularizations. A **coronary, carotid, or peripheral arterial revascularization** procedure will be defined as a catheter-based or open surgical procedure designed to improve myocardial, carotid, or peripheral arterial blood flow. Insertion of a guide wire through a coronary guide catheter into a coronary artery or bypass graft for the purpose of PCI is considered intention for PCI. The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guide wire through a guide catheter into a peripheral artery. The CEC Charter will contain the final detailed event definitions used for adjudication.

Revascularization events must be reported to the CRO as soon as (for example, within 2 business days) the site staff learns of the clinical event. Study sites should send the requested source documentation to the CEC in a timely fashion for adjudication of the event.

10.1.3.4. Other Measures

A Hospitalization will be defined as a hospital admission (including admission to a chest pain observation unit) or a visit to an emergency department that results in a stay >24 hours.

A Fracture will be defined as a clinically or radiologically apparent fracture of any bone.

Development of cholelithiasis will be defined as any new diagnosis of cholelithiasis after randomization, as evidenced on an imaging examination (for example, ultrasound or computerized tomography scan).

Measurement of **weight** and **waist and hip circumferences** are discussed in Section 10.2.3.2.

10.2. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the CRO 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.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.2.1. Adverse Events (AEs)

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

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

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to the CRO.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to the CRO.

Investigators will be instructed to report to the CRO their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, investigational product, and/or drug delivery system.

Study site personnel must alert the CRO within 1 business day of the investigator's **unblinding** a patient's treatment group assignment for any reason.

Clinically significant findings from ECGs, labs, or vital sign measurements should be reported to the CRO.

If a patient's treatment is temporarily or permanently discontinued as a result of an AE, study site personnel must clearly report to the CRO the circumstances and data leading to any such discontinuation of treatment. Patients who temporarily or permanently discontinue study drug

prior to completing the study will remain in the study to be evaluated for efficacy and safety endpoints (Section 8.3.3).

Events leading to the clinical outcome of death, nonfatal MI, hospitalization for HF or unstable angina, an urgent HF visit, nonfatal stroke, or coronary, carotid, or peripheral revascularizations will be reported as study outcomes, and will not be reported to the CRO as AEs except as noted in Section 10.2.1.1.1.

10.2.1.1. Serious Adverse Events (SAEs)

Serious adverse event (SAE) collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert the CRO of any **serious** adverse event within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes (exceptions noted in Section 10.2.1.1.1):

- death (Note exception; Section 10.2.1.1.1)
- 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 adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs occurring within 30 days of a patient's last visit (defined as the last study visit or phone contact) will be collected, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

10.2.1.1.1. Primary, Secondary, and Additional Study Endpoints Not Considered Adverse Events or Serious Adverse Events

The following primary and secondary efficacy events will not be required to be reported as AEs or SAEs *unless* the investigator believes the event may have been caused by the study drug, drug delivery system, or study procedure:

- death,
- nonfatal MI,
- nonfatal stroke,
- hospitalization for HF or an urgent HF visit,
- hospitalization for unstable angina, or
- coronary, carotid, or peripheral revascularizations

If one of the above endpoint events is reported but does not meet a prespecified event definition detailed in the CEC Charter, as reviewed by the independent CEC, the study site subsequently will be required to report the event as an AE or SAE to comply with regulatory reporting requirements.

10.2.2. Adverse Events of Interest

The incidence of the following adverse events of interest will be evaluated:

- acute pancreatitis
- serious gastrointestinal events
- any cancer (excluding basal or squamous cell skin cancer) and specific categories of
    - pancreatic cancer
    - medullary thyroid carcinoma (MTC) and C-cell hyperplasia
    - thyroid carcinomas
- severe hypoglycemia
- immune mediated reactions including serious allergic and hypersensitivity reactions
- serious hepatic events
- clinically significant supraventricular arrhythmias and cardiovascular conduction disorders
- serious renal events
- discontinuation of study drug for any reason

10.2.2.1. Adverse Event of Interest: Acute Pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

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

Chronic pancreatitis differs from acute pancreatitis in that the primary process is a chronic, irreversible inflammation that leads to fibrosis with calcification. It is characterized by a clinical spectrum that encompasses pain, loss of exocrine pancreatic function, diabetes mellitus, and various complications usually involving organs adjacent to the pancreas (Büchler et al. 2009). The single most frequent symptom of chronic pancreatitis is pain, either intermittent episodes or a more chronic, persistent form.

If a patient experiences severe or serious abdominal pain or if acute/chronic pancreatitis is suspected, administration of study drug should be temporarily discontinued (Section 8.3.2). Appropriate diagnostic tests (such as levels of amylase [total and pancreatic] and/or lipase and/or imaging studies) should be obtained locally according to the judgment of the investigator. If diagnostic testing does not support the diagnosis of acute or chronic pancreatitis, study drug may be resumed as soon as it is safe to do so, in the judgment of the investigator. If diagnostic testing supports the diagnosis of acute or chronic pancreatitis, the patient must permanently discontinue study drug but will remain in the trial (Section 8.3.3) to be evaluated for efficacy and safety endpoints and monitored for all visits and testing. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

The independent CEC will adjudicate all AEs of severe or serious abdominal pain and suspected or definite acute or chronic pancreatitis. The CEC Charter will contain the final detailed event definitions used for adjudication. Study sites should send the requested source documentation to the CEC in a timely fashion for adjudication of the event.

10.2.2.2. Adverse Event of Interest: Serious Gastrointestinal Events

Clinically significant gastrointestinal events and any serious gastrointestinal disease diagnosed after randomization will be prospectively collected during the study.

Patients who develop a clinically significant gastric emptying abnormality (eg, severe diabetic gastroparesis or gastric outlet obstruction) or other serious gastrointestinal disease should be discontinued from study drug.

10.2.2.3. Adverse Event of Interest: Cancers

Any new or recurrent cancer (excluding basal or squamous cell skin cancer) diagnosed after randomization, will be prospectively collected during the study.

10.2.2.3.1. Pancreatic Cancer

Post randomization reports of diagnosed pancreatic cancer will be prospectively collected during the study. Patients diagnosed with pancreatic cancer should be discontinued from study dr ug but

should remain in the trial to be evaluated for efficacy and safety endpoints and monitored for all visits and testing.

10.2.2.3.2. Medullary Thyroid Carcinoma and C-Cell Hyperplasia

Medullary thyroid carcinoma (MTC) presents as part of an autosomal dominant inherited disorder in about 20% to 25% of cases and as a sporadic tumor in the balance of the cases. From the familial cases a progression from C-cell hyperplasia to microcarcinoma and eventually macroscopic carcinoma has been delineated by following calcitonin (Wolfe et al. 1973). Since calcitonin is being monitored, events of MTC and C-cell hyperplasia may be detected at very early stages before these lesions become clinically symptomatic. Physiologic or secondary C-cell hyperplasia with mild elevations of calcitonin may be associated with follicular diseases such as Hashimoto's thyroiditis and follicular neoplasms and with aging, hyperparathyroidism, and hypergastrinemia (Perry et al. 1996; LiVolsi 1997).

If a patient is diagnosed with MTC, the patient must permanently discontinue study drug.

Calcitonin, a 32 amino acid peptide, is excreted primarily by the kidneys and may be elevated in moderate to severe renal dysfunction. Approximately 30% of individuals with renal insufficiency (stage not specified) will have some degree of hypercalcitoninemia due to secondary hormonal stimulation and poor clearance. At any level of renal insufficiency, a nonstimulated calcitonin of ≥40 pg/mL would provide nearly 100% sensitivity for MTC with specificity of approximately 60%.

10.2.2.3.3. Other Thyroid Cancers

Any new or recurrent papillary, follicular or other thyroid cancer diagnosed after randomization, will be prospectively collected during the study. Patients diagnosed with thyroid cancer should be discontinued from study drug but should remain in the trial to be evaluated for efficacy and safety endpoints and monitored for all visits and testing.

10.2.2.3.3.1. Calcitonin Monitoring

Participants in this trial will have measurements of calcitonin taken according to the Study Schedule (Attachment 1). The purpose of calcitonin monitoring is to assess the potential of dulaglutide to affect the thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

10.2.2.3.3.2. Calcitonin Monitoring Algorithm

After randomization, if a patient is observed to have a serum calcitonin >35 pg/mL, a calcitonin measurement must be repeated within 1 month. If the repeat value is <35 pg/mL, the patient may continue in the trial on study drug and will continue to be followed per the Study Schedule (Attachment 1). If the repeat value is confirmed >35 pg/mL, the patient must permanently discontinue study drug. The patient should undergo additional endocrine assessment and longer term follow-up by a thyroidologist or endocrinologist.

Data on patients who are requested to undergo further thyroid assessment either due to the calcitonin algorithm, development of thyroid neoplasms or for any other clinical reason will be

prospectively collected during the study. The independent CEC will adjudicate thyroid evaluations that result in a surgical biopsy of the thyroid gland and/or a thyroidectomy or a diagnosis of a thyroid malignancy or C-cell hyperplasia. The CEC Charter will contain the final detailed event definitions used for adjudication. Study sites should send the requested source documentation to the CEC in a timely fashion for adjudication of the event.

10.2.2.4. Adverse Event of Interest: Severe Hypoglycemia

Investigative sites are responsible to educate patients about the detection of hypoglycemia, the factors that may increase the risk of hypoglycemia, and treatment of hypoglycemia (Section 9.5.2.1.1).

Severe hypoglycemia will be defined as an event with clinical symptoms consistent with hypoglycemia requiring the assistance of another person (that is, patient could not treat himself or herself) to actively administer carbohydrate, glucagon, or other resuscitative measures and one of the following: a) the event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or parenteral glucagon administration; or b) the event was associated with a fingerstick or laboratory plasma glucose level ≤54 mg/dL (≤3 mmol/L).

Severe hypoglycemia events will be collected at each visit and are to be recorded as serious on the Adverse Events CRF (that is, recorded as an SAE).

10.2.2.5. Adverse Event of Interest: Immune-Mediated Reactions and Allergic/Hypersensitivity Reactions

All immune mediated reactions including allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data, such as type of reaction and treatment, will be collected prospectively on any AEs or SAEs that the investigator deems as being related to study drug. Study drug should be temporarily discontinued in any individual suspected of having a severe immune-mediated or severe or serious allergic reaction to study drug (Section 8.3.2). Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator.

10.2.2.6. Adverse Event of Interest: Serious Hepatic Events

Reported cases of serious hepatic dysfunction including acute liver failure or injury occurring in randomized patients will be prospectively collected during the study.

Patients with signs and symptoms of hepatic injury or failure should be evaluated and treated according to local standards of care. Study drug should be temporarily discontinued in any individual suspected of having serious hepatic dysfunction, injury or failure. The investigator should consult with the designated medical monitor before restarting the study drug.

10.2.2.7. Adverse Event of Interest: Clinically Significant Supraventricular Arrhythmias and Cardiovascular Conduction Disorders

All events of supraventricular arrhythmias and cardiovascular conduction disorders will be prospectively collected and evaluated.

Patients who develop supraventricular arrhythmias or cardiovascular conduction disorders should undergo an ECG and diagnostic tests to determine exact diagnosis. The specific diagnosis will be recorded as an AE or SAE. All supraventricular arrhythmias and cardiovascular conduction disorders deemed clinically significant by the investigator will be listed as SAE's. 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.

10.2.2.8. Adverse Event of Interest: Serious Renal Events

Adverse events related to worsening renal function will be prospectively collected and evaluated. Renal events will be categorized according to the following criteria:

- An increase ≥30% above baseline in serum creatinine level reported in two consecutive laboratory results obtained on different days.
- A sustained decline ≥30% from baseline in estimated glomerular filtration rate (eGFR) recorded in two consecutive calculations utilizing the MDRD equation
- Clinical proteinuria (macroalbuminuria) albumin-creatinine ratio (ACR) >300 mg/g (33.9 mg/mmol)
- Progression to end stage renal disease (ESRD), or Requirement for Renal Replacement Therapy or eGFR <15 mL/min/1.73m^2
- Renal transplantation

Patients that develop severe renal insufficiency, ESRD or receive renal transplantation should be discontinued from study drug.

10.2.2.9. Discontinuation of Study Drug for Any Reason

After randomization, the reason for temporary or permanent study drug discontinuation will be recorded. See Section 8.3.2 and Section 8.3.3 for more details. If study drug discontinuation is due to AE, the event is to be documented and followed according to the procedures in Section 10.2.

10.2.3. Other Safety

10.2.3.1. Vital Sign Measurements

Vital signs (heart rate and blood pressure) will be measured in the seated position according to instructions in this section and the Study Schedule (Attachment 1).

Heart Rate and Blood Pressure

Heart rate (HR) should be measured after the patient has been seated for at least 5 minutes. Heart rate measurements should be taken by palpation of the radial or brachial artery for 1 full minute.

Blood pressure (BP) should be measured after the patient has been seated for at least 5 minutes and the patient should have emptied his/her bladder prior to the measurements. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of blood pressure measurements. Position the middle of the cuff bladder directly over the

brachial artery. The lower edge of the cuff should be 2 to 3 cm above the midpoint of the brachial artery pulsation. The arm should be supported at the level of the heart. The same method used to assess BP should be used consistently throughout the trial.

At screening (Visit 1), HR and BP should be measured 3 times in each arm in the seated position. The measurements should be taken at least 1 minute apart. Blood pressure measurements in each arm should be averaged. Only HR and BP measurements from the arm with the higher mean SBP will be recorded. This arm should be used to measure HR and BP at all subsequent study visits (unless contraindicated) and at all study visits, 3 HR and 3 BP measurements should be taken at least 1 minute apart.

10.2.3.2. Anthropomorphic Measurements

Anthropomorphic measurements will be taken according to the Study Schedule (Attachment 1).

Body Weight and Height

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

Waist and Hip Circumferences

Waist and hip circumference measurements should be obtained with the patient in the standing position. The waist circumference should be measured immediately above the iliac crest and the hip circumference at the maximal circumference of the buttocks.

10.2.3.3. ECGs

Twelve-lead ECGs will be obtained according to Study Schedule (Attachment 1). ECGs should be recorded after the patient has been supine for 5 minutes in a quiet room.

The ECGs must be interpreted by a qualified physician (the investigator or designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate patient management, if needed. The investigator or designee must document their review of the ECG. If a clinically relevant abnormality is observed on the patient's ECG, then the investigator should assess the patient for symptoms (such as palpitations, near syncope, syncope, chest pain).

The 12-lead ECGs also will be assessed by the independent ECG reading center. The purpose of the qualitative review is to identify electrocardiographic abnormalities consistent with MI or myocardial ischemia, as well as other abnormalities (for example, arrhythmias). The original ECG will be retained at the investigative site. The ECG tracing also will be submitted either electronically (original) or on paper (that is, a copy) via traceable courier to the ECG reading center. Each 12-lead ECG will be evaluated qualitatively and will be compared to the prior time point. All ECG findings of new, postbaseline MI/myocardial ischemia not clearly associated with a previously reported MI will be considered as a potential silent MI endpoint. The site will be notified and further information ascertained. As appropriate, all new endpoint events of

MI/myocardial ischemia not already reported by the site will be submitted for adjudication as a possible silent MI as described in the CEC Charter.

The ECG Charter will describe the methodology employed in the acquisition and expert analysis of 12-lead ECGs. The CEC Charter will contain the final detailed event definition for silent MI used for adjudication. Study sites will be requested to send appropriate documentation to the CEC in a timely fashion for adjudication of the event.

The investigator or qualified designee's interpretation will prevail for immediate patient management purposes, and the ECG reading center's interpretation will prevail for data analysis purposes.

10.2.4. Safety Monitoring

The blinded Lilly clinical research physician and the blinded CRO physician will monitor safety data throughout the course of the study. The CRO physician will be responsible for safety monitoring follow-up at the site throughout the course of the study. The Lilly physician will consult, as is appropriate, with the functionally independent blinded Global Patient Safety therapeutic area physician or clinical scientist, and review trends in laboratory analyses and SAEs at periodic intervals.

Clinical endpoints adjudicated as such and SAEs will be reviewed regularly for safety and efficacy by the external IDMC. The IDMC will operate under a written charter.

Lilly Global Patient Safety and CRO will review SAEs within time frames mandated by company procedures. If a death or clinical AE is deemed serious, unexpected, and possibly related to study drug, Lilly Global Patient Safety and CRO will be unblinded to comply with regulatory reporting and safety monitoring requirements. These measures will preserve the integrity of the data collected during this study and minimize any potential for bias while providing for appropriate safety monitoring.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the IDMC and independent statistical analysis center (ISAC), that provides support to the IDMC, can view group unblinded data and conduct additional analyses of the safety data.

10.2.5. Complaint Handling

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

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.3. Sample Collection and Testing

Protocol Attachment (Attachment 1) provides a study schedule of events.

Protocol Attachment (Attachment 3) lists the specific tests performed for this study.

Protocol Attachment (Attachment 4) provides a summary of the maximum number and volume of invasive samples for tests collected centrally during the study. Additional samples will be collected if a patient participates beyond 84 months; but this will not require a protocol amendment. Samples also will be collected for laboratory testing performed locally; the maximum number and volume of samples for these tests will be determined locally.

10.3.1. Samples for Standard Laboratory Testing

Fasting blood samples and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including HbA1c, ALT, lipids, serum creatinine, and urine albumin/creatinine ratio, will be performed locally. For HbA1c testing, a DCCT or IFCC standardized assay must be used in this study; point of care HbA1c assays will not be acceptable. Pregnancy tests, if applicable, will be performed locally. Calcitonin will be analyzed by a central laboratory.

Investigators must document their review of each laboratory safety report.

Samples collected for central 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.

10.3.2. Samples for Exploratory Work

10.3.2.1. Nonpharmacogenetic Biomarker Stored Samples

Samples will be collected for nonpharmacogenetic biomarker analysis where allowed by local regulations or policies. Blood samples will be collected at the visits specified in the Study Schedule (Attachment 1).

Samples may be used for research on the GLP-1 pathway, type 2 diabetes, pathways associated with CV disease, the mechanism of action of dulaglutide, or for validating diagnostic tools or assay(s) related to type 2 diabetes.

Samples will be identified by the patient number (coded) and may be stored at a facility selected by the sponsor for 1 year after study completion or a maximum of 15 years after the last patient visit for the study, as allowed by local regulations.

10.3.2.2. Samples for Pharmacogenetic Analysis

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow and the patient provides consent, a blood sample may be collected for pharmacogenetic analysis. It is a 1-time collection, as noted in the Study Schedule (Attachment 1).

Samples will be stored and analysis may be performed on pharmacogenetic variants thought to play a role in type 2 diabetes, pancreatitis, or CV disease, including, but not limited to, cystic fibrosis transmembrane conductance regulator (CFTR), serine peptidase inhibitor, Kazal type 1 (SPINK1), or TCF7L2, to evaluate their association with observed clinical outcomes to dulaglutide in this study.

In the event of an unexpected AE or the observation of unusual response, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to dulaglutide. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to the disease or drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Samples will be identified by the patient number (coded) and stored at a facility selected by the sponsor for 1 year after study completion or a maximum of 15 years after the last patient visit for the study, as allowed by local regulations. The duration allows the sponsor to respond to regulatory requests related to the study drug. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.

10.4. Appropriateness of Measurements

All safety and efficacy measures are widely used and generally regarded as reliable, accurate, and relevant in studies of patients with type 2 diabetes at high risk for CV events.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly and/or the CRO will do the following:

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

In addition, Lilly or its representatives may 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.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethical review boards (ERBs) with direct access to original source documents.

11.1. Data Capture System

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

Case report form (CRF) data collected by the contract research organization (CRO) will be encoded by the CRO and stored electronically in the CRO's database system. Validated data will subsequently be transferred to the sponsor's data warehouse, using standard Lilly file transfer processes.

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 CRO database for data validation and analysis. The CRO will then transfer the central lab data to the sponsor, along with the CRF data as described above.

Any data for which the CRF or paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a dosing schedule, or documents used to collect patient-reported outcome (PRO) measures (IIEF, MoCA, DSST).

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

A sample size of approximately 9600 patients is required to show superiority of dulaglutide over placebo (with 90% power), as was calculated using nQuery Advisor® Version 7.0. This software provides sample size estimates for tests based on exponential survival, accrual period, and dropouts. The sample size and other trial characteristics, such as interim analysis power, were also assessed through trial simulation. Trial assumptions were based on information from the scientific leadership of the study and a review of the relevant literature. For sample size determination the following assumptions were used: (1) two-sided significance level of 0.05; (2) 90% power for the primary endpoint; (3) patient accrual over 3 years; (4) annual placebo group event rate of 2.0% for the primary endpoint; (5) maximum duration of follow-up of 8 years; (6) a detectable hazard ratio of 0.82 between dulaglutide and placebo in terms of the primary endpoint; and (7) annual dropout rate of 0.15%.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

All entered data will be verified, and archived at a CRO external to Lilly and/or at Lilly. An ISAC will perform analyses for the IDMC prior to unblinding. After database lock at the conclusion of the study, analyses for the major key manuscripts will be conducted by the same or another ISAC based on data supplied by the CRO and the relevant manuscripts will be prepared by a writing group chosen by the Operations Committee. Data listings, summaries, and analyses will also be performed by a CRO and/or by Lilly for the purpose of the final clinical study report.

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) that will be finalized before any unblinding has occurred, and/or in the clinical study report. Additional exploratory analyses will be conducted, as deemed appropriate.

Efficacy and safety analyses will be conducted on the intent-to-treat (ITT) population. This population includes all randomized patients within the treatment group the patients were assigned to regardless of whether or not they took study drug or the correct study drug. A patient is considered randomized once the call has been made to IVRS and a treatment is assigned at Visit 3.

Unless otherwise specified, listings will be provided using all randomized patients. The primary efficacy analyses and safety analyses will be conducted using the ITT population (and will include all patients allocated to the 2 groups regardless of protocol deviations, adherence, or use of any prohibited drugs). An “as treated” analysis of the primary endpoint events that occurred while patients were on study drug irrespective of protocol deviations will be conducted. Additional analyses will also be conducted using the Per-Protocol population (PP). The PP

population is a subset of the ITT population, defined as all randomized patients who have not discontinued study drug or discontinued from the study, have an overall adherence of ≥75%, and have no important protocol deviations.

The analysis populations used in this study are defined in Table GBDJ.1.

The data collected in this study will be presented as listings by investigator site, patient, and treatment.

Table GBDJ.1. Analysis Populations for Study H9X-MC-GBDJ

Population	Definition
All Entered:	All patients who signed an informed consent form
All Randomized:	All patients who were randomized to a treatment arm
Non-Randomized:	All patients entered but not randomized to a treatment arm
Intent-to-Treat:	All patients randomized within their treatment group regardless of whether or not they took study drug or correct study drug (same as all randomized population)
Per-Protocol:	All patients in ITT and also meet the following criteria: • have not permanently discontinued study drug • no important protocol deviations • have completed the study • have an overall adherence with study drug of ≥75%

Abbreviation: ITT = intent to treat.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and confidence intervals (CIs) will be calculated at a 2-sided 95% confidence level. A graphical approach for multiple comparisons (Bretz et al. 2009; Bretz et al. 2011) will be used to strongly control the overall Type I error (2-sided alpha of 0.05) for testing the null hypothesis of no treatment effect with respect to the secondary endpoints.

For subgroup analyses, all tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

Countries in similar geographic regions with less than 10 patients will be pooled in order to achieve a pooled country of at least 10 patients. All analyses using country in the model will use pooled country, unless otherwise specified. The final pooling by country and geographic region will be specified prior to data lock.

The baseline is Visit 3 unless otherwise specified. If baseline data are missing, the last measurement taken prior to this visit will be used for the baseline measurement.

The primary analyses of the primary endpoints and key secondary endpoints will be based on adjudicated events that occurred after randomization. The endpoint for the primary analysis is defined as the first occurrence of death from CV causes, nonfatal MI or nonfatal stroke. The

primary analysis model will be a Cox proportional hazards regression model for the time to the first occurrence of a primary endpoint event, with treatment as a fixed effect.

For continuous measures, analysis of covariance (ANCOVA) and or mixed-effects model for repeated measures (MMRM) will be used to analyze changes from baseline with the baseline value as the covariate. The MMRM model will include fixed effects for treatment, visit, treatment-by-visit interaction, the baseline as a covariate and the patient as a random effect. Summary statistics will include sample size, mean, standard deviation, median, 10^{th} and 90^{th} percentiles for both the actual and the change from baseline measurements. Least-squares mean (LS Mean) and standard error derived from the model will also be displayed for the change from baseline measurement. Treatment comparisons will be displayed showing the treatment difference LS Mean and the 95% confidence limits along with the p-value.

For continuous lab measurements, an analysis of variance (ANOVA) on ranks will be used and p-values for the difference between the dulaglutide and placebo will be reported.

For categorical measures, summary statistics will include sample size, frequency, and percentage. Frequencies will be analyzed using Chi-square tests if the expected count is at least 5, in at least 80% of the cells', otherwise a Fisher's exact Test will be used.

All analyses will be implemented using SAS® Version 8.2 or higher.

12.2.2. Trial Design

There will be 1 interim analysis and 1 final analysis. The interim analysis will be performed when approximately 61% (730 events) of the positively adjudicated primary endpoint events have occurred. The final analysis will be performed at 100% (approximately 1200) of the positively adjudicated primary endpoint events, if the study is not stopped early. At the interim analysis timepoint (Figure GBDJ.2), superiority will be tested first; if successful, the trial may stop and superiority will be declared. Otherwise, the trial will continue to the end, where, at 1200 events, superiority will be tested followed by noninferiority. The interim and final analyses will be performed on unblinded study data. The interim analysis results and these decision rules are used by the IDMC as guidelines. If the interim analysis shows clear benefit of dulaglutide over placebo for the primary endpoint, the IDMC may recommend early termination of the study. Alternatively, if the boundaries are crossed at the interim analysis, the IDMC may still recommend the trial continue and not stop for early efficacy. At anytime during the trial, the IDMC could recommend stopping the trial for safety reasons. The alpha used across the analyses will be monitored by an O'Brien-Fleming spending function (O'Brien and Fleming 1979; Jennison and Turnbull 2000), (eg, with 730 events at the interim, 2-sided alpha = 0.0081). The alpha used at the final analysis will be adjusted to maintain the overall type I error control at a 2-sided significance level of 0.05. This will be accomplished using EAST software to calculate the alpha level for the final analysis considering the actual amount of information at the interim analysis (eg, with 1200 events at the final analysis, 2-sided alpha = 0.0475; overall power = 92.8%). If the true hazard ratio is as high as 0.85, this sample size would provide at least 80% overall power to show superiority. At the final analysis, superiority will be tested. The adjusted 95% CI for the hazard ratio will be calculated.

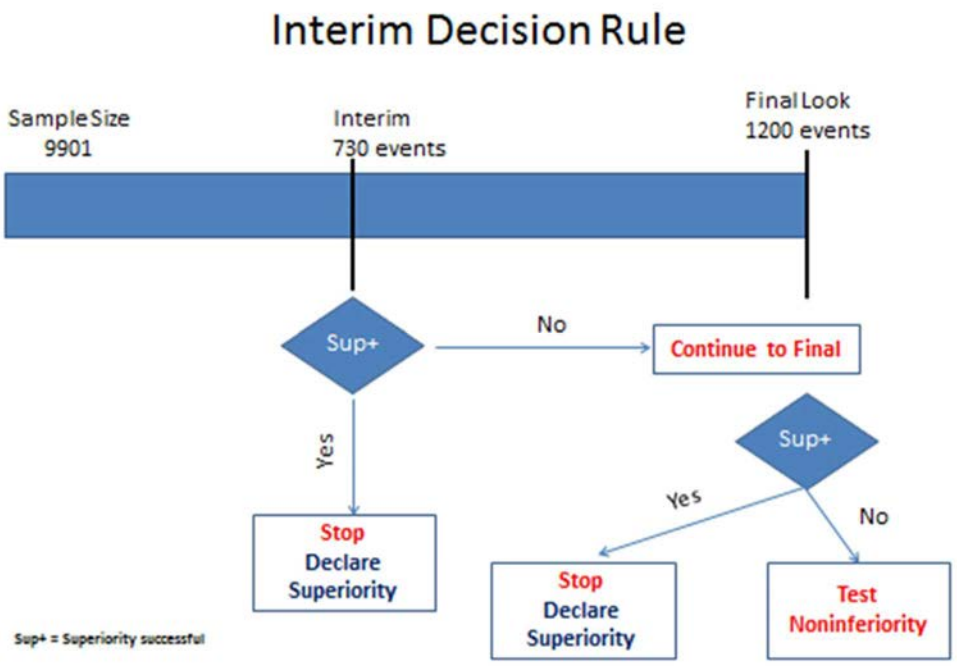


Figure GBDJ.2. Interim decision rule.

12.2.3. Patient Disposition

A listing of patient discontinuation will be presented for all randomized patients. Summary analyses will be conducted for all entered ITT population and PP population.

Frequency counts and percentages will be presented for each treatment group and compared across treatment groups using Chi-square tests or Fisher's exact tests.

12.2.4. Patient Characteristics

Demographic and baseline characteristics will be summarized by treatment group using ITT and PP populations. For continuous measures, summary statistics will include sample size, mean, median, 10^{th} and 90^{th} percentiles and standard deviations. Means will be analyzed using ANOVA. For categorical measures, summary statistics will include sample size, frequency, and percentages.

12.2.5. Concomitant Therapy

Concomitant medications will be summarized by classes of medications like hypoglycemic agents, antithrombotics, antihypertensives, and antihyperlipidemic agents and by treatment group using the ITT population. All concomitant therapies that originally mapped using the WHO DRUG dictionary in the clinical trial database will be further classified using ATC codes for reporting purpose. Frequencies will be analyzed using Chi-square tests or Fisher's exact tests.

12.2.6. Treatment Adherence

Treatment adherence will be listed and summarized using the ITT population. Treatment adherence for each visit is defined as taking between 75% and 120% of the study drug syringes dispensed for the visit interval (see Section 9.9).

Treatment adherence for each visit will be calculated as follows:

Study drug adherence for each visit = [(number of syringes dispensed – number of syringes returned) / (number of weeks between the 2 consecutive visits)]*100%.

The frequency and percentage of patients who are adherent at each visit by treatment group will be summarized and compared using a Chi-square test or a Fisher's exact test.

In addition, the overall adherence during the study will be calculated for each patient. This will be calculated by taking the number of visits the patient was adherent divided by the total number of visits with nonmissing adherence data for this patient (that is, the proportion of visits at which the patient was adherent among visits with nonmissing compliance data for the patient). The overall adherence will be summarized and presented in descriptive statistics that include the sample size, mean, median, 10^{th} and 90^{th} percentiles, and standard deviation. The overall adherence will be used as one of the factors when determining if a patient is eligible for the PP population (see Section 9.9).

12.2.7. Primary Outcome and Methodology

The primary efficacy measure is the time to first occurrence (after randomization) of a composite of death from CV causes, nonfatal MI, or nonfatal stroke (Section 10.1.1).

The primary analysis at the conclusion of the trial will be a superiority comparison of dulaglutide versus placebo. If the superiority test fails, then a noninferiority test with a 1.3 margin will be performed. If the upper limit of the 95% CI is below 1.0 (after adjustment for interim looks), dulaglutide will be declared superior to placebo in reducing the incidence of CV events. If the upper limit of the adjusted 95% CI of dulaglutide versus placebo is above 1.0 but below 1.3, dulaglutide will be declared noninferior to placebo in its effects on CV events. The analyses for the primary efficacy measures will be based on the ITT population.

The primary analysis model is a Cox proportional hazards regression model. The model includes treatment as a fixed effect.

12.2.8. Efficacy Analyses

Analysis of the composite primary endpoint as well as detailed analyses of the components of death from CV causes, nonfatal MI, and nonfatal stroke, will be performed. Time-to-event analyses will be performed for the composite endpoint as well as for each of the components. Counts and proportions of patients who experience a primary endpoint event and each component event will be calculated. Person-years of follow-up, incidence rates, and absolute risk differences (ARD) will be provided. The incidence rate for an endpoint is calculated by dividing the number of patients who developed the event during the study period by the event specific person-years of follow-up. The ARD will then be calculated by subtracting the

incidence in the dulaglutide arm from that in the placebo arm. The number needed to treat (NNT) statistic will be calculated as the reciprocal of the ARD for each analysis provided that the p-value from the Cox model is statistically significant.

Similar analyses will also be performed for all secondary endpoints. The eGFR values will be calculated using the MDRD equation [eGFR (mL/min/1.73 m^2) = 175 X standardized Scr $^{-1.154}$ X age $^{-0.203}$ X1.212 [if black] X 0.742 [if female] (Levey et al. 2006)]. The percentage change from baseline in eGFR will be calculated using the post-randomization values and the values calculated at Visit 3 (randomization) as baseline, and compared to -30%. The outcome will be the 1st of 2 consecutive eGFR calculations that are <-30%.

12.2.9. Safety Analyses

Unless otherwise noted, all listings will be conducted using all randomized patients. All summary analyses will be conducted using the ITT population. The safety analyses will include analyses of the prespecified safety measures and AEs, SAEs, laboratory analytes, vital signs, and ECGs.

12.2.9.1. Adverse Events

An AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to a drug. Adverse events will be coded from the actual term described by the investigator using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Unless otherwise specified, AEs will be reported using the MedDRA system organ class and preferred term. Selected AEs may be reported using MedDRA high level terms.

All AEs will be listed by patient and may include information on treatment group, visit, preferred term, severity, seriousness, and relationship to the study medication, procedure, or device.

Treatment-emergent adverse events (TEAEs) will be defined as events that first occur or worsen (increase in severity) after the first injection of study drug following randomization. Study drug overdose will also be reported as a TEAE. Study drug overdose is defined as documented evidence of study drug injection more than once in a 3-day period. The count and proportion of patients with TEAEs will be summarized for each treatment group. Overall treatment group differences will be compared using Chi-square tests or Fisher's exact tests.

SAEs will also be summarized. The counts and proportion of patients experiencing the event of interest will be reported for each treatment arm. Treatment groups will be compared by Chi-square tests or Fisher's exact tests.

Permanent discontinuations of study drug due to AEs will be listed. The count and proportion of discontinuations will be reported. Time to discontinuation (due to AE) will be compared between treatment groups using a Cox proportional hazard regression model with treatment as a fixed effect. Kaplan-Meier curves for both treatment groups will be reported.

The number and percentage of patients who temporarily discontinue study drug will be compared between treatment groups with separate analyses for the reasons for the

discontinuation, such as AE. In addition, the number of patients with temporary discontinuations in categories of 1, 2, and ≥3 will be summarized by treatment groups.

12.2.9.2. Severe Hypoglycemic Episodes

Severe hypoglycemic episodes by patient by visit will be listed using all randomized patients.

The incidence of severe hypoglycemic episodes will be summarized using frequency and percentage by treatment group and by visit. The overall frequency and percentage will be reported; the Kaplan-Meier estimates of the proportion of patients having 1 or more events by treatment group will also be reported. The frequency and percentage at each visit are calculated as the number of patients and percentage of patients reporting severe hypoglycemic episodes at that visit. The overall frequency and percentage are calculated as the total number of patients and percentage of patients reporting severe hypoglycemic episodes during the entire study treatment period. Treatment group comparison will be assessed using a Chi-square or Fisher's exact test or a log-rank test, as appropriate.

Severe hypoglycemia rate per year will be summarized by visit by treatment group. The rate will be analyzed if enough data points are available. The rate of hypoglycemia will be analyzed using a generalized estimation equations (GEE) model with a negative binomial distribution and a logit link (via Proc Genmod with repeated statement in SAS). An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following covariance structures will be tested in this order: compound symmetry, then, autoregressive. The empirical covariance matrix estimated by the GEE method is robust to misspecification of the covariance structure, so the particular choice of the covariance structure is not of primary importance. The model will include treatment, visit, visit*treatment interaction, and baseline. Baseline antihyperglycemic therapies and other covariates of interest, including categorical, continuous and time-dependent may be included.

12.2.9.3. Analysis for Other Safety Objectives

Each of the following events will be analyzed using the ITT population: pancreatitis, any cancer (excluding basal or squamous cell skin cancer), medullary thyroid carcinoma (MTC), C-cell hyperplasia, allergic/hypersensitivity reactions and discontinuation of study drug for any reason. The reasons for temporary discontinuation and reasons for permanent discontinuation of study drug will be summarized. Pancreatitis will be analyzed based on adjudicated events and on events as reported by investigators. The analyses of MTC and C-cell hyperplasia will be based on adjudicated events. The analysis of cancers (excluding basal or squamous cell skin cancer) will be based on events reported by investigators. The incidence will be summarized using frequency and percentage by treatment group and by visit. The frequency and percentage at each visit will be calculated as the number of patients and percentage of patients reporting the event at that visit. The overall frequency and percentage will be reported. The overall frequency and percentage will be calculated as the total number of patients and percentage of patients reporting the event during the entire study treatment period. Treatment group comparison will be assessed using a Chi-square or Fisher's exact test.

12.2.9.4. Analysis of Laboratory Analytes

Laboratory measurements collected at scheduled visits will be listed by patient by visit using all randomized patients. An additional listing will be presented for all laboratory measurements that are outside the SI units (International System of Units) normal range. Baseline for calcitonin, ALT, and hemoglobin A1c, will be Visit 1 and for serum creatinine, urine ACR and lipids will be Visit 3. All summary analyses will be based on the ITT population. Laboratory measurements that fall within a visit window will be associated with that visit. The laboratory measurement within the window that was taken closest to the visit date will be representative of that patient's lab value for that visit.

Unless otherwise specified, continuous laboratory measures will be analyzed using an ANOVA model on the rank-transformed data. The model includes treatment. Treatment group comparisons will be performed with no multiplicity adjustment. Categorical lab oratory measures will be analyzed using Chi-square tests or Fisher's exact tests. For lipids (total cholesterol, LDL-C, HDL-C, triglycerides, and non-HDL-C) the summary analysis will be conducted based on the percentage change from baseline using an ANOVA model described above. The change from baseline will be used for the ratio of total cholesterol to HDL-C.

12.2.9.5. Vital Signs

Vital signs (SBP, DBP, and heart rate) will be collected 3 times in the seated position at each visit.

Measurements will be averaged for each patient at each visit; the average values will be used in the descriptive summaries and analyses.

Descriptive statistics for the actual measurements and change from baseline by treatment arm and visit will be presented. Summary analyses will be conducted using ITT population. The change from baseline will be analyzed using an MMRM model. The incidence of vital signs with selected thresholds will be summarized by frequency and percentage and compared using either a Chi-square test or a Fisher's exact test.

12.2.9.6. ECG Analyses

Both scheduled and unscheduled ECGs at each visit will be listed for all randomized patients. The ECGs will be qualitatively evaluated (see Section 10.2.3.3). The qualitative characteristics assessed will be summarized in the major categories of findings: normal ECG, abnormal ECG findings, and the subcategories of abnormal findings. The number of patients in each category will be compared between treatment groups and by visit using a Chi-square or Fisher's exact test.

12.2.10. Analysis for the Additional Objectives

For HbA1c, weight, and waist/hip ratio, an ANCOVA for the change from baseline to each visit and to endpoint (last available observation) will be performed for the ITT population. The model includes treatment as a fixed effect and the baseline value as a covariate. Missing endpoints will be imputed using a multiple imputation procedure on available postbaseline values of the variable. If there are no data after the date of randomization, the endpoint will be considered missing. The baseline data will not be used as an endpoint.

Time-to-event analyses will be performed for each of the following endpoints: the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina; the composite endpoint of coronary, carotid, or peripheral revascularization and each of the components; and any hospitalization. A Cox proportional hazards regression model for the time to the first occurrence of the event, with treatment as a fixed effect will be performed for the ITT population.

Frequency counts and percentages of patients with fractures and patients, who developed cholelithiasis, will be presented for each treatment group and compared across treatment groups using Chi-square tests or Fisher's exact tests.

Cognitive function will be assessed in patients using the MoCA instrument and the DSST.

The DSST score is the number of correct number–symbol matches. The number attempted will also be recorded. Analyses of the last score and visit-specific analyses will be performed using ANCOVA for each continuous test measurement. The analysis will be based on change from baseline. Patients will be required to have a baseline and at least 1 postbaseline score to be included in these analyses.

The MoCA score is a continuous variable with a range of [0, 30]. It will be analyzed as a categorical variable using the categories: below the threshold for normal cognitive function (that is, mild cognitive dysfunction, MoCA score <26), and above the evaluation threshold (that is, normal cognitive function, MoCA score ≥26).

Erectile function will be assessed in male patients. The International Index of Erectile Function (IIEF) scores will be used to assess for degree of erectile function. Changes from baseline to endpoint in total IIEF scores from the erectile function, orgasmic function, sexual desire, overall satisfaction, and intercourse satisfaction domains will be analyzed using an ANCOVA model that includes terms for treatment and the baseline values minus their mean as covariate.

12.2.11. Subgroup Analyses

The effects of dulaglutide and placebo on the incidence of primary endpoint events will be examined across the following subgroups:

- Gender (Female vs. Male)
- Age (Age <65 years, and Age ≥65 years)
- Prior CV event
- Duration of diabetes (Duration <5 years, 5 years ≤ Duration <10 years, and Duration ≥10 years)
- Body mass index (<median and ≥median)
- Baseline HbA1c (<median and ≥median)
- Geography (North America, South America, Europe, Asia, Other)

Forest plots of the hazard ratio will be provided for each subgroup. Other subgroups may be examined if determined to be of interest. As the number of these subgroups may be large, the probability of observing at least 1 statistically significant result just by chance is nontrivial. Thus, these analyses will be considered exploratory. All tests of interactions between treatment and subgroup will be conducted at a 2-sided alpha level of 0.10.

12.2.12. Interim Analyses

The IDMC will be authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know results for the safety of their patients.

Unblinding details are specified in the unblinding plan section of the SAP.

There will be 1 interim and 1 final analysis for this study. The interim analysis will occur when approximately 61% (730 events) of the expected number (1200) of primary endpoint events have accrued (Section 12.2.2).

Standard safety analyses of data from this trial will be conducted by the IDMC at regularly scheduled intervals. The IDMC will receive and consider information that is relevant to the safety of the participants in the study including results from other published studies. Anytime over the course of the trial, the IDMC may recommend stopping, pausing, or modifying the trial if it determines from its periodic safety reviews of data from this trial that dulaglutide harms patients or clearly benefits them.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including 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.

The informed consent form (ICF) will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring 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. As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly must agree with all ICFs before they are submitted to the ethical review board (ERB) and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonization (ICH) guideline on good clinical practice (GCP). Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations and performed in accordance with a written process approved by Lilly.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly. The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

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

- the current IB or package labeling and updates during the course of the study
- ICF
- study protocol
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Eli Lilly and Company certifies that this study was initiated under an active US investigational drug application (IND) at clinical sites within the US. Since the study was initiated, dulaglutide has received regulatory approval in the US and other countries and is pending regulatory review and approval in additional countries. All investigators (at IND and non-IND sites) are expected to comply with GCP and all applicable local clinical trial regulations.

All or some of the obligations of the sponsor will be assigned to a CRO.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in endocrinology, diabetes, cardiology, internal medicine, family medicine, and nephrology will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The Operations Committee and 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 or its designee.

13.3.3. Final Report Signature

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

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Attachment 1. Protocol GBDJ (REWIND) Study Schedule

Study Schedule, Protocol H9X-MC-GBDJ

Visit Type	Screen	Run-in	Treatment																			
Visit Number	1[j]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19[k]	EVa[k]	EVb[k]	FV
Study Month	-1	-0.75	0	0.5	3	6	12	18	24	30	36	42	48	54	60	66	72	78	84	(+6)	(+12)	-
Allowable Deviation (days)	-	±7	±7	±3	±7	±7	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	
Informed consent	X																					
Entry criteria reviewed	X	X	X																			
Randomization			X																			
Clinical Assessments																						
Medical history	X																					
Physical examination	X																					X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Heart rate and Blood pressure [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [b]			X				X		X		X		X		X		X		X		X	X
Height	X								X				X				X					X
Weight	X						X		X		X		X		X		X		X		X	X
Waist/hip circumference	X		X						X				X				X				X	X
Events [c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive function (MoCA)			X						X						X							X
Cognitive function (DSST)			X						X						X							X
Erectile function (IIEF), men only			X						X						X							X
Laboratory Tests																						
Pregnancy test [d]	X																					
Calcitonin	X						X		X		X		X		X		X		X		X	X
ALT	X																					
HemoglobinA_{1c} [e]	X				X		X		X		X		X		X		X		X		X	X
Serum creatinine	X						X		X		X		X		X		X		X		X	X
Urine albumin/creatinine ratio (ACR) [f]	X						X		X		X		X		X		X		X		X	X
Lipids (fasting)			X						X						X							

Study Schedule, Protocol H9X-MC-GBDJ

Visit Type	Screen	Run-in	Treatment																			
Visit Number	1[j]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19[k]	EVa[k]	EVb[k]	FV
Study Month	-1	-0.75	0	0.5	3	6	12	18	24	30	36	42	48	54	60	66	72	78	84	(+6)	(+12)	-
Allowable Deviation (days)	-	±7	±7	±3	±7	±7	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	
Nonpharmacogenetic samples			X						X													X
Pharmacogenetic samples[g]			X																			
Study drug and adherence																						
Adherence/Lifestyle reinforcement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Instruct/review injection[h]		X	X																			
Dispense study drug[i]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect (unused) study drug			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Schedule, Protocol H9X-MC-GBDJ (Concluded)

Abbreviations: ACR = albumin/creatinine ratio; ALT = alanine aminotransferase; BP = blood pressure; CV = cardiovascular; DCCT = Diabetes Control And Complications Trial Research Group; DSST = the digit symbol substitution test; ECG = electrocardiogram; eCRF = electronic case report form; EVa = Extended follow-up Visit a; EVb = Extended follow-up Visit b; FV = final visit; HR = heart rate; IFCC = International Federation of Clinical Chemistry; IIEF = International Index of Erectile Function Questionnaire; IVRS = interactive voice response system; IWRS = interactive web response system; MoCA = Montreal Cognitive Assessment; SBP = systolic blood pressure.

[a] At screening (Visit 1), HR and BP should be measured in both arms in the seated position (triplicates). Only HR and BP measurements from the arm with the higher mean SBP will be recorded; this arm should be used to measure HR and BP at all subsequent study visits. Three measurements should be taken at least 1 minute apart using the same arm. Each measurement of BP/HR is to be recorded on the eCRF.

[b] The order of conducting the ECG, vital sign measurements, and blood samples for laboratory testing is determined at the investigative site.

[c] Solicitation of new CV or microvascular events, hospitalizations, fractures, cholelithiasis, severe hypoglycemia episodes, allergic/hypersensitivity reactions, cancer, pancreatitis, or thyroid events will be collected and recorded for all visits after randomization.

[d] A serum pregnancy test is to be performed at Visit 1 in women of childbearing potential (see Section 8.2); however if this test is unavailable a urine pregnancy test should be performed. A local (urine) pregnancy test should be performed approximately every 6 months thereafter in women of childbearing potential only, unless otherwise indicated, at the discretion of the investigator.

[e] HbA1c values, reference range, and standardization method used (DCCT or IFCC) will be recorded on the eCRF. Point of care HbA1c assays will not be acceptable.

[f] A morning urine sample for measuring urinary albumin and creatinine and for calculation of ACR is preferred; if not available a spot urine sample will be accepted.

[g] Pharmacogenetic sample will be collected 1 time only, preferably at the randomization (Visit 3), but may be collected at any later visit.

[h] After Visit 3, injection instructions will be reviewed as needed.

[i] Study drug will be dispensed at Visit 2, at randomization (Visit 3), and every visit thereafter with the exception of Visit 4 and the Final Visit. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug. See also Attachment 2. Sites will access IWRS for assigning study drug.

[j] If a patient is not eligible for the trial after the initial screen and is willing to participate, the patient may be re-screened on 1 occasion. The re-screen visit should be conducted after 6 or more weeks following Visit 1. All other patients who do not meet eligibility criteria and do not wish to undergo re-screening will not participate further in the study.

[k] Approximately 84 months (Visit 19) of follow-up are planned, if required, additional visits will occur beyond 84 months. Additional visits after Visit 19 will occur every 6 months. The semi-annual visits occurring after Visit 19 will follow the Extended Visit a (EVa) schedule. Annual visits occurring after Visit 19 will follow the Extended Visit b (EVb) schedule (such that follow-up visits will alternate between EVa and EVb).

Attachment 2. Protocol GBDJ (REWIND) Additional Study Drug Dispensing Schedule

Additional Study Drug Dispensing Schedule, Protocol H9X-MC-GBDJ

Visit Type	**Treatment**														
Study Drug Dispensing Visit Number [a]	6B	7B	8B	9B	10B	11B	12B	13B	14B	15B	16B	17B	18B	19B	EVB
Study Month	9	15	21	27	33	39	45	51	57	63	69	75	81	87	(+3)
Allowable Deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence/Lifestyle reinforcement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect (unused), study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: EVB = study drug dispensing visit occurring 3 months after Extended follow-up Visit a or b (EVa or EVb); IVRS/IWRS = interactive voice/web response system.

[a] Study drug will be dispensed at Visit 2, at randomization (Visit 3), and every visit thereafter with the exception of Visit 4 and the Final Visit. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug. See also Attachment 1. A study drug dispensing visit occurring after a scheduled clinic visit number (referred to as Visit X) will be called Visit "XB" on the IWRS. Sites will access IWRS for assigning study drug.

[b] After Visit 3, injection instructions will be reviewed as needed.

Attachment 3. Protocol GBDJ (REWIND) Clinical Laboratory Tests

Clinical Laboratory Tests

Clinical Chemistry Serum Concentrations of:

Calcitonin[a]
Serum creatinine[b]
Alanine aminotransaminase (ALT/SGPT)

HbA1c

Urinalysis
Albumin [c]
Creatinine [c]

Lipid Panel
Total Cholesterol
LDL
HDL
Triglycerides

Pregnancy test serum and urine [d]

Stored samples
Non-pharmacogenetic samples
Pharmacogenetic Samples

Abbreviations: HbA1c = Hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

[a] This test will be performed by a Lilly-designated central laboratory; all other laboratory tests will be performed locally.

[b] Serum creatinine will be used to calculate eGFR.

[c] Urinary albumin and urinary creatinine will be measured. The albumin/creatinine ratio may be calculated, if not reported.

[d] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential; however if this test is unavailable a urine pregnancy test should be performed. A urine pregnancy test may be repeated locally for any follow-up visit, as needed.

Attachment 4. Protocol GBDJ (REWIND) Sampling Summary

This table summarizes the maximum number of blood samples and volumes for all sampling (screening, standard laboratory, pharmacogenetic, and biomarker) and tests collected centrally during the study. Other laboratory testing will be performed locally and therefore similar information is not provided in the table below; maximum volume per sample and maximum number of samples will be determined locally. Fewer samples may actually be taken, but additional samples will be collected if patient participates beyond 84 months; but this will not require a protocol amendment.

Protocol H9X-MC-GBDJ (REWIND) Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Calcitonin testing (Central) [a]	Blood	5 mL	8	40 mL
Pharmacogenetic samples	Blood	10 mL	1	10 mL
Nonpharmacogenetic biomarkers	Blood (Serum and Plasma)	14.5 mL	3	43.5 mL
Total [Blood]	Blood	29.5 mL	12	93.5 mL

[a] Additional samples may be drawn if needed for safety purposes or if patient participates beyond 84 months.

Attachment 5. Protocol Amendment H9X-MC-GBDJ(d) Summary [The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)]

Overview

Protocol H9X-MC-GBDJ(d) [**The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)**] has been amended. The new version of the protocol is indicated by **amendment (d)** and will be used to conduct the study in place of any preceding version.

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

- **Synopsis**: The planned last patient visit was estimated to occur Second Quarter 2019 versus Autumn 2019.
- **Section 7.1, Section 7.3; similar modifications were also included in the Synopsis, Section 12.2.2 and Section 12.2.12**: The protocol previously stated that patients will be followed until approximately 1067 patients experience a primary endpoint event, adjudicated as such. The plan was modified to indicate that patients will be followed until approximately 1200 patients experience a primary endpoint event, adjudicated as such.

  Evidence from recently completed Cardiovascular Outcome trials (CVOTs) in diabetes suggested that the true hazard ratio in REWIND may be higher than the previously stated assumption of 0.82. A total of 1200 primary MACE events at the final analysis would provide at least 80% overall power to detect a hazard ratio of 0.85 or lower. For example, if the true hazard ratio is 0.85 (or 0.84), the overall power is 80% (85.2%, respectively).
- **Section 7.1; similar modifications were included in Section 7.3 and the Synopsis**: Increased the minimum follow-up duration to 5.6 years from 5 years and added the word "approximately" to the estimated average follow-up duration of 6.5 years.

  Enrollment was completed in 2.1 years and based on a 2% annual event rate, 1200 events were projected to occur in Second Quarter 2019, leading to a minimum patient follow-up of 5.6 years.
- **Section 7.1, Section 7.1.4, Section 7.1.4.1, Attachment 1 [Protocol GBDJ (REWIND) Study Schedule], Attachment 2 [Protocol GBDJ (REWIND) Additional Study Drug Dispensing Schedule]**: Text was added to allow for the dispensing of a 6-month supply of study drug, at the investigator's discretion and after confirming sufficient non-expiring study drug is available onsite, with the objective of enhancing the flexibility of the dispensing visit schedule and maintaining patient adherence.
- **Section 7.1**: Clarified that study drug dispensing will not occur at the Final Visit to improve consistency with the Study Schedule.

- **Section 7.1.6:** As modifications were made in this protocol amendment to allow for dispensing of a 6-month supply of study drug, text was added to provide additional instruction to the investigative site that in the case the patient is unable to return to the site for the next planned study visit, the site should confirm a sufficient supply of study drug is available at the site and notify the sponsor of the request to dispense a 6-month supply of the study drug to the patient. Additional changes were made to instruct the investigational site staff that the site should consider alternatives for conducting the potentially missed visit, including telephone contact, in order to attempt to collect and record as much visit information as possible according to the Study Schedule (Attachment 1).
- **Section 12.2.2; similar modifications were included in the Synopsis and Section 12.2.12**: The previous version of the protocol indicated that the interim analysis will be performed when approximately 68% (730 events) of the positively adjudicated primary endpoint events have occurred. The text was modified to state the interim analysis will be performed when approximately 61% (730 events) of the positively adjudicated primary endpoint events have occurred. This new percentage is based on the new total number of events (1200).
- **Section 12.2.2**: The decision rules at the interim analysis time point were modified as follows: a) removed the possibility that conditional probablility for superiority (CpSup) at the end of the trial will be calculated; b) removed the text that indicated if the CpSup is ≥10%, the trial will continue to the end; and c) removed the possibility (i.e., CpSup <10%) that noninferiority will be tested and, if successful, the trial may stop and noninferiority will be declared.

  There is now evidence from recently completed CVOTs in diabetes that REWIND could show superiority; therefore, the trial is unlikely to stop at the interim for noninferiority only.

  Text was modified to indicate: a) the 2-sided alpha = 0.0081 at interim from 2-sided alpha = 0.0134 at interim; and b) the calculation of alpha level at final analysis, considering the actual amount of information at the interim analysis will be 1200 events at the final analysis, 2-sided alpha = 0.0475; overall power = 92.8%; changed from 1067 events at the final analysis, 2-sided alpha = 0.0458; overall power = 88.2% to give the corresponding alpha spend and power based on the total number of events at 1200. Text was added to support the selection of the increase to 1200 events and to clarify the overall power is 80% for a HR of 0.85.

  Modified Figure GBDJ.2 to be consistent with amended interim decision rule.

Revised Protocol Sections

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

Global changes:

- Page headers: H9X-MC-GBDJ(de) (REWIND) Clinical Protocol
- Minor editorial changes for consistency and formatting were made but are not outlined here

Section 2. Synopsis

Name of Investigational Product: Dulaglutide (LY2189265)	
Title of Study: The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)	
Approximate Number of Planned Patients/Subjects: Entered: 16,000 Enrolled/Randomized: 9600 Completed: 9500	**Phase of Development:** 3
Length of Study: This is an event-driven study and will complete when approximately 1200~~1067~~ patients experience a primary endpoint event, adjudicated as such. The estimated follow-up duration will depend on the observed cardiovascular (CV) event rate. Planned first patient visit: June 2011 Planned last patient visit: Second Quarter ~~Autumn~~ 2019	

Objectives: The primary objective is to test the hypothesis that once-weekly injection of 1.5-mg dulaglutide reduces the occurrence of the composite primary endpoint of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke when added to the glucose-lowering regimen of patients with type 2 diabetes, compared to the addition of a once-weekly placebo injection.

The secondary efficacy objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the occurrence of :

- the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy, or anti-vascular endothelial growth factor (anti-VEGF) therapy; development of clinical proteinuria, a 30% decline in estimated glomerular filtration rate (eGFR), or need for chronic renal replacement therapy
- hospitalization for unstable angina
- each component of the composite primary endpoint
- all-cause mortality
- heart failure (HF) requiring hospitalization or an urgent HF visit

The prespecified safety objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the incidence of:

- acute pancreatitis
- serious gastrointestinal events
- any cancer (excluding basal or squamous cell skin cancer) and specific categories of
    - pancreatic cancer
    - medullary thyroid carcinoma (MTC) and C-cell hyperplasia
    - thyroid carcinomas
- severe hypoglycemia
- immune mediated reactions including serious allergic and hypersensitivity reactions
- serious hepatic events
- clinically significant supraventricular arrhythmias and cardiovascular conduction disorders
- serious renal events
- discontinuation of study drug for any reason

The additional objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the following:

- hemoglobin A1c (HbA1c) levels
- weight
- waist/hip ratio
- the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
- coronary, carotid, or peripheral revascularization, individually and compositely
- any hospitalization
- cognitive function as measured by the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST)
- erectile function using the International Index of Erectile Function Questionnaire (IIEF)
- any fracture
- development of cholelithiasis

Study Design: Phase 3, event-driven, multicenter, international, randomized, double-blind, placebo-controlled, parallel study to assess the effect of once-weekly 1.5-mg dulaglutide on CV outcomes when added to the existing antihyperglycemic regimen of patients with type 2 diabetes. The study will consist of a screening visit followed by a single-blind placebo run-in period. Afterwards, patients will be randomized to either dulaglutide or placebo and followed at approximately 6-month intervals. Patients will be followed until approximately 1200~~1067~~ patients experience a primary endpoint event, adjudicated as such.

The international steering committee (SC) will be responsible for the overall scientific conduct of the study and all scientific trial-related decisions. The SC will be chaired by the Principal Investigator and will include, as members, all National Leaders, one representative from Lilly, and one representative from the clinical research organization (CRO). An independent data-monitoring committee (IDMC) will be responsible for monitoring patient safety throughout the study and review of interim analyses. An independent clinical endpoint committee (CEC) will adjudicate all deaths and CV, pancreatic, and thyroid events. Lilly will assign the obligation of study operation management to a CRO.

Diagnosis and Main Criteria for Inclusion and Exclusions: Men or women with type 2 diabetes (HbA1c ≤9.5%) treated with various antihyperglycemic regimens who are at high risk for CV events (aged ≥50 years old with clinical vascular disease, ≥55 years and subclinical vascular disease, or ≥60 years and at least 2 or more CV risk factors)

Test Product, Dosage, and Mode of Administration: Dulaglutide, 1.5 mg administered subcutaneously once weekly

Planned Duration of Treatment: This is an event-driven study and patients will be followed until approximately 1200~~1067~~ patients experience a primary endpoint event, adjudicated as such. The estimated follow-up duration will depend on the observed CV event rate.

Screening period: 1-2 weeks

Run-in period: 3 weeks

Treatment period: Visits will continue until a sufficient number of primary endpoint events, adjudicated as such, have occurred. The estimated average follow-up duration is approximately 6.5 years.

Statistical Methods:

The primary efficacy measure is the time to first occurrence of the composite endpoint of death due to CV causes, nonfatal MI, or nonfatal stroke (adjudicated as such). The primary analyses will be based on the intent-to-treat principle and will use time-to-event analyses via a Cox proportional hazards regression model. Estimates of hazard ratios and 95% confidence intervals will be calculated and treatment group comparisons will be based on the p-value from the Cox model. Dulaglutide will be considered different from placebo if the 2-sided p-value from the primary analysis (adjusted for interim looks) is <0.05. Kaplan-Meier estimates of the survival curve for each treatment will be generated. The incidence rate per 100 person-years of follow-up will be calculated for each treatment group.

Analyses of the secondary efficacy and select additional measures will be based on the time from randomization to the occurrence of the first event, with patients analyzed in the treatment group to which they were randomized (according to the intent-to-treat principle). Where applicable, analyses will be based upon adjudicated events. Patients who complete the study but do not experience an outcome will be censored on the last day of their follow-up. Patients who discontinue from the study will be censored on their discontinuation dates or their last contact dates, whichever is later. Patients who die during the study will be censored as of the date of death for all time-to-event analyses where death is not an outcome of interest. Patients who prematurely discontinue assigned treatment will be followed until the end of the study.

Demographic and baseline characteristics will be summarized by treatment group. Separate subgroup analyses of the primary endpoint will be performed based on patient demographics and baseline characteristics. Predefined key subgroups include gender, age group (age <65 years and age ≥65 years), prior CV event, body mass index below and at or above the median, duration of diabetes (0 to 5 years, 5 to 10 years, and 10 or more years), baseline HbA1c below and at or above the median, and geography. Consistency of treatment effects across subgroups will be assessed using an interaction term in the Cox regression model. As the number of these subgroup variables may be large, the probability of observing at least 1 statistically significant result just by chance is nontrivial. Thus, these analyses will be considered exploratory.

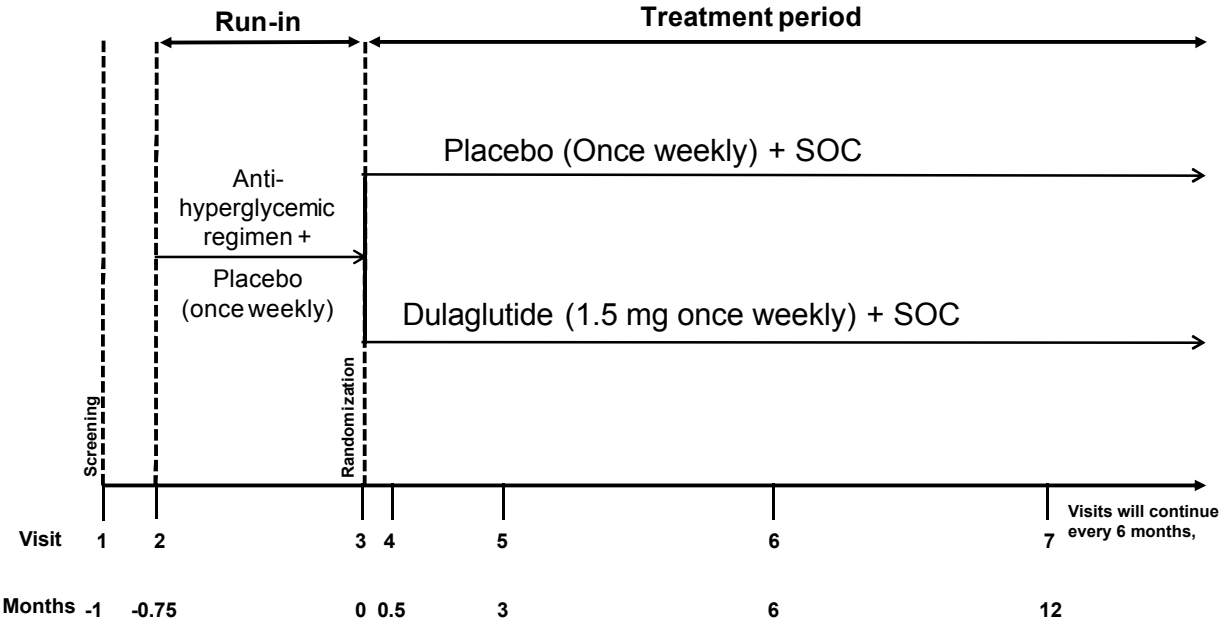
For other analyses, including analyses of prespecified safety measures, the number and proportion of patients will be calculated for binary data and summary statistics (mean, median, standard deviation, 10th and 90th percentiles) will be presented for continuous data. Summary statistics of change from baseline for HbA1c per year will be presented along with percentage of patients within ranges of clinical interest (for example, HbA1c <7.0%).

Safety data will be monitored on an ongoing basis. Clear evidence of net harm that is consistent over time and across subgroups would justify early stopping of the trial. One interim and 1 final analysis of the efficacy data will be performed. The interim analysis will occur when approximately 61~~68~~% (730 events) of the expected number (1200~~1067~~) of primary endpoint events have accrued. The final analysis will occur when approximately 1200~~1067~~ patients have experienced a primary endpoint event if the trial is not stopped early.

The secondary analyses will follow a graphical statistical approach for multiple comparisons to strongly control the overall Type I error rate in the trial at a 2-sided α level of 0.05.

An IDMC will monitor unblinded study data on a regular basis to assess study progress, efficacy, and patient safety.

7.1 Summary of Study Design



Study drug ~~is~~ should be dispensed every 3 months. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available onsite, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug.

Abbreviation: SOC = standard of care for type 2 diabetes management.

Figure GBDJ.1. REWIND trial design.

Approximately 9600 patients will be enrolled at approximately 480 sites globally and randomized to 1 of 2 treatment groups: 1.5-mg dulaglutide or placebo. Patients will be followed until approximately 1200~~1067~~ patients experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after a minimum of 5.6 years and an average of approximately 6.5 years of follow-up on all patients, unless the trial is stopped early on the basis of an independent data monitoring committee (IDMC) safety review or the interim analysis.

Section 10 contains a discussion of specific study measures. Details regarding the study procedures at each visit are presented in the Study Schedule Attachment 1). A treatment duration of approximately 84 months (Visit 19) is planned but, if required, additional visits may occur beyond 84 months. These additional follow-up visits will occur in 6-month intervals (semiannually and annually). Activities for these visits will alternate between schedules for the Extended Follow-Up Visit a (EVa) for semiannual visits and the Extended Follow-Up Visit b (EVb) for annual visits (Attachment 1). Study drug dispensing will occur at every scheduled clinic visit (Attachment 1) except for Visit 4 and the Final Visit. Additional study drug-dispensing visits ~~will~~ should occur at 3-month intervals between scheduled clinic visits (Attachment 2). At the investigator's discretion, and after confirming sufficient non-expiring study drug is available onsite, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug.

7.1.4. Treatment Period (Visit 4 and Beyond)

Visit 4 will occur 2 weeks, Visit 5 at 3 months, and Visit 6 at 6 months after randomization; subsequent study visits will occur approximately every 6 months thereafter until study closure. Study drug dispensing ~~will~~ should occur approximately every 3 months after randomization. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug.

7.1.4.1. Additional Study Drug Dispensing Visits

Study drug will be dispensed at Visit 2, at randomization (Visit 3), and should be dispensed every 3 months thereafter. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug. Study drug will be dispensed at clinic visits as per the Study Schedule (Attachment 1) and in between clinic visits (Attachment 2). Sites will access (starting February 2015) IWRS to assign study drug. Patients will be instructed to inject study drug subcutaneously once weekly on the same day at approximately the same time each week. Patients should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering the study medication. Patients should be advised about the appropriate course of action in the event that study drug is not taken at the required time (see Section 9.5.1). Unused prefilled syringes will be returned at each visit (that is, scheduled clinic visit or study drug dispensing visit) to assess study drug adherence and for drug accountability at all visits; the only exception to this will be that study drug dispensed at Visit 3 will be returned at Visit 5 (that is, unused study drug will not be returned at Visit 4). Used syringes should be placed in the sharp items container provided to patients. The sharp items container should be returned when full or sooner, if appropriate.

7.1.6. Missed Study Visit(s)

Every attempt should be made to encourage all patients to attend all study visits regardless of study drug adherence. In the event a study visit (ie, a scheduled clinic visit or a study drug dispensing visit) is missed, the site should attempt to contact the patient and have the patient return for the missed study visit. Study visits should resume in accordance with the Study Schedule (Attachment 1 and Attachment 2).

In the event a patient on study drug is unable to return to the site for the next planned study visit, the site should confirm a sufficient supply of study drug is available at their site and notify the sponsor of their request to dispense a 6-month supply of study drug to the patient. The site should consider alternatives for conducting the potentially missed visit, including through telephone contact, and attempt to collect and record as much visit information as possible according to the Study Schedule (Attachment 1).

7.3. Discussion of Design and Control

Approximately 9600 patients will be enrolled and randomized to 1 of 2 treatment groups: 1.5-mg dulaglutide or placebo. Patients will be followed until approximately 1200~~1067~~ patients

experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after an average of approximately 6.5 years of follow-up on all patients, unless the trial is stopped early following an IDMC safety review or an interim analysis. Maximum duration of follow-up is dependent upon the primary endpoint event rate. Patients will be followed at approximately 6-month intervals. Management of glycemic control will be at the discretion of the study investigator and will be informed by current guidelines and/or local standards of medical care. The management of blood pressure, lipids, other CV risk factors and comorbid conditions will be at the discretion of the study investigator or the patient's usual physician(s), as informed by current guidelines and the patient's clinical state.

Superiority will be assessed by the reduction in risk of the primary composite endpoint of death from CV causes, nonfatal MI, or nonfatal stroke. This same primary efficacy endpoint was used in the ACCORD study (ACCORD 2008) and in many other studies in CV research (ADVANCE 2008; Duckworth et al. 2009). The CV event rate is assumed to be about 2% annually, based on recently completed trials in patients with type 2 diabetes (ACCORD 2008; ADVANCE 2008). Given this, in order to assess long-term clinical CV outcomes, patients are expected to be followed for between 5 and 8 years; however, the actual duration of the study will depend on the observed CV event rate and time to accrue the number of anticipated primary CV events (approximately 1200~~1067~~). As the primary analysis of this study is an intent-to-treat analysis, every randomized patient will be followed until death or study end. Every attempt will be made to encourage all patients to come for their study visits. The long duration of this trial will also enable a robust assessment of dulaglutide on other measures, including its effects on thyroid C-cell function, microvascular complications, and the incidence of pancreatitis.

12.2.2. Trial Design

There will be 1 interim analysis and 1 final analysis. The interim analysis will be performed when approximately 61~~68~~% (730 events) of the positively adjudicated primary endpoint events have occurred. The final analysis will be performed at 100% (approximately 1200~~1067~~) of the positively adjudicated primary endpoint events, if the study is not stopped early. At the interim analysis timepoint (Figure GBDJ.2), superiority will be tested first; if successful, the trial may stop and superiority will be declared. ~~Otherwise, conditional probability for superiority (CpSup) at the end of the trial will be calculated. If the CpSup is ≥10%, the trial will continue to the end; otherwise (i.e., CpSup <10%), noninferiority will be tested and, if successful, the trial may stop and noninferiority will be declared; O~~otherwise, the trial will continue to the end, where, at 1200~~1067~~ events, superiority will be tested followed by noninferiority. The interim and final analyses will be performed on unblinded study data. The interim analysis results and these decision rules are used by the IDMC as guidelines. If the interim analysis shows clear benefit of dulaglutide over placebo for the primary endpoint, the IDMC may recommend early termination of the study. Alternatively, if the boundaries are crossed at the interim analysis, the IDMC may still recommend the trial continue and not stop for early efficacy. At anytime during the trial, the IDMC could recommend stopping the trial for safety reasons. The alpha used across the analyses will be monitored by an O'Brien-Fleming spending function (O'Brien and Fleming 1979; Jennison and Turnbull 2000), (eg, with 730 events at the interim, 2-sided alpha =

0.00810.0134). The alpha used at the final analysis will be adjusted to maintain the overall type I error control at a 2-sided significance level of 0.05. This will be accomplished using EAST software to calculate the alpha level for the final analysis considering the actual amount of information at the interim analysis (eg, with 12001067 events at the final analysis, 2-sided alpha = 0.04750.0458; overall power = 92.888.2%). If the true hazard ratio is as high as 0.85, this sample size would provide at least 80% overall power to show superiority. At the final analysis, superiority will be tested. The adjusted 95% CI for the hazard ratio will be calculated.

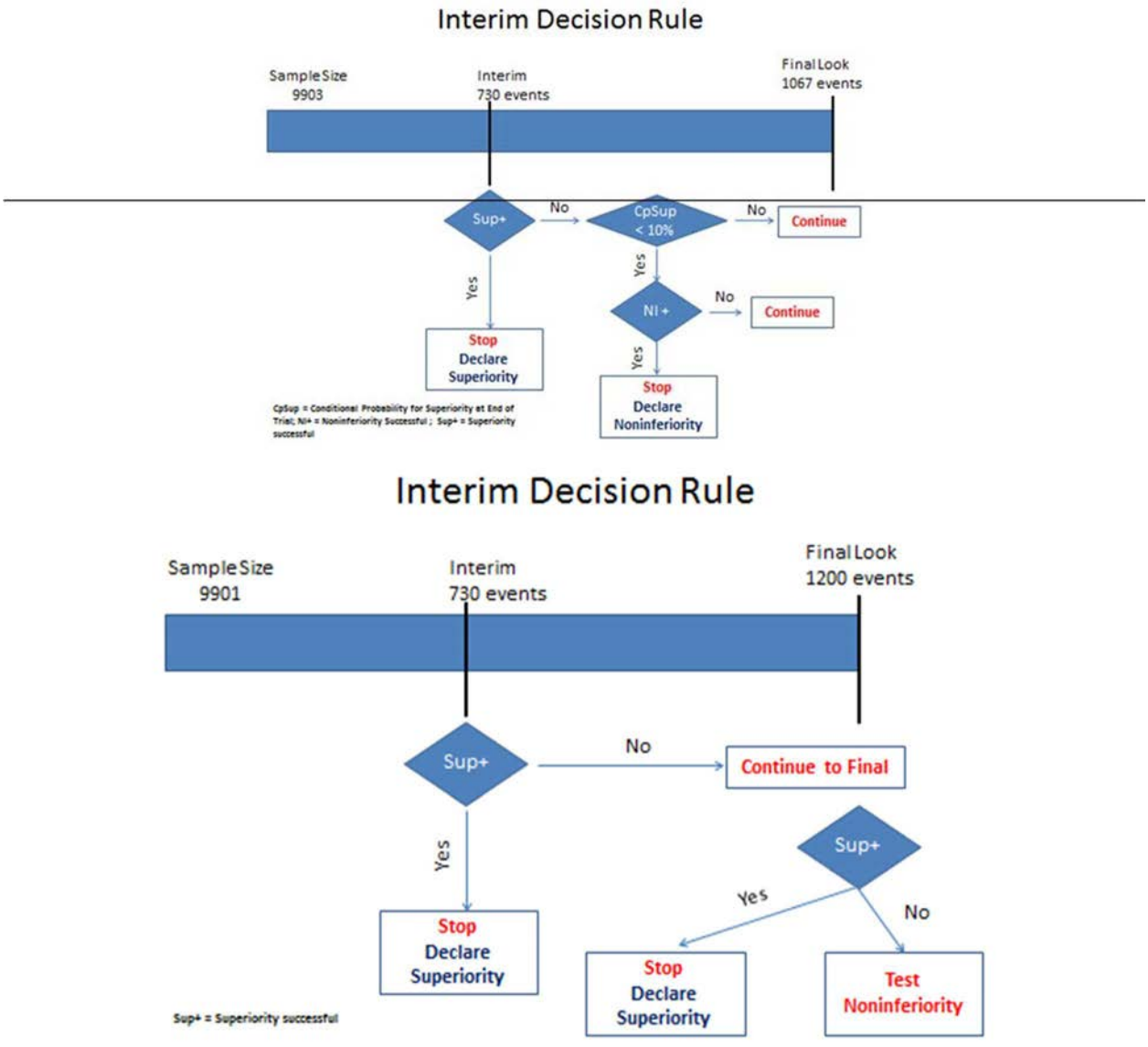


Figure GBDJ.2. Interim decision rule.

12.2.12. Interim Analyses

There will be 1 interim and 1 final analysis for this study. The interim analysis will occur when approximately 61~~68~~% (730 events) of the expected number (1200~~1067~~) of primary endpoint events have accrued (Section 12.2.2).

(Attachment 1) Study Schedule, Protocol H9X-MC-GBDJ

Visit Type	**Screen**	**Run-in**	**Treatment**																			
Visit Number	1 [j]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 [k]	EVa [k]	EVb [k]	FV
Study Month	-1	-0.75	0	0.5	3	6	12	18	24	30	36	42	48	54	60	66	72	78	84	(+6)	(+12)	-
Allowable Deviation (days)	-	±7	±7	±3	±7	±7	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	
Nonpharmacogenetic samples			X						X													X
Pharmacogenetic samples [g]			X																			
Study drug and adherence																						
Adherence/Lifestyle reinforcement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Instruct/review injection [h]		X	X																			
Dispense study drug [i]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect (unused) study drug			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[i] Study drug will be dispensed at Visit 2, at randomization (Visit 3), and every visit thereafter with the exception of Visit 4 and the Final Visit. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug. See also Attachment 2. Sites will access IWRS for assigning study drug.

(Attachment 2) Additional Study Drug Dispensing Schedule, Protocol H9X-MC-GBDJ

Visit Type	**Treatment**														
Study Drug Dispensing Visit Number [a]	6B	7B	8B	9B	10B	11B	12B	13B	14B	15B	16B	17B	18B	19B	EVB
Study Month	9	15	21	27	33	39	45	51	57	63	69	75	81	87	(+3)
Allowable Deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence/Lifestyle reinforcement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect (unused), study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: EVB = study drug dispensing visit occurring 3 months after Extended follow-up Visit a or b (EVa or EVb); IVRS/IWRS = interactive voice/web response system.

[a] Study drug will be dispensed at Visit 2, at randomization (Visit 3), and every visit thereafter with the exception of Visit 4 and the Final Visit. At the investigator's discretion, and after confirming sufficient non-expiring study drug is available on site, a 6-month supply of study drug may be dispensed to maintain a patient's compliance with study drug. See also Attachment 1. A study drug dispensing visit occurring after a scheduled clinic visit number (referred to as Visit X) will be called Visit "XB" on the IWRS. Sites will access IWRS for assigning study drug.

[b] After Visit 3, injection instructions will be reviewed as needed.

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