

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial



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Summary

Background Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk with high glycated haemoglobin A_{1c} (HbA_{1c}) concentrations. We assessed the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control.

Methods This multicentre, randomised, double-blind, placebo-controlled trial was done at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1.5 mg) or placebo. Randomisation was done by a computer-generated random code with stratification by site. All investigators and participants were masked to treatment assignment. Participants were followed up at least every 6 months for incident cardiovascular and other serious clinical outcomes. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes), which was assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01394952.

Findings Between Aug 18, 2011, and Aug 14, 2013, 9901 participants (mean age 66.2 years [SD 6.5], median HbA_{1c} 7.2% [IQR 6.6–8.1], 4589 [46.3%] women) were enrolled and randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952). During a median follow-up of 5.4 years (IQR 5.1–5.9), the primary composite outcome occurred in 594 (12.0%) participants at an incidence rate of 2.4 per 100 person-years in the dulaglutide group and in 663 (13.4%) participants at an incidence rate of 2.7 per 100 person-years in the placebo group (hazard ratio [HR] 0.88, 95% CI 0.79–0.99; p=0.026). All-cause mortality did not differ between groups (536 [10.8%] in the dulaglutide group vs 592 [12.0%] in the placebo group; HR 0.90, 95% CI 0.80–1.01; p=0.067). 2347 (47.4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34.1%) participants assigned to placebo (p<0.0001).

Interpretation Dulaglutide could be considered for the management of glycaemic control in middle-aged and older people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

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Introduction

Despite the widespread use of many proven cardio-protective therapies and a concomitant fall in risk of cardiovascular events¹ during the past 20 years, diabetes continues to increase the risk of death and cardiovascular events by 1.5–2 times.^{2,3} Although reasons for this higher incidence are debated, the importance of knowing whether glucose-lowering drugs alter these outcomes has justified many large cardiovascular trials in this population.⁴ Evidence that three glucagon-like peptide-1 (GLP-1) receptor agonists^{5–8} and three sodium-glucose

co-transporter-2 (SGLT2) inhibitors^{9,10} reduce cardiovascular events in middle-aged and older (≥50 years) people with type 2 diabetes and mean glycated haemoglobin A_{1c} (HbA_{1c}) concentrations of 8.0% or more has changed clinical practice guidelines^{11,12} and fuelled debate regarding mechanisms linking diabetes to cardiovascular disease.

Dulaglutide is a GLP-1 receptor agonist approved for the management of hyperglycaemia in people with type 2 diabetes in many countries. It comprises two modified human GLP-1 molecules covalently linked

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for reports published in English between Jan 1, 2010, and March 31, 2019, of double-blind, randomised, placebo-controlled trials that were designed to test the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on incident cardiovascular events in people with type 2 diabetes. Search terms were "type 2 diabetes", "GLP1-RA", "glucagon-like peptide receptor 1 agonist", "glucagon-like peptide receptor 1 analogue", "lixisenatide", "liraglutide", "semaglutide", "taspoglutide", "albiglutide", "dulaglutide", "cardiovascular disease", and "randomized controlled trial". This search identified five trials that assessed the effects of lixisenatide (ELIXA; n=6068), albiglutide (Harmony Outcomes; n=9463), liraglutide (LEADER; n=9340), semaglutide (SUSTAIN-6; n=3297), or long-acting exenatide (EXSCEL; n=14752) versus placebo on incident cardiovascular outcomes in people with type 2 diabetes whose mean age ranged from 54 years to 64 years and mean glycosylated haemoglobin A_{1c} (HbA_{1c}) ranged from 7.7% to 8.8%. The trials were done in people with previous cardiovascular disease (ELIXA and Harmony Outcomes), or with a prevalence of cardiovascular disease ranging from 73% to 83% (LEADER, SUSTAIN-6, and EXSCEL). Median follow-up durations ranged from 1.6 years to 3.8 years. Trials that reported a reduced hazard ratio (HR) for the primary composite cardiovascular outcome of the first occurrence of non-fatal

myocardial infarction or stroke, or death from cardiovascular causes were LEADER (HR 0.87, 95% CI 0.78–0.97), SUSTAIN-6 (HR 0.74, 0.58–0.95), and Harmony Outcomes (HR 0.78, 0.68–0.90). These five trials suggested that GLP-1 receptor agonists might only reduce cardiovascular outcomes in people with previous cardiovascular disease. They also were unable to determine the cardiovascular effects of GLP-1 receptor agonists across a wide range of glycaemic control.

Added value of this study

The REWIND trial of 9901 people had a long median follow-up period of 5.4 years, recruited a low proportion of people (31.5%) with previous cardiovascular disease, a high proportion of women (46.3%), and followed people with a mean HbA_{1c} of 7.3%. Findings showed that weekly injections of the GLP-1 receptor agonist dulaglutide reduced cardiovascular outcomes in both men and women with or without previous cardiovascular disease, and had an effect size similar to that observed in the other GLP-1 receptor agonist cardiovascular outcomes trials.

Implications of all the available evidence

GLP-1 receptor agonists that have been shown to reduce cardiovascular outcomes should be considered for the management of glycaemic control in people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

to an IgG4 heavy chain molecule, has a half-life of 5 days, and is administered subcutaneously at weekly doses of 0.75 mg or 1.5 mg.¹³ Evidence that it safely reduces glucose concentration, blood pressure, weight,¹⁴ and albuminuria,¹⁵ and has other actions suggesting possible cardiovascular benefits¹⁶ supported its testing in a large cardiovascular superiority trial. Moreover, the fact that the cardiovascular effects of other GLP-1 receptor agonists were being tested in middle-aged people with high HbA_{1c} concentrations and a 4% or higher annual risk of cardiovascular events highlighted the need to test the effect of dulaglutide on cardiovascular events in people with a broader cardiovascular risk and a wider range of glycaemic control. Thus, the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial was designed to assess whether the addition of dulaglutide to the diabetes medication regimen of middle-aged and older people with type 2 diabetes safely reduces the incidence of cardiovascular outcomes compared with placebo.

Methods

Study design and participants

REWIND was a multicentre, randomised, double-blind, placebo-controlled trial done at 371 sites in 24 countries. Details of the study design and baseline characteristics of participants have been published previously.¹⁷ Men and women (aged ≥50 years) with established or newly

detected type 2 diabetes whose HbA_{1c} was 9.5% or less (with no lower limit) on stable doses of up to two oral glucose-lowering drugs with or without basal insulin therapy were eligible if their body-mass index (BMI) was at least 23 kg/m². Additionally, patients aged 50 years or older had to have vascular disease (ie, a previous myocardial infarction, ischaemic stroke, revascularisation, hospital admission for unstable angina, or imaging evidence of myocardial ischaemia); those aged 55 years or older had to have myocardial ischaemia, coronary, carotid, or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m², or albuminuria; and those aged 60 years or older had to have at least two of tobacco use, dyslipidaemia, hypertension, or abdominal obesity. Key exclusion criteria were an eGFR¹⁸ less than 15 mL/min per 1.73 m², cancer in the previous 5 years, severe hypoglycaemia in the previous year, life expectancy less than 1 year, a coronary or cerebrovascular event within the previous 2 months, and plans for revascularisation. A complete list of trial inclusion and exclusion criteria is given in the appendix (pp 151–55). The REWIND protocol was approved by research ethics boards for all sites and all participants provided written informed consent. The trial was carefully monitored by members of an independent data monitoring committee who reviewed accruing and unblinded data every 6 months.

The study consisted of two phases: a run-in period and a treatment period. During the 3-week single-blind placebo run-in period, all patients received placebo and were instructed on how to inject study drug. Patients were instructed to remain on their antihyperglycaemic therapy with the exception of patients taking a dipeptidyl peptidase-4 (DPP-4) inhibitor or GLP-1 receptor agonist at screening, who discontinued these therapies at the start of the run-in period.

Randomisation and masking

Participants who were 100% adherent to weekly placebo injections during the single-blind run-in period and who still met eligibility criteria were randomly assigned to weekly subcutaneous injections of either masked dulaglutide 1.5 mg or the same volume of masked placebo (containing the same excipients but without dulaglutide) using a preloaded syringe. Syringes containing dulaglutide and placebo were identical in appearance. Randomisation was done by a computer-generated random code with an interactive web response system with stratification by site. All investigators and participants were masked to treatment allocation. The independent data monitoring committee and the statisticians supporting the committee's activities were the only people with access to unblinded data.

Procedures

During the treatment period, participants in both groups were instructed to inject study drug on the same day at approximately the same time, each week. Participants were seen at 2 weeks, 3 months, and 6 months and then every 3 months for drug dispensing and every 6 months for detailed assessments until 1200 confirmed primary outcomes had accrued. Assessments included cardiovascular events, adverse events, vital signs, and periodic questionnaires, laboratory tests, and electrocardiograms (ECGs). Investigators were advised to promote a healthy lifestyle and to manage glucose concentrations according to local guidelines and were free to add any glucose-lowering drug apart from another GLP-1 receptor agonist or pramlintide. Management of blood pressure, lipids, other cardiovascular risk factors, and medical conditions was at the discretion of either the study investigator or the patient's usual physician(s) as informed by current country guidelines. Unless consent was explicitly withdrawn, all randomly assigned participants were followed up until the end of the trial, irrespective of adherence to study medication. Those who stopped study medication were encouraged to restart it unless there was a clear contraindication.

Outcomes

The primary endpoint was the first occurrence of any component of the composite outcome, which comprised non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown causes. The

seven secondary outcomes were a composite clinical microvascular outcome comprising diabetic retinopathy (defined as photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy) or renal disease (defined as development of a urinary albumin-to-creatinine ratio >33.9 mg/mmol in those with a lower baseline concentration, a sustained 30% or greater decline in eGFR [ie, based on two consecutive eGFR concentrations], or chronic renal replacement therapy); hospital admission for unstable angina; each component of the primary composite cardiovascular outcome; death; and heart failure requiring either hospital admission or an urgent visit requiring therapy. Potential cardiovascular outcomes, all deaths, and pancreatic and thyroid safety outcomes were adjudicated by an independent clinical endpoint committee that was masked to treatment assignment. Criteria for adjudication of clinical events are listed in the appendix (pp 12–27).

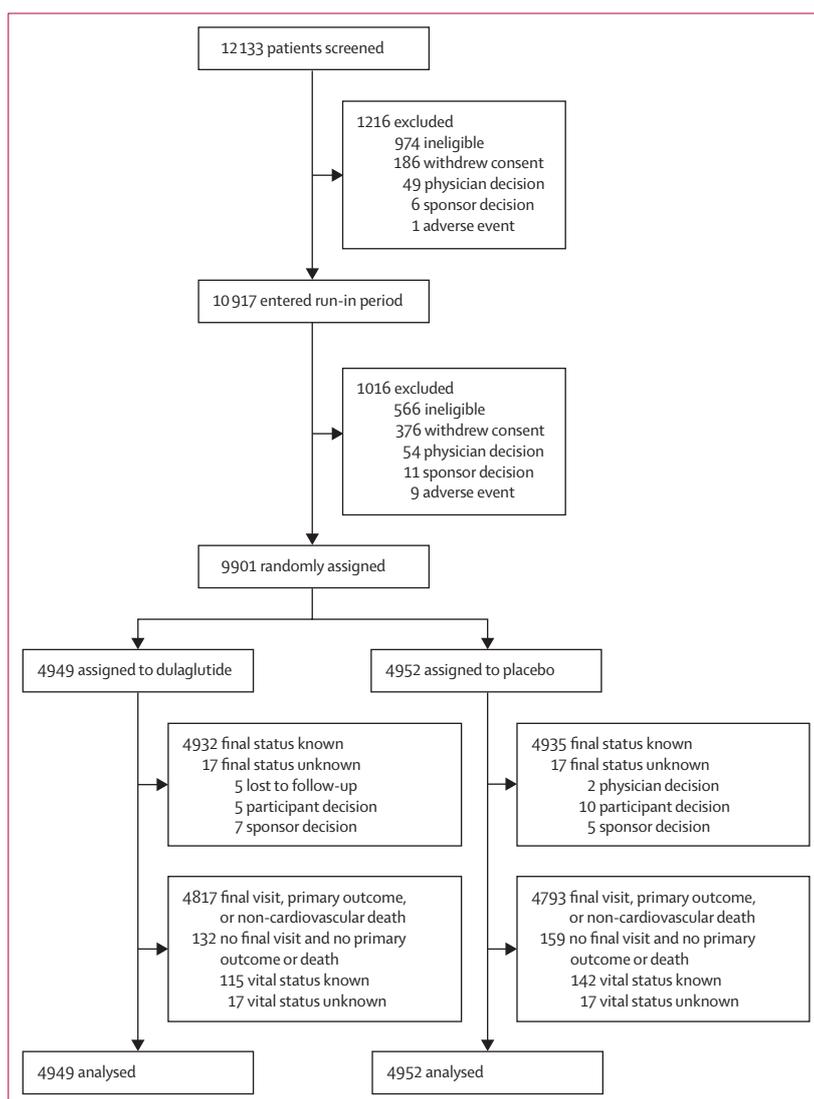


Figure 1: Trial profile

Prespecified and all other adverse events were reported by investigators on case report forms. They included study drug discontinuation; acute pancreatitis; cancer;

C-cell hyperplasia; serious hepatic, gastrointestinal, renal, or urinary events; immune reactions; supra-ventricular tachycardia; conduction disorders; or severe hypoglycaemia.

Statistical analysis

Assuming a primary outcome rate of 2% per year in the placebo group, a two-sided significance level of 5%, a 3-year recruitment period, and an annual dropout rate of 0.15%, follow-up of at least 9600 people for a maximum of 8 years, and accrual of 1200 unique primary outcomes was estimated to provide at least 90% power to detect a hazard ratio (HR) of 0.82 or lower for the primary outcome and 80% power to detect an HR of 0.85 or lower. The independent data monitoring committee did a formal interim analysis for superiority after 756 unique primary outcomes had occurred, after which continuation of the trial was recommended.

All efficacy and safety analyses were done according to an intention-to-treat approach that included all randomly assigned participants irrespective of adherence, as described in the protocol and prespecified statistical analysis plan (appendix pp 42–319). Participants were censored at the time of the last known follow-up date. Continuous data were summarised as either means and SDs or medians and IQRs, and count data were summarised as numbers and percentages.

All outcomes occurring on or after randomisation were included in the analysis. Incidence rates were estimated as the number of first events per 100 person-years of outcome-specific follow-up (ie, time from randomisation until either the first occurrence of the outcome or the last follow-up with no outcome). Kaplan-Meier estimates were used to generate cumulative risks and Cox proportional hazards models were used to determine the effect of the intervention on the outcome and to estimate HRs and 95% CIs. The assumptions of the Cox models were verified by plotting the log of negative log of the survival function against the log of time, and consistency of the effect across the three components of the composite outcome was assessed by a composite treatment heterogeneity test.¹⁹ All reported p values are two-sided. To account for the significance level of 0.009 used for the interim analysis and maintain an overall type I error of 0.05, the final adjusted p value for declaring superiority for the primary outcome was 0.0467.²⁰ To address multiplicity related to testing the effect of allocation on the secondary outcomes, a predetermined, graphical approach for multiple comparisons was used to strongly control the overall type I error.^{21–23}

The effect of the intervention on the primary outcome was tested in seven predefined subgroups (ie, age, sex, BMI, duration of diabetes, baseline HbA_{1c}, history of cardiovascular disease, and geographical region) by including the subgroup and interaction term in the Cox model. Tests for nominally significant interactions between treatment and the seven prespecified subgroups

	Dulaglutide (n=4949)	Placebo (n=4952)
Age (years)	66.2 (6.5)	66.2 (6.5)
Sex		
Female	2306 (46.6%)	2283 (46.1%)
Male	2643 (53.4%)	2669 (53.9%)
Race		
White	3754 (75.9%)	3744 (75.6%)
Current tobacco use	694 (14.0%)	713 (14.4%)
Cardiovascular disease*	1560 (31.5%)	1554 (31.4%)
Cardiovascular event†	1028 (20.8%)	1007 (20.3%)
Hypertension	4605 (93.0%)	4619 (93.3%)
Previous heart failure	421 (8.5%)	432 (8.7%)
Diabetes		
Duration of diabetes (years)‡	10.5 (7.3); 9.5 (5.5–14.5)	10.6 (7.2); 9.5 (5.5–14.5)
Diabetic retinopathy	448 (9.1%)	443 (8.9%)
HbA _{1c} (%)‡	7.3% (1.1); 7.2% (6.6–8.1)	7.4% (1.1); 7.2% (6.6–8.1)
eGFR <60 mL/min per 1.73 m ²	1081 (21.8%)	1118 (22.6%)
Albuminuria§	1707 (34.5%)	1760 (35.5%)
Antidiabetic medications		
Metformin	4022 (81.3%)	4015 (81.1%)
Sulfonylurea	2270 (45.9%)	2282 (46.1%)
Insulin	1189 (24.0%)	1174 (23.7%)
DPP-4 inhibitor	266 (5.4%)	298 (6.0%)
Thiazolidinedione	100 (2.0%)	68 (1.4%)
Other glucose-lowering drugs	14 (0.3%)	18 (0.4%)
Cardiovascular		
Body-mass index (kg/m ²)	32.3 (5.7)	32.3 (5.8)
Systolic blood pressure (mm Hg)	137.1 (16.6)	137.3 (17.0)
Diastolic blood pressure (mm Hg)	78.4 (9.8)	78.5 (9.9)
Heart rate (beats per min)	71.4 (10.7)	71.6 (11.0)
Serum creatinine (µmol/L)	83.7 (27.4)	84.5 (27.3)
eGFR (mL/min per 1.73 m ²)	75.3 (61.6–91.8)	74.7 (61.2–90.6)
UACR (mg/mmol)	1.80 (0.70–6.60)	1.88 (0.70–7.38)
Cholesterol (mmol/L)	4.52 (1.16)	4.52 (1.16)
LDL cholesterol (mmol/L)	2.56 (0.98)	2.56 (0.98)
HDL cholesterol (mmol/L)	1.18 (0.33)	1.18 (0.36)
Triglycerides (mmol/L)	1.60 (1.15–2.20)	1.60 (1.20–2.25)
Cardiovascular medications		
ACE inhibitor or ARB	4009 (81.0%)	4059 (82.0%)
β blocker	2237 (45.2%)	2274 (45.9%)
Other blood pressure drug	2767 (55.9%)	2833 (57.2%)
Statin	3279 (66.3%)	3268 (66.0%)
Fibrate	452 (9.1%)	446 (9.0%)
Antiplatelet	2662 (53.8%)	2680 (54.1%)

Data are mean (SD), n (%), or median (IQR), unless otherwise stated. HbA_{1c}=glycated haemoglobin A_{1c}; eGFR=estimated glomerular filtration rate. DPP-4=dipeptidyl peptidase-4. UACR=urinary albumin-to-creatinine ratio. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *Myocardial infarction, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial ischaemia on imaging or stress test, or coronary, carotid, or peripheral revascularisation. †Myocardial infarction or ischaemic stroke. ‡Data are mean (SD); median (IQR). §UACR 3.39 mg/mmol or more.

Table 1: Baseline characteristics

were not adjusted for multiple testing. The change from baseline in continuous variables was analysed using linear mixed models with baseline value as a covariate, participant as a random effect, and fixed effects for treatment, visit, and treatment–visit interaction, and reported as the least-squares mean (LSM) value.²⁴ A set of plausible ranges for laboratory tests were defined before unblinding (appendix p 34) and tests with values outside these ranges were excluded from the analyses. The proportion of participants in each group who had prespecified adverse events of special interest were compared using log-rank tests, and the proportion who had serious adverse events and adverse events were compared using χ^2 tests. Data were analysed with SAS software (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT01394952.

Role of the funding source

The trial was sponsored and funded by Eli Lilly and Company led by an international steering committee coordinated by the Population Health Research Institute in Hamilton, Canada, which also did all data analyses. Site management and data collection were provided by ICON Clinical Research. Scientists employed by the funder were on the steering committee and contributed to trial design, trial implementation, and data interpretation. All authors and the sponsor jointly made the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 18, 2011, and Aug 14, 2013, 12 133 patients were screened at 371 sites in 24 countries. 10 917 eligible patients began the 3-week run-in period, of whom 9901 were randomly assigned to treatment group (dulaglutide, n=4949; placebo, n=4952; figure 1). Follow-up ended on Aug 21, 2018.

Mean age of participants was 66.2 years [SD 6.5], and 4589 [46.3%] were female (table 1, appendix p 35).¹⁷ At baseline, 3114 (31.5%) participants reported previous cardiovascular disease and 2199 (22.2%) had a baseline eGFR less than 60 mL/min per 1.73 m². The median duration of diabetes was 9.5 years (IQR 5.5–14.5), median HbA_{1c} was 7.2% (IQR 6.6–8.1), and median eGFR was 74.9 mL/min per 1.73 m² (IQR 61.4–91.1).

During a median follow-up of 5.4 years (IQR 5.1–5.9) comprising 51 820 person-years, the primary composite outcome status was known in 9610 (97.1%) participants (figure 1). 2092 (42.3%) of 4949 participants assigned to dulaglutide and 2171 (43.8%) of 4952 participants assigned to placebo had at least one discontinuation of study drug during follow-up, whereas 3621 (73.2%) assigned to dulaglutide and 3520 (71.1%) assigned to placebo were taking study drug at the last visit. Participants assigned to dulaglutide took study drug for

82.2% of the follow-up time from randomisation until either a primary outcome event or final follow-up, compared with 83.1% of the follow-up time for patients assigned to placebo. Study drug was well tolerated; 451 (9.1%) participants assigned to dulaglutide and 310 (6.3%) assigned to placebo permanently stopped study drug during follow-up because of an adverse event. There were no between-group differences in use of other medications at baseline (table 1), but fewer participants in the dulaglutide group than in the placebo group were taking a GLP-1 receptor agonist, SGLT2 inhibitor, metformin, sulfonylurea, insulin, or angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker at the last visit (appendix p 36).

The primary composite outcome occurred in 594 (12.0%) participants (2.4 per 100 person-years) assigned to dulaglutide and 663 (13.4%) participants (2.7 per 100 person-years) assigned to placebo (HR 0.88, 95% CI 0.79–0.99; p=0.026; figure 2, table 2). Consistent effects were observed for all three components of the composite primary outcome ($p_{\text{heterogeneity}}=0.89$),¹⁹ with HRs of 0.91 (95% CI 0.78–1.06; p=0.21) for cardiovascular death, 0.96 (0.79–1.16; p=0.65) for non-fatal myocardial infarction, and 0.76 (0.61–0.95; p=0.017) for non-fatal stroke (figure 2, table 2).

When assessed within subgroups, the HR of the intervention on the primary outcome was similar in participants with and without previous cardiovascular

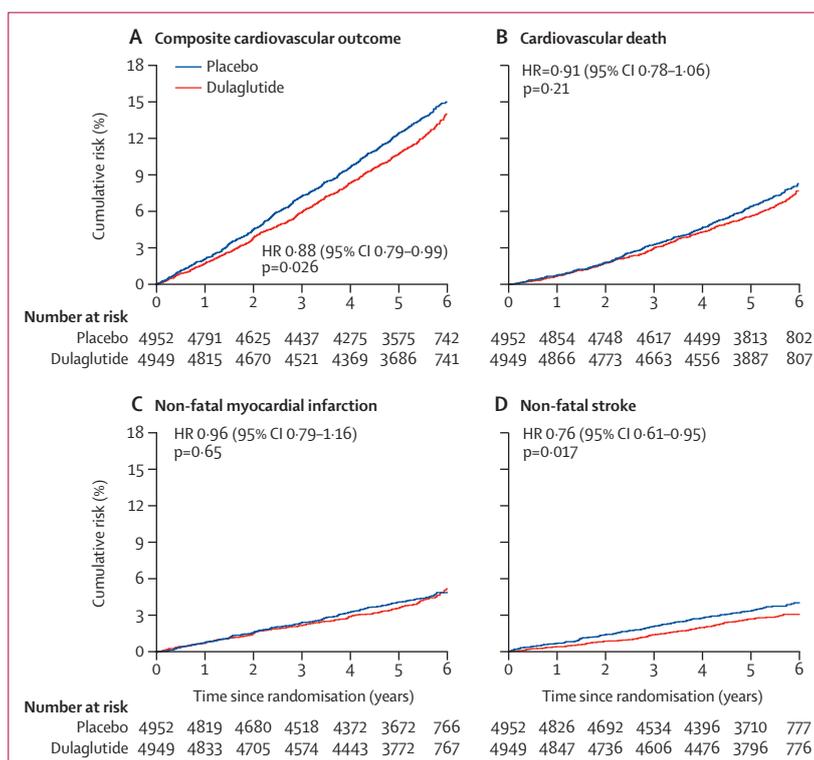


Figure 2: Cumulative incidence of cardiovascular outcomes

HR=hazard ratio. HbA_{1c}=glycated haemoglobin A_{1c}.

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Primary composite outcome	594 (12.0%)	2.35	663 (13.4%)	2.66	0.88 (0.79–0.99)*	0.026
Myocardial infarction	223 (4.5%)	0.87	231 (4.7%)	0.91	0.96 (0.79–1.15)	0.63
Non-fatal myocardial infarction	205 (4.1%)	0.80	212 (4.3%)	0.84	0.96 (0.79–1.16)	0.65
Fatal myocardial infarction	26 (0.5%)	0.10	20 (0.4%)	0.08	1.29 (0.72–2.30)	0.40
Stroke	158 (3.2%)	0.61	205 (4.1%)	0.81	0.76 (0.62–0.94)	0.010
Non-fatal stroke	135 (2.7%)	0.52	175 (3.5%)	0.69	0.76 (0.61–0.95)	0.017
Fatal stroke	26 (0.5%)	0.10	33 (0.7%)	0.13	0.78 (0.47–1.30)	0.34
Cardiovascular death†	317 (6.4%)	1.22	346 (7.0%)	1.34	0.91 (0.78–1.06)	0.21
Non-cardiovascular death	219 (4.4%)	0.84	246 (5.0%)	0.95	0.88 (0.73–1.06)	0.18
All-cause death	536 (10.8%)	2.06	592 (12.0%)	2.29	0.90 (0.80–1.01)	0.067
Hospital admission for heart failure or urgent visit	213 (4.3%)	0.83	226 (4.6%)	0.89	0.93 (0.77–1.12)	0.46
Hospital admission for unstable angina	88 (1.8%)	0.34	77 (1.6%)	0.30	1.14 (0.84–1.54)	0.41
Composite microvascular outcome (eye or renal outcome)	910 (18.4%)	3.76	1019 (20.6%)	4.31	0.87 (0.79–0.95)	0.0020
Eye outcome‡	95 (1.9%)	0.37	76 (1.5%)	0.30	1.24 (0.92–1.68)	0.16
Renal outcome§	848 (17.1%)	3.47	970 (19.6%)	4.07	0.85 (0.77–0.93)	0.0004

All hazard ratios (HRs) were estimated with Cox proportional hazards models and p values are two-sided. *After accounting for $\alpha=0.009$ spent on the primary outcome for the interim analysis, the α for the final analysis is 0.0467, and the HR is 0.88 (95.33% CI 0.79–0.99). †Includes deaths of unknown cause. ‡Photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy. §New macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy.

Table 2: Primary and secondary outcomes

disease ($p_{\text{interaction}}=0.97$), in participants whose HbA_{1c} was less than 7.2% or greater-than or equal to 7.2% ($p_{\text{interaction}}=0.75$), and in participants analysed according to age, sex, duration of diabetes, and BMI (figure 3). There was nominally significant heterogeneity with respect to geographical region ($p_{\text{interaction}}=0.0080$). Similar HRs were also noted when the effect of dulaglutide was explored in post-hoc subgroups based on a previous cardiovascular event (ie, myocardial infarction or ischaemic stroke), different HbA_{1c} or BMI categories, or ethnicity (appendix p 37).

The incidence of the composite microvascular outcome was lower in participants assigned to dulaglutide than in those assigned to placebo (3.8 per 100 person-years vs 4.3 per 100 person-years, respectively; HR 0.87, 95% CI 0.79–0.95; table 2, appendix p 30). This difference was characterised by fewer composite renal outcomes in the dulaglutide group than in the placebo group (3.5 per 100 person-years vs 4.1 per 100 person-years, respectively; HR 0.85, 95% CI 0.77–0.93). Dulaglutide did not significantly affect the incidence of all-cause mortality, heart failure, revascularisation, hospital admissions, fractures, or cholelithiasis (table 2; appendix p 31, 38).

During follow-up, differences from baseline were greater in the dulaglutide group than in the placebo group for several measurements. Compared with participants in the placebo group, participants assigned to dulaglutide

had a 0.61% (95% CI 0.58–0.65) lower LSM HbA_{1c} ($p<0.0001$), 1.46 kg (1.25–1.67) lower LSM bodyweight ($p<0.0001$), 0.53 kg/m² (0.46–0.61) lower LSM BMI ($p<0.0001$), 1.70 mm Hg (1.33–2.07) lower LSM systolic blood pressure ($p<0.0001$), 0.49 mm Hg (0.25–0.73) lower LSM mean arterial blood pressure, 1.82 mm Hg (1.53–2.12) lower LSM pulse pressure, 1.87 beats per min (1.62–2.11) higher LSM heart rate ($p<0.0001$), 0.07 mmol/L (0.03–0.10) lower LSM total cholesterol, 0.05 mmol/L (0.02–0.08) lower LSM LDL cholesterol, and a lower ratio of waist-to-hip circumference in men and women (figure 4, appendix pp 32, 39).

Frequencies of prespecified adverse events of special interest, including first study drug discontinuation, serious gastrointestinal events, severe hypoglycaemia, cancers, or pancreatitis, did not differ significantly between the dulaglutide and placebo groups (table 3). The numbers of serious adverse events did not differ significantly between groups (appendix p 40). However, 2347 (47.4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34.1%) participants assigned to placebo ($p<0.0001$; appendix p 41).

Discussion

This long-duration randomised controlled trial of people with type 2 diabetes and only a 31.5% prevalence of previous cardiovascular disease showed that a weekly

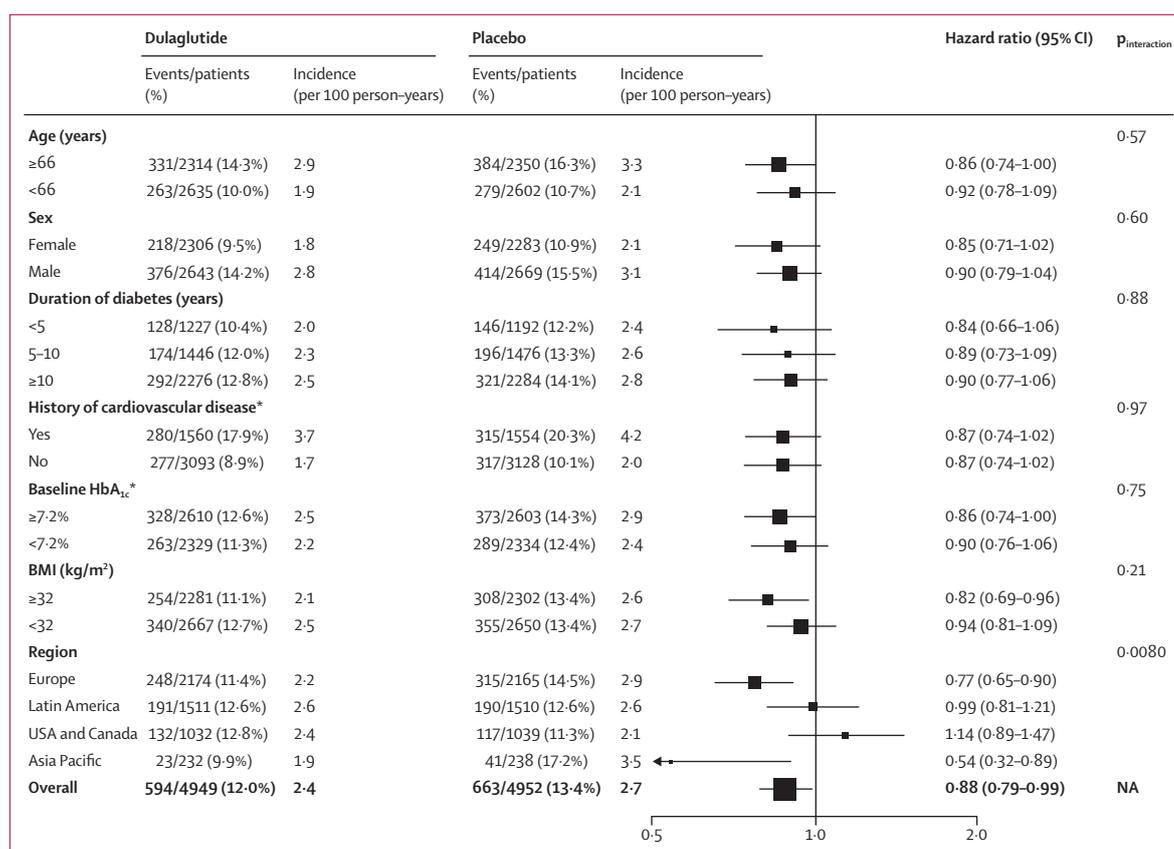


Figure 3: Subgroup analyses for the primary cardiovascular outcome

The size of each box is proportional to the number of events. BMI=body-mass index. NA=not applicable. *Participants were not included in a category if the criteria or test result needed to assign them to a category were unknown or missing.

injection of 1.5 mg dulaglutide reduced the risk of cardiovascular outcomes compared with placebo, with the Kaplan-Meier curves starting to diverge within the first year. Across the three components of the composite primary outcome, the greatest between-group difference was seen in the number of non-fatal strokes. In this population of people with a mean duration of type 2 diabetes of 10 years, in whom 25% had a baseline HbA_{1c} less than 6.6% and 25% had a level more than 8.1%, dulaglutide durably reduced HbA_{1c} by a mean absolute amount of 0.6% more than placebo while not increasing hypoglycaemia. It also modestly reduced weight, LDL cholesterol, and systolic blood pressure, modestly increased heart rate, and was well tolerated with high adherence. For every 60 people with type 2 diabetes and additional cardiovascular risk factors who were treated with dulaglutide for a median of 5.4 years versus placebo, one cardiovascular event was prevented. The number needed to treat is 18 for people with a previous cardiovascular event.

The REWIND trial differs from previous cardiovascular outcomes trials with GLP-1 receptor agonists^{7,8} in several ways. First, the other trials were designed to show non-inferiority to placebo with respect to cardiovascular

events, whereas REWIND prospectively tested the hypothesis that dulaglutide was superior. Second, most of the participants in REWIND did not have previous cardiovascular disease or a previous cardiovascular event. Thus, the average cardiovascular incidence of participants assigned to placebo was 2.7%, which was lower than the annual placebo incidence rates for the same composite outcome of 3.9% or higher in the other trials.⁵ Moreover, the broad inclusion criteria, high proportion of women, and the representativeness of the recruited participants²⁵ in REWIND suggest that dulaglutide might be effective for both primary and secondary cardiovascular prevention in a high proportion of people with type 2 diabetes. Third, the 5.4-year median follow-up was much longer than that in the other cardiovascular outcomes trials, in which median follow-up ranged from 1.5 years to 3.8 years,^{5,7} showing that the cardiovascular benefits of GLP-1 receptor agonists extend much longer than previously reported. Fourth, our trial shows the durability and safety of the effect of dulaglutide on glucose, blood pressure, and weight, and represents the longest trial of the effect of a GLP-1 receptor agonist on these measures. Finally, our findings show that dulaglutide reduces cardiovascular events in people with HbA_{1c}

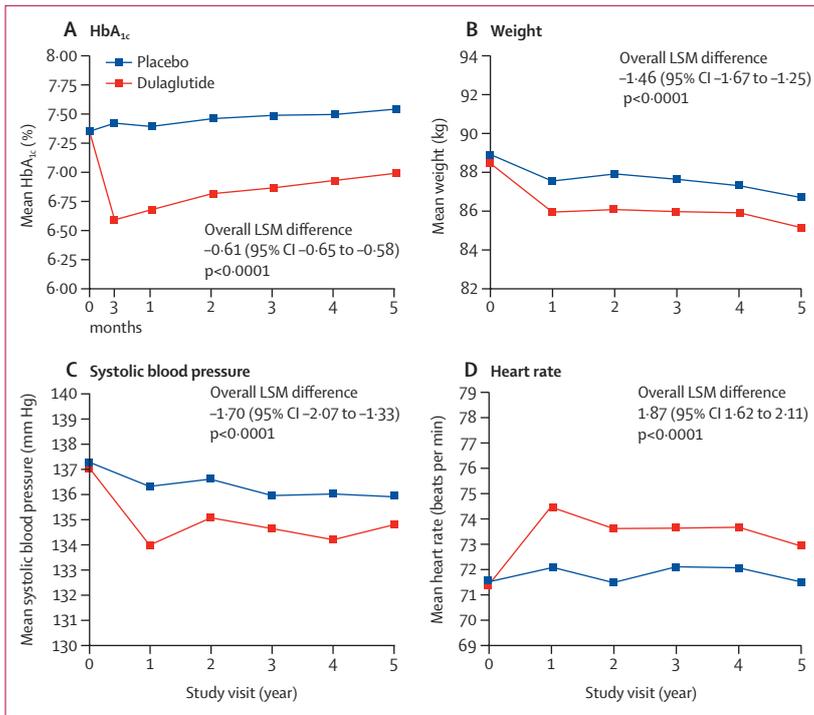


Figure 4: Continuous measures during follow-up
 LSM=least-square means. HbA_{1c}=glycated haemoglobin A_{1c}.

	Dulaglutide (n=4949)	Placebo (n=4952)	Log-rank test p value
First study drug discontinuation	2092 (42.3%)	2171 (43.8%)	0.38
Acute pancreatitis*	23 (0.5%)	13 (0.3%)	0.11
Imaging and enzymes†	4 (0.1%)	3 (0.1%)	0.71
Imaging, enzymes, and symptoms‡	4 (0.1%)	3 (0.1%)	0.71
Any cancer§	351 (7.1%)	348 (7.0%)	0.98
Medullary thyroid carcinoma or C-cell hyperplasia¶	1 (<0.1%)	0	0.32
Thyroid cancer	7 (0.1%)	3 (0.1%)	0.21
Pancreatic cancer	19 (0.4%)	12 (0.2%)	0.22
Serious hepatic event	25 (0.5%)	40 (0.8%)	0.057
Serious renal or urinary event	84 (1.7%)	93 (1.9%)	0.46
Immune reactions	8 (0.2%)	20 (0.4%)	0.022
Serious gastrointestinal event	120 (2.4%)	117 (2.4%)	0.87
Supraventricular tachycardia or cardiovascular conduction disorders	216 (4.4%)	192 (3.9%)	0.26
Severe hypoglycaemia	64 (1.3%)	74 (1.5%)	0.38

*Based on the first occurrence of acute pancreatitis, diagnosed on the basis of at least two of the three diagnostic criteria (symptoms, elevated pancreatic enzymes, or an abnormal pancreatic image). †The subset of participants with first acute pancreatitis who had both elevated pancreatic enzymes and an abnormal pancreatic image. ‡The subset of participants with first acute pancreatitis who had all three of elevated pancreatic enzymes, an abnormal pancreatic image, and symptoms. §Excluding non-melanoma skin cancers. ¶There were no cases of medullary thyroid carcinoma. ||Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

Table 3: Prespecified adverse events of special interest reported during the trial

concentrations both within and higher than guideline-recommended targets, without increasing weight or the risk of hypoglycaemia, and has effect sizes that are

similar to those in the other trials with higher baseline HbA_{1c} concentrations.^{5-7,26,27}

Several possibilities could account for the salutary effects of dulaglutide and other GLP-1 receptor agonists on cardiovascular outcomes. These include the reduction in HbA_{1c}, LDL cholesterol, blood pressure, and weight. Emerging evidence also suggests that these drugs might independently improve endothelial function, endothelial cell responses to ischaemia, and platelet function, and might have direct neuroprotective effects.²⁸ These drugs might also attenuate progression of atherosclerosis, vascular inflammation, and vasoconstriction.²⁹

Irrespective of the mechanism, the unique features of this trial add to a growing body of literature describing the cardiovascular effects of GLP-1 receptor agonists,⁸ and suggest that most middle-aged and older people with type 2 diabetes can achieve cardiovascular benefits with GLP-1 receptor agonists such as dulaglutide. Consistent with the findings from three cardiovascular outcomes trials of other GLP-1 receptor agonists,^{5,6,27,30} the REWIND trial raises the possibility of a greater effect on stroke than on myocardial infarction. Although it also raises the possibility of some geographical variation of effect, this variation loses statistical significance after accounting for the seven subgroups that were assessed (for which the Bonferroni-corrected p value for significance is <0.05/7 or 0.007), and might therefore be a spurious finding. Finally, the suggestion of a protective effect of dulaglutide on renal outcomes is consistent with the other trials in which renal outcomes were reported,^{5,6,27} and supports further analyses of these effects. The long-term effect of dulaglutide on renal outcomes has been assessed in an exploratory analysis, published elsewhere.³¹

Strengths of these findings include the trial's broad and representative inclusion criteria and recruited participants,²⁵ long follow-up, high retention, measurement of clinically relevant outcomes, and investigator freedom to use any non-GLP-1 receptor agonist drug. Although less than a third of participants had previous cardiovascular disease, the observed cardiovascular effect size is similar to the HR of 0.87 from a meta-analysis of outcome trials of other GLP-1 receptor agonists in mainly secondary prevention populations.³² This observation, and the fact that there was a numerically greater use of proven cardioprotective drugs in the placebo group (which might have diminished the effect size of dulaglutide) further support these findings. The major limitation is the observation that more than 25% of participants were not taking study drug at the time of their last visit. Although this might have also diminished the benefit of allocation to dulaglutide, the observation that participants took study drug for more than 80% of the follow-up time is reassuring.

Our findings show that the addition of dulaglutide to the medical regimen of people with type 2 diabetes and a broad range of glycaemic control reduced a composite of cardiovascular outcomes over a 5 year period. Moreover,

our results suggest that dulaglutide could be added to the management of people with diabetes and additional cardiovascular risk factors to reduce glucose concentrations, minimise hypoglycaemia, reduce weight and blood pressure, and reduce cardiovascular events.

Contributors

HCG (REWIND Chair) prepared the first draft of the report, and together with HMC, GRD, RD, ML, PP, JP, JSR, MCR, LR, and DX reviewed the literature, provided overall trial leadership, and interpreted the data. LD, PR-M, GW, and CMA did or confirmed the statistical analyses, and LD and PR-M prepared the figures. All other authors led the trial overall or in their respective countries and all authors critically reviewed and revised the report before submission.

Declaration of interests

HCG holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly, AstraZeneca, Merck, Novo Nordisk, and Sanofi; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Janssen, Sanofi, Kowa, and Cirus. HMC reports research grants from Eli Lilly, AstraZeneca, Regeneron, Pfizer, Roche, Sanofi, and Novo Nordisk; honoraria for speaking from Eli Lilly and Regeneron; consulting fees from Eli Lilly, Novartis, Regeneron, Sanofi, and Novo Nordisk; and shares in Bayer and Roche. RD reports research grants from the Population Health Research Institute, Duke Clinical Research Institute, Montreal Health Innovations Coordinating Center, CPC Clinical Research, DalCor, Amgen, Lepetit, and Cirus; honoraria for speaking from Sanofi; and consulting fees from Sanofi and Cirus. MCR reports grants to his institution from Eli Lilly, AstraZeneca, and Novo Nordisk; honoraria for consulting from Adocia, DalCor, GlaxoSmithKline, and Theracos; and honoraria for speaking from Sanofi. LR reports grants from the Swedish Heart Lung Foundation, Stockholms Läns Landsting, and Boehringer Ingelheim, and fees for consulting and speaking from Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Merck, and Bayer. ML is employed by Eli Lilly, owns stock, and has a patent pending. JSR is employed by Eli Lilly and has a patent pending. CMA is employed by Eli Lilly and owns stock. DX reports grants from Cadila, Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, Pfizer, Bristol-Myers Squibb, the UK Medical Research Council, and the Wellcome Trust. JB reports consulting fees from Eli Lilly, ReCor, and Medtronic. WCC reports grants from Eli Lilly. EF reports consulting and speaking fees from AstraZeneca, Boehringer Ingelheim, Bioton, Mundipharma, MSD, Novartis, Novo Nordisk, and Servier. MH reports honoraria for speaking from Sanofi, Novo Nordisk, Amgen, MSD, and AstraZeneca. FL reports grants from the Population Health Research Institute. LAL reports grants from Eli Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, and GSK; honoraria for speaking from Eli Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Novo Nordisk, and Sanofi; and consulting fees from Eli Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Novo Nordisk, Sanofi, and Servier. JES reports grants from Eli Lilly, and consulting fees or speaking honoraria from AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, Mylan, Boehringer Ingelheim, Merck Sharp and Dohme, and Abbott. TT-K reports consulting fees from Bayer, AstraZeneca, and Hamilton Health Sciences. All other authors declare no competing interests.

Data sharing

The data sharing policy is described in the appendix (pp 28–29).

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Supplementary appendix

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APPENDIX 1 - REWIND Trial

Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND): A Double-blind, Randomised Placebo-controlled Trial

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Criteria for Adjudication of Reported Clinical Events

Individual members of the CEC committees will perform adjudication based on definitions adapted from the October 2010 draft of the FDA task force Standardized Definitions for Endpoint Events in Cardiovascular Trials document. Definitions of acute and chronic pancreatitis, medullary thyroid carcinoma, and C-cell hyperplasia are based on clinical practice guidelines.

1. DEATH

1.1. Definition of CV Death

CV death includes death due to myocardial infarction (MI), sudden cardiac death, death due to heart failure or cardiogenic shock, death due to stroke, and death due to other cardiovascular causes.

- **Death due to Acute MI**

Death due to Acute MI refers to a death by any mechanism (arrhythmia, heart failure, low output) within 30 days after an MI related to the immediate consequences of the MI, such as progressive heart failure (HF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., HF and arrhythmia free period of at least one week), they will be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an MI). The MI will be verified to the extent possible by the diagnostic criteria outlined for MI or by autopsy findings showing recent MI or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy will be considered as death resulting from an MI, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Death resulting from an emergent procedure to treat an MI such as a percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), or to treat an immediate complication resulting from an MI, will also be considered as a death due to MI.

Death resulting from a procedure to treat myocardial ischemia (angina) or death due to MI that occurs as a direct consequence of a CV investigation/procedure/operation will be considered as a death due to other CV causes.

- **Sudden Cardiac Death**

Sudden cardiac death refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths:

- a. Witnessed and instantaneous without new or worsening symptoms
- b. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms unless the symptoms suggest MI
- c. Witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- d. Death after unsuccessful resuscitation from cardiac arrest
- e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)

- f. Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided)

A subject seen alive and clinically stable 12 to 24 hours prior to being found dead without any evidence or information of a specific cause of death will be classified as "sudden cardiac death." Typical scenarios include:

- a. Subject was well the previous day but found dead in bed the next day
b. Subject found dead at home on the couch with the television on

Unwitnessed deaths for which there is no information beyond "Patient found dead at home" will be classified as "death due to other CV causes."

- **Death due to Heart Failure or Cardiogenic Shock**

Death due to Heart Failure or Cardiogenic Shock refers to death occurring in the context of new or clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death and not following an MI. Deaths due to heart failure can have various etiologies, including one or more MIs (late effect), ischemic or non-ischemic cardiomyopathy, or valve disease.

Death due to Heart Failure or Cardiogenic shock will include sudden death occurring during an admission for new or worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of HF include any of the following:

- a. New or increasing symptoms, and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
b. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration for hypoxia due to pulmonary edema
c. Confinement to bed predominantly due to heart failure symptoms
d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an MI, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
e. Cardiogenic shock not occurring in the context of MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock will be defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Oliguria (urine output < 30 mL/hour) or
- Altered sensorium or
- Cardiac index < 2.2 L/min/m²

Cardiogenic shock may also be defined if SBP < 90 mm Hg and increases to ≥90 mm Hg in less than 1 hour (with positive inotropic or vasopressor agents alone and/or with mechanical support.)

- **Death due to Stroke**

Death due to Stroke refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

- **Death due to Other Cardiovascular Causes**

Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories (e.g., dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, CV intervention [other than one related to an MI], aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization will be classified as CV deaths.

1.2. Definition of Non-CV Death

Non-CV death is defined as any death that is not thought to be due to a CV cause. The CEC will attempt to classify Non-CV Causes into one the following categories:

- Pulmonary
- Renal (includes renal organ failure)
- Gastrointestinal (includes hepatobiliary, pancreatic, GI organ failure)
- Primary Infection (not nosocomial infection or complication of other or protracted illness)
- Malignancy/Hematologic Disorder
- Complication of Non-CV Surgery
- Degenerative Neurologic\Non-Stroke or ICH (Parkinson's, Alzheimer's)
- Other, Non-CV

Death due to a gastrointestinal bleed will be considered a non-CV death.

1.3. Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be infrequent and should only apply to a minimal number of patients.

2. MYOCARDIAL INFARCTION

The term myocardial infarction (MI) will be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI will require the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

The totality of the clinical, electrocardiographic, and cardiac biomarker information will be considered to determine whether or not an MI has occurred. Specifically, timing and trends in cardiac biomarkers and

electrocardiographic information will be carefully analyzed. The adjudication of MI will also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2.1. Criteria for MI

- Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI will be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, HF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information will also be considered from myocardial and coronary imaging. The totality of the data may help differentiate MI from the background disease process.

- Biomarker Elevations

For cardiac biomarkers, sites should report the laboratories' upper reference limit (URL). If the 99th percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory will be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory will be used as the URL. Sites can also report both the 99th percentile of the URL and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK-MB, troponin, or CK will be required. The specific criteria will be referenced to the URL.

In patients who present acutely to hospitals which are not participating sites, and it is not practical to stipulate the use of a single biomarker or assay, the locally available results will be used as the basis for adjudication.

- Electrocardiogram (ECG) Changes

Electrocardiographic changes will be used to support or confirm an MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- **Criteria for MI (in absence of left ventricular hypertrophy (LVH) and left bundle branch block [LBBB]):**

- ST elevation

New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: 2: 0.2 mV in men (> 0.25 mV in men < 40 years) or 2: 0.15 mV in women in leads V2-V3 and/or 2: 0.1 mV in other leads.

- ST depression and T-wave changes

New horizontal or down-sloping ST depression 2: 0.05 mV in two contiguous leads and/or new T inversion 2: 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for Pathological Q-wave**

- Any Q-wave in leads V2-V3 2: 0.02 seconds or QS complex in leads V2 and V3
- Q-wave 2: 0.03 seconds and 2: 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF). The same criteria will be used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

2.2. Myocardial Infarction Subtypes

MIs will be classified into the following subtypes as defined below:

- **Spontaneous MI:**

1. Detect ion of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:
 - Clinical presentation consistent with ischemia
 - ECG evidence of MI (new pathological Q waves)
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
 - Autopsy evidence of MI
2. If biomarkers are elevated from a prior infarction, then a spontaneous MI will be defined as
 - a. One of the following:
 - Clinical presentation consistent with ischemia
 - ECG evidence of MI (new pathological Q waves)
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
 - Autopsy evidence of MI

AND

- b. Both of the following:
 - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI
 - $\geq 20\%$ increase (and $>$ URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

- **PCI-Related MI**

PCI-related MI will be defined by any of the following criteria. Symptoms of cardiac ischemia will not be required.

1. Biomarker elevations within 48 hours of PCI:

- Troponin or CK-MB (preferred) >3 x URL and
- No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

Both of the following must be true:

- A minimum of 50% increase in the cardiac biomarker result
 - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI
2. New pathological Q waves
 3. Autopsy evidence of MI

- **Coronary Artery Bypass Grafting-Related Myocardial Infarction**

CABG -related MI will be defined by the following criteria. Symptoms of cardiac ischemia will not be required.

1. Biomarker elevations within 72 hours of CABG:
 - Troponin or CK-MB (preferred) >5 x URL and
 - No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

Both of the following must be true:

- \geq 50% increase in the cardiac biomarker result
- Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

AND

2. One of the following:
 - New pathological Q-waves persistent through 30 days
 - New persistent non-rate-related LBBB
 - Angiographically documented new graft or native coronary artery occlusion
 - Other complication in the operating room resulting in loss of myocardium
 - Imaging evidence of new loss of viable myocardium

OR

3. Autopsy evidence of MI

- **Silent MI**

Silent MI will be defined by the following:

1. No symptomatic or biomarker evidence of MI

AND one of the following

2. New pathological Q-waves as compared to baseline or most proximate/prior ECG recorded post randomization

OR

3. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause

2.3. Clinical Classification of MI by the Universal MI Definition²

Each MI confirmed by the CEC to have met the definition of MI also will be classified using the following definitions:

- **Type 1**

Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

- **Type 2**

MI secondary to ischemia due to either increased oxygen demand or decreased supply, eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

- **Type 3**

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- **Type 4a**

MI associated with PCI

- **Type 4b**

MI associated with stent thrombosis as documented by angiography or at autopsy

- **Type 5**

MI associated with CABG.

2.4. Electrocardiographic Categorization of MI

Events of MI confirmed by the CEC also will be classified based on electrocardiographic features into the following classifications:

- ST-ElevationMI (STEMI)

- o a -wave

- o Non-Q wave
- Non-ST Elevation MI (NSTEMI)
 - o Q-wave
 - o Non-Q wave
- ECG not available or not interpretable

3. HOSPITALIZATION FOR UNSTABLE ANGINA

Unstable angina requiring hospitalization will be defined as:

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) **within 24 hours** of the most recent symptoms (or a date change if the time of admission/discharge is not available)

AND

3. At least one of the following:
 - a. New or worsening ST or T wave changes on ECG.
 - o ST Elevation
 - New ST elevation at the J-point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads
 - o ST depression and T-wave changes
 - New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads.

It is recognized that lesser ECG abnormalities may represent an ischemia response and will be accepted under the category of abnormal ECG findings.

- b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs
- c. Angiographic evidence of $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs
- d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criterion would be fulfilled if the admission for myocardial ischemia led to transfer to

another institution for the revascularization procedure without interceding home discharge.

AND

4. No evidence of MI.

Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of - blockers, will be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy without any of the additional findings listed under category 3, will be insufficient alone to support classification as hospitalization for unstable angina.

4. HEART FAILURE EVENT TYPES

4.1. Heart Failure Requiring Hospitalization

Heart failure (HF) requiring hospitalization will be defined as an event that meets the following criteria:

- a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour* stay (or a date change if the time of admission/discharge is not available).

AND

- b. Clinical symptoms of heart failure including at least one of the following: New or worsening
 - dyspnea
 - orthopnea
 - paroxysmal nocturnal dyspnea
 - increasing fatigue/worsening exercise tolerance

AND

- c. Physical signs of heart failure, including at least two of the following:
 - Edema (greater than 2+ lower extremity)
 - Pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress not occurring in the context of an MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure)
 - Jugular venous distension
 - Tachypnea (respiratory rate > 20 breaths/minute)
 - Rapid weight gain
 - S3 gallop
 - Increasing abdominal distension or ascites
 - Hepatojugular reflux

- Radiological evidence of worsening heart failure
- A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg or a cardiac index < 2.2 U min/m²

AND

- d. Need for additional/increased therapy
1. Initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF and including at least one of the following:
 - Initiation of or a significant augmentation in oral therapy for the treatment of HF
 - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
 - Uptitration of intravenous therapy, if already on therapy
 - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of HF.

AND

- e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms are identified.

Biomarker results (e.g., brain natriuretic peptide [BNP]) consistent with HF will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the URL, may also be supportive of the diagnosis of HF in selected cases (e.g., morbid obesity).

It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of HF requiring hospitalization, the diagnosis of HF would need to be the primary disease process accounting for the above signs and symptoms.

4.2. Urgent Heart Failure Visit

An Urgent Heart Failure Visit is defined as an event that meets all of the following:

1. The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
2. All signs and symptoms for HF hospitalization must be met as defined in above section
3. The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy which will not be sufficient.

5. REVASCULARIZATION PROCEDURES

Revascularization procedures will be defined as follows:

- **A coronary revascularization procedure** will be defined as a catheter based or open surgical procedure designed to improve myocardial blood flow. Insertion of a guidewire through a coronary guide catheter into a coronary artery or bypass graft for the purpose of PCI is considered intention for PCI.
- **A carotid revascularization procedure** will be defined as a catheter-based or open surgical procedure designed to improve carotid arterial blood flow. This procedure may include endarterectomy or stent placement. The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guidewire through a guide catheter into a peripheral artery.
- **A peripheral arterial revascularization procedure** will be defined as a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow. This procedure may include thrombectomy, embolectomy, atherectomy, dissection repair, angioplasty or stent placement. The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guidewire through a guide catheter into a peripheral artery.

5.1. Procedural Success/Failure

For any revascularization procedure, procedural success will be classified into one of the following categories:

Success:

- **Procedure Successful Based Upon Procedure Report and Medical Record** is a procedure that will be considered a complete success if the post-procedure visual residual stenosis is $<30\%$ with no decrement in flow. A procedure will be classified as a partial success if there is either a $>50\%$ residual stenosis by visual assessment or for coronary revascularization procedures, if at least TIMI Grade 2 Flow is not attained. For the procedure to be successful the patient must have been discharged to home and/or the hospitalization was not prolonged due to specific, procedure-related complications.
- **Procedure Successful Based Upon Medical Record, Absent Procedure Report** will apply if the patient was discharged to home and/or hospitalization was not prolonged due to specific procedure-related complications.

Failure:

- **Procedure a Failure Based Upon Procedure Report and Medical Record** is a procedure that will be classified a failure if there is a persistent total occlusion, if the lesion cannot be crossed, or if there is persistent abrupt closure. The procedure will also be classified as a failure if the patient's hospitalization was prolonged specifically due to procedure related complications.
- **Procedure a Failure Based Upon Medical Record, Absent Procedure Report** will apply if the patient's hospitalization was prolonged specifically due to procedure related complications.

Procedure Could not be Classified as a Success or Failure due to Absence of Source Documentation Despite Efforts to Obtain Source Documents.

6. CEREBROVASCULAR EVENT (STROKE)

6.1. TIA

TIA will be defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

6.2. Stroke

Stroke will be defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

6.3. Classification

A. Ischemic Stroke

Ischemic stroke will be defined as an acute episode of focal cerebral, spinal or retinal dysfunction caused by an infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke will be an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke will be defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a non-traumatic, intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke will be defined as a stroke with insufficient information to allow categorization as A or B.

6.4. Stroke Disability

Stroke disability will be measured using the modified Rankin Scale³ and will be assessed at approximately 30 days following the stroke diagnosis.

Scale Disability

0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

6.5. Additional Considerations

The distinction between a TIA and an Ischemic Stroke is the presence of infarction, not the transience of the symptoms. In addition to documentation of infarction, persistence of symptoms is an acceptable indicator of infarction.

7. PANCREATITIS

Events of pancreatitis will be classified as acute, chronic, or unknown.

7.1. Acute Pancreatitis

Acute pancreatitis (AP) will be defined as an event that meets 2 of the following 3 criteria.

1. Abdominal pain
 - Pain is generally located in the epigastric region
 - Pain may radiate to the back
 - Swift onset with pain reaching maximum intensity within 30 minutes. Pain varies in intensity, may be severe and persist for more than 24 hours without relief.
 - Pain is commonly associated with nausea and vomiting
 - Physical examination may reveal fever, tachycardia, and upper abdominal tenderness on palpation, associated with guarding. Rebound tenderness may be present.

2. Laboratory Criteria
 - Serum amylase and/or lipase > 3 x URL

3. CT, MRI, or other imaging modalities (eg, magnetic resonance cholangiopancreatography [MRCP], endoscopic ultrasound) showing findings consistent with inflammatory changes in the pancreas. Findings on imaging studies may include:
 - Enlargement of the pancreas with diffuse edema
 - Heterogeneity of pancreatic parenchyma
 - Peripancreatic stranding
 - Peripancreatic fluid collections
 - Pancreatic necrosis

7.2. Chronic Pancreatitis

Chronic pancreatitis (CP) is a chronic, irreversible inflammation (monocyte and lymphocyte) 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. CP will require at least 1 of the following clinical criteria and must be accompanied by well-defined abnormalities in imaging findings. These criteria were adapted from Bornman et al. (BMJ 2001;322:660-663) and Buchler et al (BMC Gastroenterology 2009;9[93]).

- Clinical Criteria:
 - a. Abdominal Pain, including some or all of the following characteristics:
 - Severe, dull epigastric pain that may radiate to the back
 - May be associated with nausea and vomiting
 - May be associated with meals or independent of meals
 - May be intermittent but it is not fleeting and can persist for days or maybe constant
 - Epigastric tenderness may be present on physical examination
 - b. Attacks of AP,
 - c. Diarrhea,
 - d. Weight loss,
 - e. Steatorrhea,

OR

- f. Complications of CP such as one of the following:
 - Bile duct obstruction/stenosis with cholestasis or jaundice
 - Duodenal obstruction/stenosis with clinical signs
 - Vascular obstruction/stenosis with clinical or morphological signs of portal/splenic vein hypertension
 - Pancreatic pseudocysts with clinical signs (compression of adjacent organs, infection, bleeding, etc)
 - Pancreatic fistula (internal or external)
 - Pancreatogenic ascites
 - Other rare complications related to organs in vicinity (ie, colonic stenosis, splenic pseudocyst, etc)
- Imaging Criteria
 - Plain abdominal x-ray showing pancreatic calcifications
 - CT, MRI, or other imaging modalities (eg, ERCP, MRCP, endoscopic ultrasound) show ductal and/or parenchymal changes consistent with chronic pancreatitis: diffuse calcification, enlarged/irregular pancreas, dilated pancreatic duct \pm strictures, intrapancreatic cysts, pseudocysts, splenic vein thrombosis

Approximately 20% of patients have painless CP and present with signs and symptoms of pancreatic exocrine or endocrine insufficiency. Patients meeting these criteria will meet the definition of CP.

Diabetes mellitus is usually a criterion for the diagnosis of chronic pancreatitis; however, all patients enrolled in the REWIND trial must have type 2 diabetes and therefore this criterion was removed from the clinical criteria.

7.3. Unknown

Events that may meet the definition of pancreatitis but are unable to be classified as either AP or CP will be classified as unknown.

7.4. Severity of AP

The severity of AP will be classified as mild, moderate, severe, or critical using the criteria proposed by Petrov and Windsor (Am J Gastroenterol 2010;105:74-76). This classification is based on peri-pancreatic complications (absent, sterile, or infectious) and organ failure (absent, transient, persistent).

- **Mild:** no peri-pancreatic complication AND no organ failure
- **Moderate*:** sterile peri-pancreatic complication OR transient organ failure
- **Severe*:** infectious peri-pancreatic complication OR persistent organ failure
- **Critical:** infectious peri-pancreatic complication AND persistent organ failure

*Severity is graded on the basis of more severe local or systemic complication (e.g., sterile pancreatic necrosis without organ failure has to be graded as moderate; sterile pancreatic necrosis with persistent organ failure has to be graded as severe)

8. THYROID EVENTS REQUIRING A BIOPSY OR THYROIDECTOMY

The 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 will classify these events as C-cell hyperplasia, carcinoma in situ (microcarcinoma), medullary thyroid carcinoma, or other (i.e., papillary, follicular, and anaplastic).

To classify these events, the CEC will use all available data including physical examination, imaging study findings (eg, ultrasound), laboratory data (eg, calcitonin), and biopsy/surgical results (as reported by the local pathologist). Tissue samples will not be required in support of the adjudication process.

C-cell hyperplasia

Even though the pathological diagnosis of c cell hyperplasia is controversial (PW Biddinger and M Ray Pathology Annual. 28 PT 1:205-229, 1993), anatomically c-cell hyperplasia for this study will be defined as more than 50 c-cells per low power field (at 10 x magnification) (VA LiVols i et al. J Clin Endocrinol Metab 37:550, 1973).

Medullary Thyroid Carcinoma

Medullary carcinoma of the thyroid (MTC) will be defined as a distinct thyroid carcinoma that originates in the calcitonin producing parafollicular C cells of the thyroid gland. MTC usually runs a slow but progressive course which may include invasion of local neck structures and cervical lymph nodes. Calcitonin, and any other supporting laboratory results provided, will be reviewed and considered in the determination of MTC.

Medullary thyroid carcinoma (MTC) often appears to be multifocal but inhomogeneous and if detected early to be microscopic. The typical tumor histology has clusters of polyhedral neoplastic cells arranged in compartments separated by amyloid-containing stroma. This appearance with the absence of neoplastic follicles and papillary elements is the diagnostic feature which differentiates MTC from follicular cell tumors (CS Hill, et al., *Medicine (Baltimore)* 52:141-171, 1973).

The clinical staging system of the American Joint Committee on Cancer (AJCC) correlates survival to size of the primary tumor, presence or absence of lymph node metastases, and presence or absence of distant metastasis. Events of MTC will be classified according to stage based on the AJCC classification⁶.

Stage 0 medullary thyroid cancer

Clinically occult disease detected by provocative biochemical screening.

Stage I medullary thyroid cancer

Tumor smaller than 2 cm.

Stage II medullary thyroid cancer

Tumor larger than 2 cm but 4 cm or smaller with no metastases or larger than 4 cm with minimal extrathyroid extension.

Stage III medullary thyroid cancer

Tumor of any size with metastases limited to the pretracheal, paratracheal, or prelaryngeal/Delphian lymph nodes.

Stage IV medullary thyroid cancer

Stage IVA (moderately advanced with or without lymph node metastases [for T4a] but without distant metastases).

Stage IVB (very advanced with or without lymph node metastases but no distant metastases).

Stage IVC (distant metastases.)

Population Health Research Institute (PHRI) Data Sharing Policy

Effective Date: July 27, 2018

Data will be disclosed only upon request and approval of the proposed use of the data by a review committee. Membership in the review committee will be determined by the executive leadership of the study. Generally only those requests made by a journal's statistician regarding the data related to the results of the publication will be considered unless the review committee sees high merit in other requests. The following principles will apply to requests:

1. The review committee will have established criteria to review the request to ensure that patient privacy and rights, and PHRI data and research integrity can be maintained with the sharing of the data. This includes (but is not limited to) demonstrated competence related to data security and data analysis by the investigator requesting access. The review committee will also ensure that provision of data to external parties does not contravene any prior agreement with any other parties.
2. PHRI will make individual participant data available, including data dictionaries, within the requirements and/or restrictions of REB/IRB and subject to the conditions set forth in the consent forms of the study. Data provided will be limited to data which underlies the results in the main publication after de-identification. Any analyses and publications should be reviewed and approved by PHRI before publication to ensure that the analyses are accurate and that the publication is not misleading.
3. The study protocol and the statistical analysis plan for analysis of the primary results will be shared.
4. For those requests that originate from concerns expressed by the journal about the data or statistical analyses, the data will be available to the journal statisticians in a timely manner.
5. Data can be disclosed for all other requests from 2 years after the main paper is published plus 6 additional months for each year of study conduct. However, there will be a maximum of 7 years to the time limit restriction.
6. Data will be shared to achieve the objective in the approved proposal with no additional analysis permitted without approval. Only proposals for analyses that do not compete with ongoing analyses or analyses proposed by study investigators will be approved.
7. Data will be made available by one of the following mechanisms. 1) The Statistics Department at PHRI can perform the analysis in accordance with the SAP provided by the investigator and under his/her supervision or 2) Arrangement can be made to transfer the data to a secure location using a process that has been verified by the Director of Statistics at PHRI.
8. Every proposal must identify and provide funding sufficient to defray the cost of data preparation, storage, transfer and analysis for the organization incurring these costs (this may include studies not fully funded from external sources i.e. industry or peer review grants). On occasions where the new analyses proposed are of sufficient scientific interest to PHRI, then a collaborative agreement for joint analyses and publication can be developed and charges may be reduced.

9. The data will be provided for a specified time limit that can allow completion of the analyses that is proposed. At the end of the proposed analyses, the requesting party undertakes to return or destroy the data base provided and provide written documentation of this.

References

1. Taichman DB, Sahni, P, Pinborg A et al. Data Sharing Statements for Clinical Trials - A Requirement of the International Committee of Medical Journal Editors. *N Engl J Med* 2017; 376: 23:2277-9.
2. International Consortium of Investigators for Fairness in Trial Data. Devereaux PJ, Guyatt G, Gerstein H, Connolly S, Yusuf S. Toward Fairness in Data Sharing. *N Engl J Med* 2016;375:405-7.
3. Supplemental Endorsers of Article listed in 2

Figure S2: Dulaglutide's Effect on the Microvascular Composite Outcome

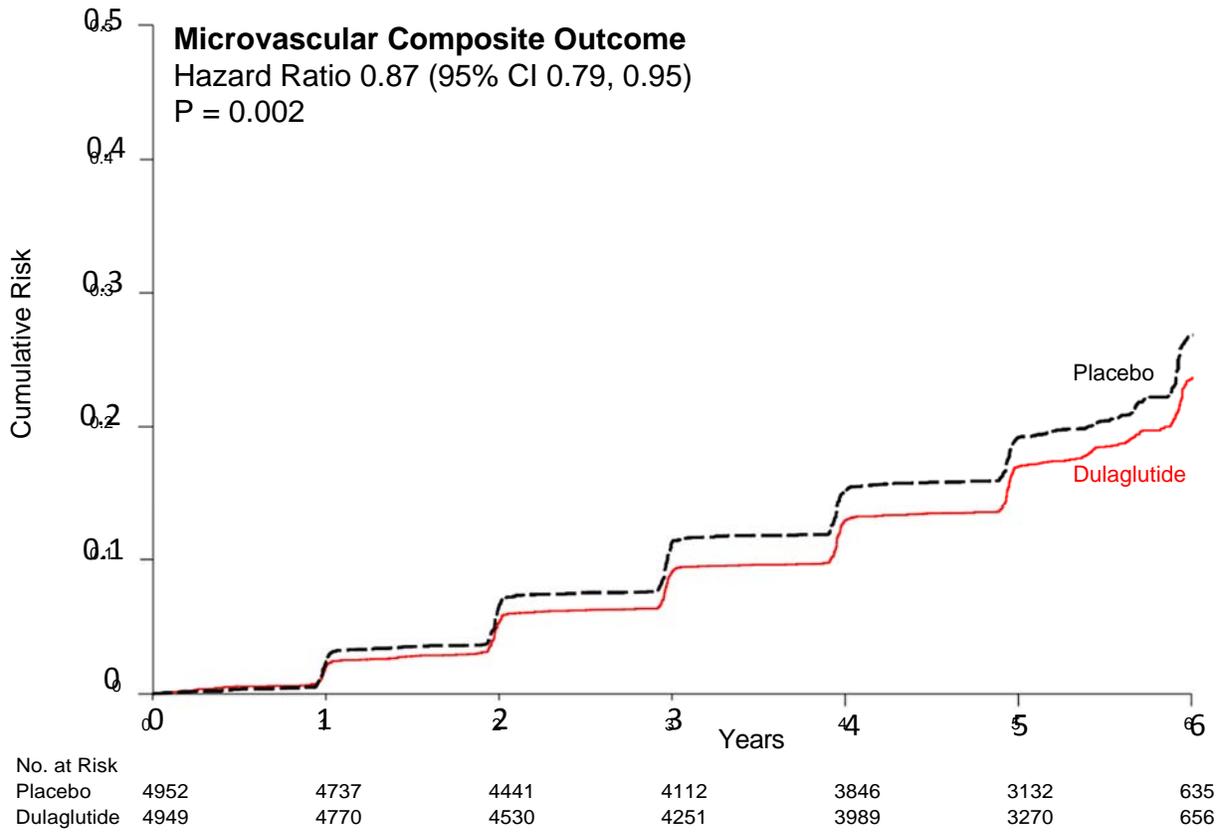


Figure S3: Dulaglutide’s Effect on All-Cause Mortality

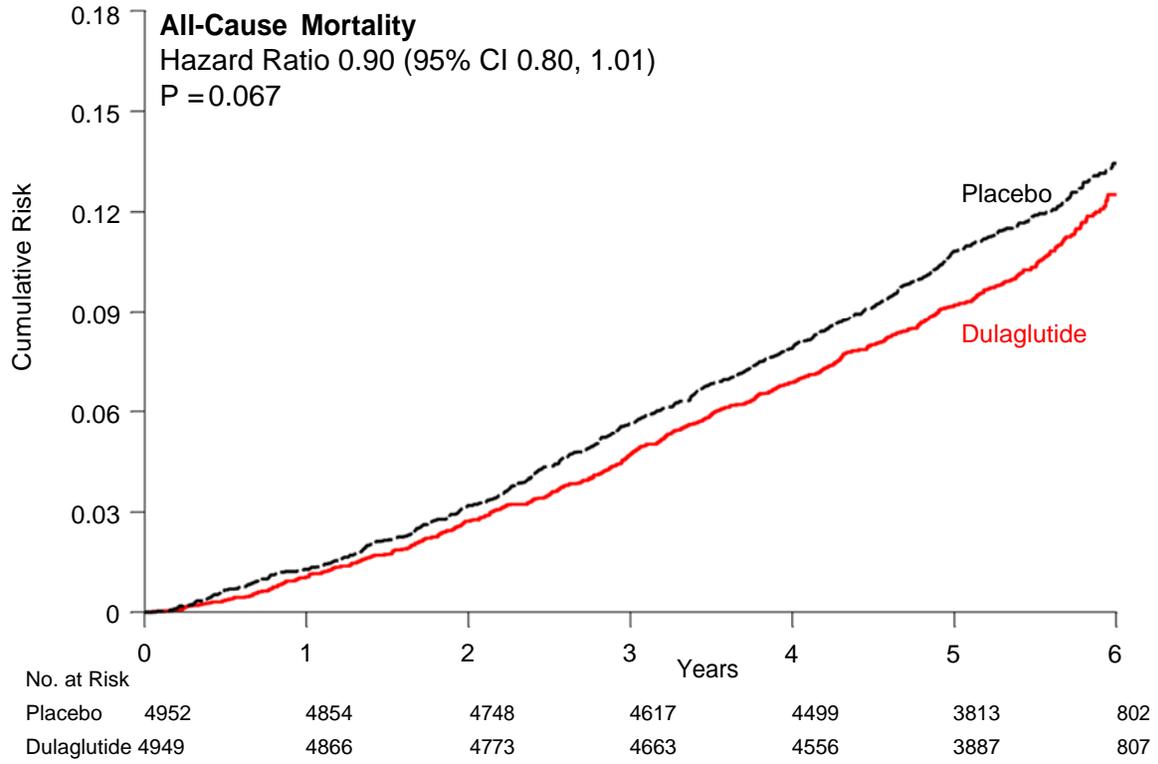


Figure S4: Effect on Dulaglutide on LDL Cholesterol

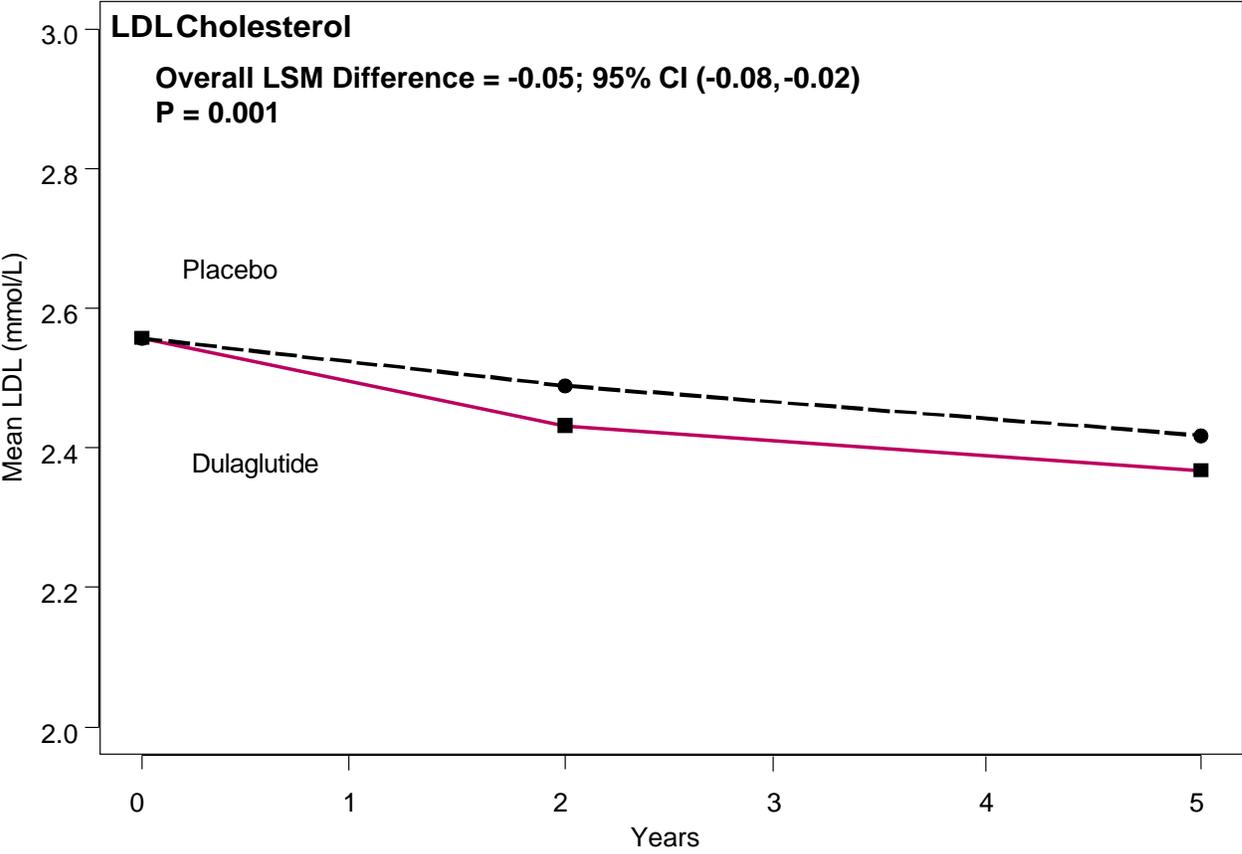


Figure S5: Summary of Primary & Secondary Outcomes

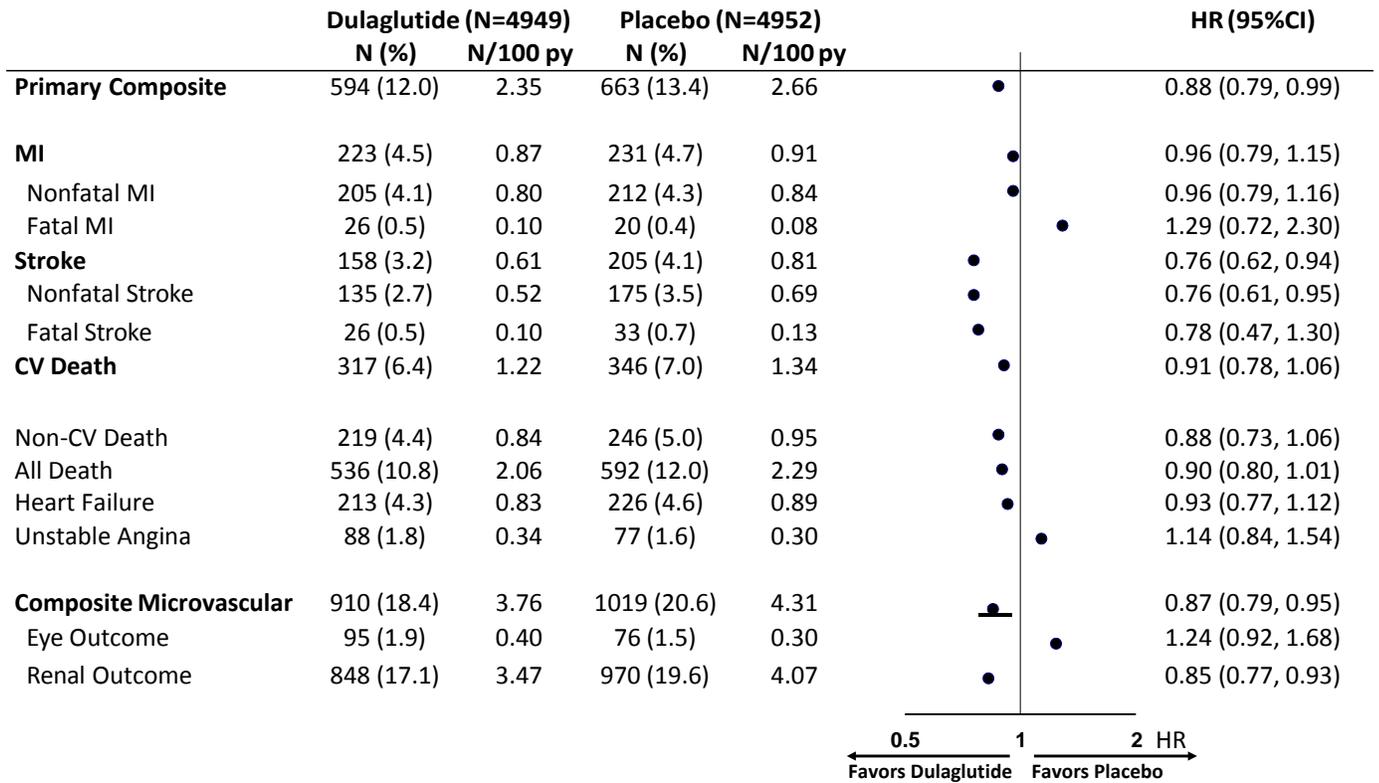


Table S1: Plausible Ranges for Measured Laboratory Tests

Measurement	Conventional Units		SI Units	
	Units	Limits	Units	Limits
HbA1c	%	2 to 20	Fraction	0.02 to 0.2
Calcitonin	pg/mL	None	pmol/L	None
Cholesterol	mg/dL	10 to 900	mmol/L	0.26 to 23.3
LDL Cholesterol	mg/dL	10 to 800	mmol/L	0.26 to 20.7
HDL Cholesterol	mg/dL	1 to 300	mmol/L	0.03 to 7.8
Triglycerides	mg/dL	10 to 2500	mmol/L	0.11 to 28.2
Serum Creatinine	mg/dL	0.2 to 5.6	umol/L	17.7 to 500
Urine ACR*	mg/g	< 9000	mg/mmol	< 1017

*For the ACR (albumin:creatinine ratio), values reported as below the limit of detection were assigned the lower limit of detection

Table S2: Key Baseline Characteristics by Geographic Region

Characteristic	Overall N=9901	Europe N=4339	Latin America N=3201	USA/Canada N=2071	Asia Pacific N=470
Age (years)	66.2 (6.5)	65.7 (6.4)	66.6 (6.7)	66.8 (6.4)	65.9 (6.7)
Female	4589 (46.4)	2169 (50.0)	1555 (51.5)	724 (35.0)	141 (30.0)
White	7498 (75.7)	3722 (85.8)	1849 (61.2)	1651 (79.7)	276 (58.7)
Current Tobacco	1407 (14.2)	754 (17.4)	351 (11.6)	236 (11.4)	66 (14.0)
Hypertension	9224 (93.2)	4126 (95.1)	2800 (92.7)	1899 (91.7)	399 (84.9)
Prior CVD*	3114 (31.5)	1292 (29.8)	914 (30.3)	686 (33.1)	222 (47.2)
Heart Failure	853 (8.6)	580 (13.4)	175 (5.8)	67 (3.2)	31 (6.60)
MI	1602 (16.2)	668 (15.4)	473 (15.7)	352 (17.0)	109 (23.3)
Stroke	687 (6.9)	342 (7.9)	206 (6.8)	108 (5.2)	31 (6.6)
Peripheral Artery Disease	856 (8.7)	466 (10.7)	231 (7.7)	134 (6.5)	25 (5.3)
Diabetes Duration	10.5 (7.2)	9.1 (6.3)	11.6 (7.8)	11.9 (7.7)	11.0 (7.1)
Diabetic Retinopathy	891 (9.0)	418 (9.6)	253 (8.4)	143 (6.9)	77 (16.4)
BMI (kg/m ²)	32.3 (5.7)	32.9 (5.6)	31.0 (5.5)	33.3 (6.1)	30.9 (5.7)
Systolic BP (mm Hg)	137.2 (16.8)	140.0 (16.4)	137.9 (16.8)	130.7 (15.5)	134.5 (17.3)
Diastolic BP (mm Hg)	78.5 (9.8)	80.6 (9.3)	78.7 (9.5)	74.0 (9.7)	76.5 (10.1)
Albuminuria	3467 (35.0)	1276 (29.4)	1405 (46.5)	576 (27.8)	139 (29.6)
Median HbA1c (%)	7.2 (6.6, 8.1)	7.2 (6.5, 8.0)	7.3 (6.5, 8.3)	7.2 (6.7, 8.0)	7.4 (6.8, 8.2)
Median eGFR (ml/min/1.73m ²)	74.9 (61.4, 91.1)	77.6 (64.1, 93.0)	69.4 (56.5, 84.6)	79.7 (63.3, 96.0)	77.0 (63.2, 91.1)
LDL Cholesterol (nmol/l)	2.56 (0.98)	2.74 (0.97)	2.76 (0.95)	1.96 (0.77)	2.16 (0.78)
ACEi/ARB	8068 (81.5)	3464 (79.8)	2495 (82.6)	1746 (84.3)	363 (77.2)
Statin	6547 (66.1)	2620 (60.4)	1741 (57.6)	1783 (86.1)	403 (85.7)

Continuous variables are shown as mean (standard deviation) or median (interquartile range); *myocardial infarction, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or coronary, carotid or peripheral revascularization

Table S3: Medications Used at Last Visit

	Dulaglutide (N=4949)	Placebo (N=4952)
Had a Final Visit	4932	4935
Metformin – N (%)	3436 (69.7)	3594 (72.8)
Sulfonylurea – N (%)	1608 (32.6)	1860 (37.7)
Insulin – N (%)	1336 (27.1)	1770 (35.9)
SGLT2i – N (%)	259 (5.3)	361 (7.3)
GLP-1 RA – N (%)	28 (0.6)	45 (0.9)
Thiazolidinedione – N (%)	71 (1.4)	97 (2.0)
Statin – N (%)	3281 (66.5)	3328 (67.4)
ARB or ACEi – N (%)	3739 (75.8)	3829 (77.6)
ASA – N (%)	2481 (50.3)	2514 (50.9)
Beta Blocker – N (%)	2302 (46.7)	2332 (47.3)

Table S4: Effect of Dulaglutide Within Novel (<i>post hoc</i>) Subgroups						
	Dulaglutide		Placebo		HR (95%CI)	P Int
	Events/Total (%)	Rate/100 py	Events/Total (%)	Rate/100 p y		
Overall	594/4949 (12.0)	2.35	663/4952 (13.4)	2.66	0.88 (0.79, 0.99)	
Prior CV* Event	196/1028 (19.1)	3.96	236/1007 (23.4)	4.99	0.79 (0.66, 0.96)	0.18
No Prior CV Event	396/3896 (10.2)	1.96	423/3920 (10.8)	2.11	0.93 (0.81, 1.07)	
BMI ≥ 30 kg/m ²	353/3027 (11.7)	2.25	401/3031 (13.2)	2.60	0.86 (0.75, 1.00)	0.67
BMI < 30 kg/m ²	241/1921 (12.5)	2.51	262/1921 (13.6)	2.76	0.91 (0.76, 1.08)	
HbA1c ≥ 7%	364/2957 (12.3)	2.42	419/2973 (14.1)	2.83	0.86 (0.74, 0.98)	0.56
HbA1c < 7%	227/1982 (11.5)	2.23	243/1964 (12.4)	2.43	0.92(0.76, 1.10)	
White	462/3754 (12.3)	2.40	505/3744 (13.5)	2.67	0.90 (0.79, 1.02)	0.77
Black	39/331 (11.8)	2.30	51/346 (14.7)	2.98	0.77 (0.51, 1.17)	
Asian	21/216 (9.7)	1.97	30/218 (13.8)	2.80	0.71 (0.40, 1.24)	
Other	72/648 (11.1)	2.23	77/644 (12.0)	2.42	0.92 (0.67, 1.28)	

*Prior myocardial infarction or ischemic stroke; P Int = P for interaction between treatment group and subgroup

Table S5: Effect of Treatment Allocation on Other Outcomes During Follow-up

Measurement	Dulaglutide	Placebo	P
Any Revascularization	365 (7.4)	387 (7.8)	0.37
Carotid Revascularization	18 (0.4)	29 (0.6)	0.10
Peripheral Revascularization	70 (1.4)	63 (1.3)	0.57
Coronary Revascularization	298 (6.0)	314 (6.3)	0.46
Any Hospitalization	2062 (41.7)	2108 (42.6)	0.18
Fracture	275(5.6)	262 (5.3)	0.65
Cholelithiasis	138 (2.8)	120 (2.4)	0.28

P values are from the Cox proportional hazards model

Table S6: Effect of Treatment Allocation on Continuous Variables During Follow-up

Measurement	Dulaglutide	Placebo	Difference ^a	P
HbA1c (%)	-0.46 (0.01)	0.16(0.01)	-0.61 (-0.65, -0.58)	<0.0001
Total Cholesterol (mM)	-0.20 (0.01)	-0.13 (0.01)	-0.07 (-0.10, -0.03)	0.0002
LDL Cholesterol (mM)	-0.15 (0.01)	-0.09 (0.01)	-0.05 (-0.08, -0.02)	0.001
Weight (kg)	-2.95 (0.08)	-1.49 (0.08)	-1.46 (-1.67, -1.25)	<0.0001
Body Mass Index (kg/m ²)	-1.08 (0.03)	-0.55 (0.03)	-0.53 (-0.61, -0.46)	<0.0001
Waist:Hip (Men)	-0.007 (0.001)	-0.004 (0.001)	-0.003 (-0.006, -0.0001)	0.04
Waist:Hip (Women)	-0.005 (0.001)	0.0 (0.001)	-0.005 (-0.008, -0.0012)	0.009
Systolic BP (mm Hg)	-3.15 (0.13)	-1.44 (0.13)	-1.70 (-2.07, -1.33)	<0.0001
Diastolic BP (mm Hg)	-1.93 (0.08)	-2.05 (0.08)	0.12 (-0.10, 0.34)	0.28
Mean BP (mm Hg)	-2.34 (0.09)	-1.85 (0.09)	-0.49 (-0.73, -0.25)	<0.0001
Pulse Pressure (mm Hg)	-1.21 (0.11)	0.61 (0.11)	-1.82 (-2.12, -1.53)	<0.0001
Heart Rate (beat/minute)	2.95 (0.09)	1.09 (0.09)	1.87 (1.62, 2.11)	<0.0001

Least square estimates (SE or 95%CI) for the within-treatment differences from baseline of people assigned to dulaglutide and placebo are shown; the P-value is the adjusted Tukey-Kramer value for the 2-group t test; ^abetween-treatment differences are expressed as dulaglutide-placebo with their 95% CI; BP – blood pressure; mean BP – mean arterial pressure = (systolic BP + 2*diastolic BP)/3

Table S7: Serious Adverse Events by System Organ Class Reported During the Trial

	Dulaglutide (N=4949)	Placebo (N=4952)	P
Blood And Lymphatic System Disorders	59 (1.2%)	49 (1.0%)	0.33
Cardiac Disorders	548 (11.1%)	560 (11.3%)	0.71
Congenital, Familial & Genetic Disorders	11 (0.2%)	6 (0.1%)	0.22
Ear & Labyrinth Disorders	11 (0.2%)	17 (0.3%)	0.26
Endocrine Disorders	24 (0.5%)	12 (0.2%)	0.05
Eye Disorders	39 (0.8%)	52 (1.1%)	0.17
Gastrointestinal Disorders	238 (4.8%)	230 (4.6%)	0.70
General Disorders & Administration Site Conditions	89 (1.8%)	108 (2.2%)	0.17
Hepatobiliary Disorders	117 (2.4%)	106 (2.1%)	0.45
Immune System Disorders	2 (0.0%)	6 (0.1%)	0.16
Infections & Infestations	487 (9.8%)	516 (10.4%)	0.34
Injury, Poisoning & Procedural Complications	263 (5.3%)	261 (5.3%)	0.92
Investigations	18 (0.4%)	24 (0.5%)	0.36
Metabolism & Nutrition Disorders	169 (3.4%)	199 (4.0%)	0.11
Musculoskeletal & Connective Tissue Disorders	227 (4.6%)	216 (4.4%)	0.59
Neoplasms Benign, Malignant & Unspecified	332 (6.7%)	333 (6.7%)	0.97
Nervous System Disorders	218 (4.4%)	250 (5.1%)	0.13
Psychiatric Disorders	34 (0.7%)	44 (0.9%)	0.26
Renal & Urinary Disorders	156 (3.2%)	177 (3.6%)	0.24
Reproductive System & Breast Disorders	53 (1.1%)	40 (0.8%)	0.18
Respiratory, Thoracic & Mediastinal Disorders	148 (3.0%)	173 (3.5%)	0.16
Skin & Subcutaneous Tissue Disorders	32 (0.7%)	49 (1.0%)	0.06
Social Circumstances	1	1	
Vascular Disorders	144 (2.9%)	153 (3.1%)	0.60
Product Issues	4 (0.1%)	10 (0.2%)	0.11

P values are based on the chi-square statistic

Table S8: Adverse Events by System Organ Class Reported During the Trial

	Dulaglutide (N=4949)	Placebo (N=4952)	P
Blood And Lymphatic System Disorders	405 (8.2%)	403 (8.1%)	0.94
Cardiac Disorders	1315 (26.6%)	1330 (26.9%)	0.75
Congenital, Familial & Genetic Disorders	48 (1.0%)	44 (0.9%)	0.67
Ear & Labyrinth Disorders	255 (5.2%)	269 (5.4%)	0.53
Endocrine Disorders	238 (4.8%)	250 (5.1%)	0.58
Eye Disorders	774 (15.6%)	777 (15.7%)	0.94
Gastrointestinal Disorders*	2347 (47.4%)	1687 (34.1%)	<0.001
General Disorders & Administration Site Conditions	860 (17.5%)	898 (18.1%)	0.32
Hepatobiliary Disorders	385 (7.8%)	363 (7.3%)	0.40
Immune System Disorders	79 (1.60%)	80 (1.6%)	0.94
Infections & Infestations	2712 (54.8%)	2739 (55.3%)	0.61
Injury, Poisoning & Procedural Complications	1122 (22.7%)	1140 (23.0%)	0.68
Investigations	606 (12.2%)	643 (13.0%)	0.27
Metabolism & Nutrition Disorders	1410 (28.5%)	1318 (26.6%)	0.037
Musculoskeletal & Connective Tissue Disorders	1874 (37.9%)	1844 (37.2%)	0.52
Neoplasms Benign, Malignant & Unspecified	589 (11.9%)	593 (12.0%)	0.91
Nervous System Disorders	1599 (32.3%)	1531 (30.9%)	0.14
Psychiatric Disorders	472 (9.5%)	507 (10.2%)	0.24
Renal & Urinary Disorders	1061 (21.4%)	1179 (23.8%)	0.005
Reproductive System & Breast Disorders	408 (8.2%)	400 (8.1%)	0.76
Respiratory, Thoracic & Mediastinal Disorders	957 (19.3%)	929 (18.8%)	0.47
Skin & Subcutaneous Tissue Disorders	674 (13.6%)	757 (15.3%)	0.018
Social Circumstances	1	0	
Vascular Disorders	832 (16.8%)	918 (18.5%)	0.024
Product Issues	10 (0.2%)	15 (0.3%)	0.32

P values are based on the chi-square statistic; *adverse events that occurred in more than 5% of participants were diarrhea, nausea, constipation, and vomiting

APPENDIX 2 - REWIND Trial

Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND): A Double-blind, Randomised Placebo-controlled Trial

Protocol and Statistical Analysis Plan

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes 43
2. Original statistical analysis plan, final statistical analysis plan, summary of changes 231

1. Protocol H9X-MC-GBDJ (REWIND)

The Effect of LY2189265 on Major Cardiovascular Events in Patients with Type 2 Diabetes: Reducing Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)

Confidential Information

The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of LY2189265, unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries. This document and its associated attachments and appendices are subject to United States Freedom of Information Act Exemption 4.

LY2189265

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

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol Electronically Signed and Approved by Lilly

Approval date provided below

Approval Date: 02-Mar-2011 GMT

2. Synopsis

Study Rationale

LY2189265 is a glucagon-like peptide-1 (GLP-1) analog being investigated as a once-weekly subcutaneous injection to improve glycemic control in patients with type 2 diabetes mellitus. Data from clinical trials have shown that LY2189265 reduces glycosylated hemoglobin (HbA_{1c}), fasting and postprandial blood glucose, and body weight, and GLP-1 analogs generally improve a variety of risk factors for cardiovascular (CV) disease. However, whether GLP-1 analogs in general or LY2189265 in particular reduces CV outcomes is unknown. The purpose of this trial is therefore to assess the effect of once-weekly administration of LY2189265 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 LY2189265 on pancreatitis and thyroid C-cell function.

Clinical Protocol Synopsis: Study H9X-MC-GBDJ (REWIND)

Name of Investigational Product: LY2189265	
Title of Study: The Effect of LY2189265 on Major Cardiovascular Events in Patients with Type 2 Diabetes: Reducing Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND)	
Number of Planned Patients/Subjects: Entered: 16,037 Enrolled/Randomized: 9622 Completed: 9507	Phase of Development: 3
Length of Study: This is an event-driven study and will complete when 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: May 2011 Planned last patient visit: September 2019	
<p>Objectives: The primary objective is to test the hypothesis that once-weekly injection of 1.5-mg LY2189265 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.</p> <p>The secondary efficacy objectives are to assess the effects of add-on therapy with 1.5-mg LY2189265 compared to placebo on the incidence of :</p> <ul style="list-style-type: none"> • all cause mortality • first occurrence of each component of the composite primary endpoint • heart failure (HF) requiring hospitalization • hospitalization for unstable angina • the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy for diabetic retinopathy, development of clinical proteinuria, a 30% decline in estimated glomerular filtration rate (eGFR), or need for chronic renal replacement therapy <p>The prespecified safety objectives are to assess the effects of add-on therapy with 1.5-mg LY2189265 compared to placebo on the incidence of:</p> <ul style="list-style-type: none"> • acute pancreatitis • any cancer (excluding basal and squamous cell skin cancer) • medullary thyroid carcinoma (MTC) • C-cell hyperplasia • discontinuation of study drug for any reason • severe hypoglycemia <p>The additional objectives are to assess the effects of add-on therapy with 1.5-mg LY2189265 compared to placebo on the following:</p> <ul style="list-style-type: none"> • hemoglobin A_{1c} (HbA_{1c}) 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 LY2189265 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 LY2189265 or placebo and followed at approximately 6-month intervals. Patients will be followed until a minimum of 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 ($HbA_{1c} \geq 6.5\%$ and $\leq 9.5\%$) 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: LY2189265, 1.5 mg administered subcutaneously once weekly

Planned Duration of Treatment: This is an event-driven study and patients will be followed until a minimum of 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 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 to all-cause mortality
- time to first occurrence (after randomization) of:
 - each individual component of the composite primary endpoint
 - HF requiring hospitalization
 - hospitalization for unstable angina
 - the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy for diabetic retinopathy, development of clinical proteinuria, a 30% decline in eGFR or need for chronic renal replacement therapy

The prespecified safety measures include the incidence of:

- acute pancreatitis
- any cancer (excluding basal or squamous cell skin cancer)
- medullary thyroid carcinoma (MTC)
- C-cell hyperplasia
- discontinuation of study drug for any reason
- severe hypoglycemia

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

The additional measures include:

- change from baseline in:
 - HbA_{1c}
 - 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
 - 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. Treatment group comparison will be assessed with p-value from the Cox model. LY2189265 will be considered different from placebo if the p-value from the primary analysis (adjusted for interim looks) is significant at $p < 0.05$. 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. Variables with treatment imbalances will be used as covariates in further exploratory analyses. These covariates will be identified on the basis of the clinical relevance of the observed treatment difference. 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), 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), and baseline HbA_{1c} below and at or above the median. 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, minimum, and maximum) will be presented for continuous data. Summary statistics of change from baseline for HbA_{1c} per year will be presented along with percentage of patients within ranges of clinical interest (for example, HbA_{1c} $< 7.0\%$).

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. Up to 2 interim and 1 final analyses of the efficacy data will be performed. The 2 interim analyses will occur when approximately 50% (533 events) and 75% (800 events) of the expected number (1067) of primary endpoint events have accrued. The final analysis will occur when a minimum of 1067 patients have experienced a primary endpoint event if the trial is not stopped early for efficacy.

An IDMC will monitor the study and ensure that it meets the highest standards of ethics and patient safety. The IDMC will be authorized to review unblinded interim efficacy and safety analyses during the trial.

3. Table of Contents

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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 differences
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 requirement(s).
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). 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 assignment(s).
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
HbA_{1c}	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 intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their adherence to the planned course of treatment.
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 created/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
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
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 events
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 treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms [TESS]).

The Effect of LY2189265 on Major Cardiovascular Events in Patients with Type 2 Diabetes: Reducing 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, the 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 several of its analogs can safely reduce glucose levels in people with type 2 diabetes, through several 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 analogs 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 inotropes used to maintain the hemodynamic function (Sokos et al. 2007).

Animal studies have shown that GLP-1 analogs reduce infarct size (Addison and Aguilar 2010). These suggest that GLP-1 or its analogs may prevent myocardial damage in response to an insult.

Second, GLP-1 and its analogs 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 analogs 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 analogs 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 analog-mediated weight loss may also reduce CV outcomes. Fifth, GLP-1 and its analogs may improve endothelial function (Addison and Aguilar 2010). Finally, GLP-1 and its analogs 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. LY2189265

LY2189265 is an analog of the endogenous hormone GLP-1, and is being investigated as a once-weekly subcutaneous injection to improve glycemic control in patients with type 2 diabetes mellitus. The biosynthetic LY2189265 molecule, produced using mammalian cell culture, consists of 2 identical disulfide-linked chains, each containing an N-terminal GLP-1 analog sequence covalently linked to a human IgG4 heavy chain by a small peptide linker. LY2189265 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 LY2189265 is approximately 90 hours, with less than 50% accumulation at steady state, supporting once-weekly dosing. The maximum LY2189265 plasma concentration (C_{max}) was observed between 24 and 72 hours following subcutaneous administration.

In clinical trials completed to date, LY2189265 has exhibited the expected GLP-1 analog pharmacological effect on insulin secretion resulting in significant reductions in glycosylated hemoglobin (HbA_{1c}). LY2189265 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 LY2189265 are those related to the gastrointestinal organ class, including nausea and vomiting. Other AEs that have been rarely reported in trials of LY2189265 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 LY2189265 may be found in the Investigator's Brochure (IB).

The purpose of this trial is to determine whether a once-weekly administration of LY2189265 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 LY2189265 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 LY2189265 compared to placebo on the incidence of:

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

6.2.2. Prespecified Safety Objectives

The prespecified safety objectives are to assess the effects of add-on therapy with 1.5-mg LY2189265 compared to placebo on the incidence of:

- acute pancreatitis
- any cancer (excluding basal and squamous cell skin cancer)
- medullary thyroid carcinoma (MTC)
- C-cell hyperplasia
- discontinuation of study drug for any reason
- severe hypoglycemia

6.3. Additional Objectives

The additional objectives are to assess the effects of add-on therapy with 1.5-mg LY2189265 compared to placebo on the following:

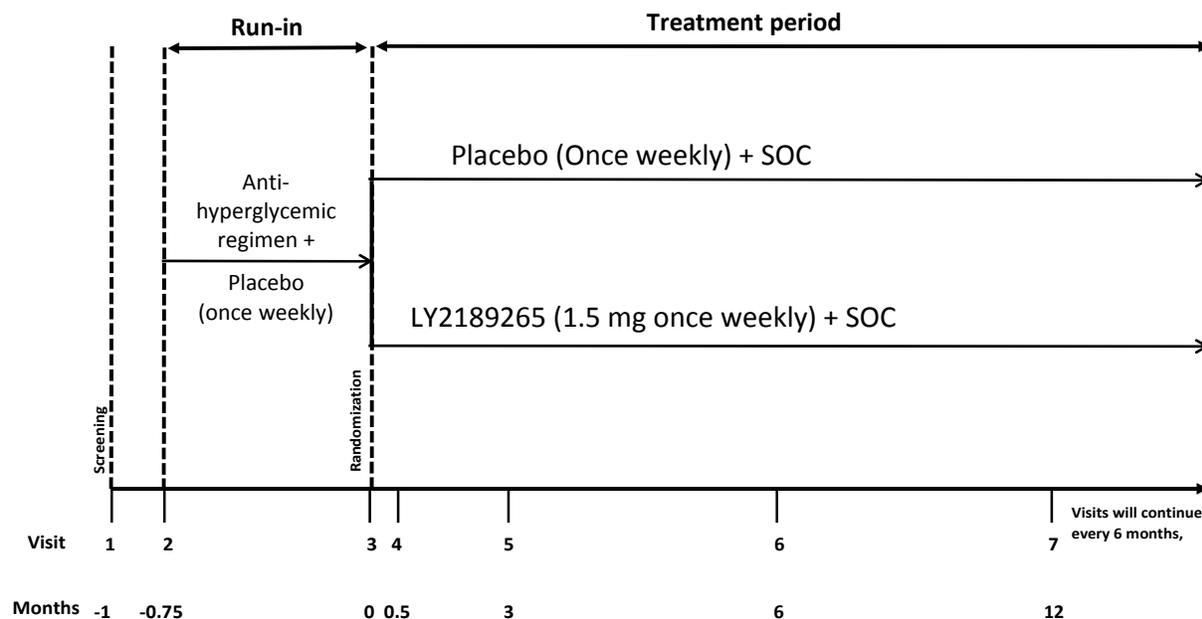
- hemoglobin A_{1c} (HbA_{1c}) levels

- 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 is dispensed every 3 months.

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 LY2189265 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 HbA_{1c} value $\geq 6.5\%$ and $\leq 9.5\%$ 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 LY2189265 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, blood pressure, lipids, and other CV risk factors will be at the discretion of the study investigator and/or the patient's primary physician and informed by current guidelines and routine patient management (Section 9.5.2). The primary analysis of this study is an intent-to-treat analysis; therefore, every randomized participant will be followed until death or study end regardless of adherence to study drug.

Approximately 9622 patients will be enrolled at approximately 486 sites globally and randomized to 1 of 2 treatment groups: 1.5-mg LY2189265 or placebo. Patients will be followed until a minimum of 1067 patients experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after a minimum of 5 years and an average of 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 an 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. Additional study drug-dispensing visits will occur at 3-month intervals between scheduled clinic visits ([Attachment 2](#)). When the number of adjudicated primary endpoint events has occurred, a final visit will be completed for all patients.

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 (except as noted in [Section 8.1](#)) between Visits 1 and 2.

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 be discontinued from the study.

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. Patients will be instructed to inject study drug, on the same day and time each week, based on the patient preference. Per the Study Schedule ([Attachment 1](#)), patients will be given sufficient study drug and will be instructed to inject study drug once-

weekly subcutaneously until the next study visit (Visit 3) and to return unused study drug at the next visit. Used syringes should be placed in the sharp items container provided to patients. 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 (for example, late or missed dose; see Section 9.5.1).

Patients will be instructed to remain on their antihyperglycemic therapy (Section 9.5.2.1).

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 be discontinued from the study.

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 also will complete the cognitive function questionnaires (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 HbA_{1c} value is <7.0% and if the patient is taking insulin or a sulfonylurea, the total daily dose of insulin may be reduced by 15% and the total daily dose of sulfonylurea may be reduced by 1 dose level.

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

- 1) placebo: once-weekly subcutaneous placebo injection
- 2) LY2189265: once-weekly subcutaneous LY2189265 (1.5 mg) injection

Patients will be instructed to inject study drug, on the same day and time each week (that is, to continue on the same schedule used during the run-in period) and to return unused study drug at the next visit. 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 will occur approximately every 3 months after randomization.

Study procedures are those outlined in the Study Schedule ([Attachment 1](#))

At all postrandomization visits, concomitant medications, AEs, and adherence to study drug and lifestyle interventions will be reviewed. New endpoint events (for example, CV events and fractures) will be collected and recorded. Vital signs will be measured. Self-monitored blood glucose testing and injection 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. All patients will complete the cognitive function questionnaires (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, blood pressure, lipids, and other CV risk factors will be at the discretion of the study investigator and/or the patient's primary care physician 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 analog or pramlintide) to maintain acceptable glycemia control and to reduce hypoglycemic episodes. Patients who are unable to tolerate study drug may discontinue the drug temporarily or permanently (Sections 8.3.2 and 8.3.3, respectively). 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. 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. Patients who refuse or are unable to attend for any particular study visit will be invited to attend a subsequent visit.

7.1.4.1. Additional Study Drug Dispensing Visits

Study drug will be dispensed at Visit 2, at randomization (Visit 3), and every 3 months thereafter. Study drug will be dispensed at clinic visits as per the Study Schedule ([Attachment 1](#)) and in between clinic visits ([Attachment 2](#)). Sites will need to call IVRS to assign study drug. Patients will be instructed to inject study drug subcutaneously once weekly on the same day and 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 (for example, late or missed dose; 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. 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. All examinations scheduled for the final study visit will be performed for all randomized patients whenever possible. Study procedures will be performed as outlined in the Study Schedule ([Attachment 1](#)). All study drug (unused and used syringes) must be returned for adherence and final drug accountability, along with the sharp items container. At a minimum, vital status must be ascertained for all randomized study participants. 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.

7.2. 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). ICON will be the CRO for this study. 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 analog LY2189265 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 participant'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 an adequate assessment of overall adherence to study drug injections.

Approximately 9622 patients will be enrolled and randomized to 1 of 2 treatment groups: 1.5-mg LY2189265 or placebo. Patients will be followed until a minimum of 1067 patients experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after an average of 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. The management of glycemia, blood pressure, lipids, and other CV risk factors will be at the discretion of the study investigator and/or the participant's primary care physician 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 has been used 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, participants 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 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 participants to come for their study visits. The long duration of this trial will also enable a robust assessment of LY2189265 on other measures, including its effects on the pancreatitis, thyroid C-cell function, and microvascular complications.

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 be discontinued from further participation 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 one of the following:
 - 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
 - HbA_{1c} $\geq 6.5\%$ (ADA 2010)
- [2] HbA_{1c} value of $\geq 6.5\%$ and $\leq 9.5\%$ at screening
- [3] Are taking:
 - a) no glucose-lowering drugs; OR
 - b) 1 or 2 classes of oral glucose-lowering drugs; with or without 1 injection of basal insulin daily; if one of the oral glucose-lowering drugs is a DPP-IV inhibitor, the patient must be willing to stop the DPP-IV inhibitor at screening; OR
 - c) 1 or 2 classes of oral glucose-lowering drugs with a GLP-1 analog; the patient must be willing to stop the GLP-1 analog at screening; OR
 - d) 1 injection of basal insulin daily
- [4] No change in the number of glucose-lowering drugs, no change in excess of doubling or halving the dose of these drugs, and 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.
- 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
 - eGFR <60 mL/minute/1.73m²
 - a history of hypertension with documented LV hypertrophy on an ECG or echocardiogram
 - microalbuminuria 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)
 - documented low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L (130 mg/dL) within the past 6 months
 - documented 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/m²

[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, 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/1.73m²) 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 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 type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) in absence of known medullary C-cell lesions, except for patients in whom genetic testing has been previously performed and is known to be NEGATIVE for the RET proto-oncogene mutation. If genetic testing has not been done with such a family history, or is POSITIVE or unknown, then the exclusion applies.
- [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, who have given birth within the past 90 days, or who are breastfeeding.
- [24] Females of childbearing potential (that is, females who are not surgically or chemically sterilized and who are between menarche and 1-year post menopause) and who do not agree to use a reliable method of birth control during the study.
- [25] Are medically unstable with life expectancy <1 year.
- [26] Are unwilling to permit sites to contact their primary physicians 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 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 LY2189265 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 LY2189265 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 LY2189265 on these conditions is not known.

Exclusion Criterion [17] excludes patients with impaired hepatic function because the effect of LY2189265 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 LY2189265.

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 LY2189265 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 LY2189265 on human fetal development are unknown.

Exclusion Criterion [26] ensures open communication between the investigative site and the patient's primary care 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 LY2189265, and excludes patients who have been randomized in studies with LY2189265, 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 3 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. Scientific design (included in the protocol) requires follow-up data from the entire intent-to-treat population.
- c. 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.

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 female patient becomes pregnant during the study.
- 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 10.2.2.3.1.
- 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 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 LY2189265 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(s) 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 and blood glucose monitoring supplies. Study drug (LY2189265 or placebo) will be provided as a clear liquid in prefilled syringes. The syringes should be kept refrigerated (not frozen) until use at 2°C to 8°C 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 1 carton of 10 prefilled syringes at Visit 2. Patients will be provided with 1 carton of 15 prefilled syringes of study drug, at clinic visits and at study drug dispensing visits ([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 along with a cooling bag for study drug. An adequate supply of glucose testing materials will be dispensed at each visit. Additional sharp items containers will be provided when needed.

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, as required.

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 LY2189265 or placebo) following a 1:1 ratio according to a computer-generated random sequence using an IVRS. To achieve between-group comparability for country factor, the randomization will be stratified by country.

9.4. Rationale for Selection of Doses in the Study

Two doses of once-weekly LY2189265 (0.75- and 1.5-mg) administered subcutaneously are being evaluated in Phase 3 studies. This trial will investigate the high dose of LY2189265 (1.5 mg). This ensures that both the CV benefits and risks of the dose with greater pharmacological activity will be identified.

9.5. Selection and Timing of Doses

9.5.1. Study Drug (Placebo and LY2189265)

Patients in the LY2189265 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 is skipped and the next regularly scheduled dose is given at the regular 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 HbA_{1c} goals, or due to frequent hypoglycemic episodes.

The investigator or the patient's primary physician 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 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 analog or pramlintide) in patients who do not attain target HbA_{1c} values and/or develop severe hyperglycemia, despite full compliance with the assigned treatment regimen. These changes may be instituted 3 months after randomization to enable the effects of study drug on HbA_{1c} 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

The investigator or the patient's primary physician is responsible for managing the patient's diabetes complications and CV risk factors according to local standards of care. However, weight loss drugs (over-the-counter or prescription) are 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. LY2189265 is currently an investigational compound and other effective therapies for patients with type 2 diabetes are available.

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 personnel or designated clinical trial material personnel will see the randomization table and treatment assignments before the study is complete. However, the SC, all investigators, all Lilly personnel (excluding those referenced above) and all CRO personnel involved with the study and anyone other than those people charged with assuring the safety of the trial and drug will be blinded to all postrandomization data. Emergency unblinding for AEs may be performed through an IVRS. 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.

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 analogs, 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

Treatment adherence will be assessed for each visit interval. The investigator will advise the patient that their injection of study drug should be given at the same time of day on the same day of each week (refer to Section 9.5.1 for the timing of missed doses). Patients will be instructed to return any unused study drug syringes at each study visit for the purposes of study drug accountability. 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%.

Adherence for each visit interval will be defined as using 75% to 120% 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.

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.

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 to all cause mortality
- Time to first occurrence (after randomization) of:
 - each individual component of the composite primary endpoint
 - heart failure (HF) requiring hospitalization
 - hospitalization for unstable angina
 - the composite microvascular endpoint of diabetic retinopathy requiring laser therapy, vitrectomy for diabetic retinopathy, development of clinical proteinuria, a 30% decline in eGFR from baseline, or need for renal replacement therapy

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.
- 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.

These 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** will be defined as a surgical procedure, for the treatment of diabetic retinopathy, 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) **Clinical proteinuria** will be defined as an albumin-creatinine ratio (ACR) >300 mg/g (macroalbuminuria).

- 4) **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.
- 5) **A 30% decline in eGFR** will be based on calculations using the MDRD equation or another equation comparing postrandomization values to baseline (Visit 3).

Sites will report events of laser therapy, vitrectomy, or RRT. Identification of clinical proteinuria and a 30% decline in eGFR will be based on laboratory 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
 - any fracture
 - development of cholelithiasis

10.1.3.1. Cognitive Function

Cognitive function will be assessed in all randomized patients using the MoCA instrument 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 are presented in an irregular order. The patient will be instructed to write the number that is appropriate for each symbol in the space below each symbol and to complete as many correct digits as possible within a 90-second test period. The DSST score will be calculated as the number of correct number–symbol matches. The number of matches attempted will also be recorded.

10.1.3.2. Erectile Function

Erectile function will be assessed in all randomized male patients using the 15-item questionnaire; the International Index of Erectile Function (IIEF). 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. The CEC Charter will contain the final detailed event definitions used for adjudication; however, high-level definitions for these endpoints are provided below. These 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.

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 guidewire 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 guidewire through a guide catheter into a peripheral artery.

10.1.3.4. Other Measures

A **Hospitalization** will be defined as a hospital admission (including 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 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 **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 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, 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 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 and Secondary 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 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 asked to report the event as an AE or SAE to comply with regulatory reporting requirements.

10.2.2. Prespecified Safety Measures

Prespecified safety measures include the incidence of:

- acute pancreatitis
- any cancer (excluding basal or squamous cell skin cancer)
- medullary thyroid carcinoma (MTC)
- C-cell hyperplasia
- discontinuation of study drug for any reason
- severe hypoglycemia

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: Cancers

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

Malignant thyroid neoplasms will be adjudicated by the independent CEC (Section 10.2.2.3). Study sites should send the requested source documentation to the CEC in a timely fashion for adjudication of the event. If a patient is diagnosed with MTC, 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.

10.2.2.3. Adverse Events of Interest: Medullary Thyroid Carcinoma and C-Cell Hyperplasia

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 LY2189265 to affect the thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

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).

Calcitonin, a 32 amino acid peptide, is primarily excreted 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%.

10.2.2.3.1. Calcitonin Monitoring Algorithm

After randomization, if a patient is observed to have a calcitonin value ≥ 1.5 times their screening value AND that value is ≥ 20 pg/mL AND ≤ 35 pg/mL, a calcitonin measurement must be repeated in 1 month. If this repeat value is stable ($< 10\%$ increase) or decreasing, the patient may

remain on study drug and will continue to be followed per Study Schedule ([Attachment 1](#)). If the repeat value is increasing ($\geq 10\%$ increase), the patient must permanently discontinue study drug (Section [8.3.3](#)). The patient should undergo additional endocrine assessment and longer-term follow-up by an endocrinologist or thyroidologist to exclude a serious adverse effect on the gland. The patient will remain in the trial to be evaluated for efficacy and safety endpoints and monitored for all visits and testing.

After randomization, if a patient is observed to have a calcitonin value ≥ 1.5 times their screening value AND that absolute value is >35 pg/mL, the patient should immediately and permanently discontinue study drug. The patient should undergo additional endocrine assessment and longer-term follow-up by an endocrinologist or thyroidologist to exclude a serious adverse effect on the gland. The patient will remain in the trial to be evaluated for efficacy and safety endpoints and monitored for all visits and testing.

If the assessment supports the diagnosis of C-cell hyperplasia or MTC, 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.

Data on patients who are requested to undergo further thyroid assessment either due to the calcitonin algorithm 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 him 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. Discontinuation of Study Drug for Any Reason

After randomization, the reason for temporary or permanent study drug discontinuation will be recorded. See Sections [8.3.2](#) and [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 the Study Schedule ([Attachment 1](#)). **Vital sign measurements must be taken before obtaining an ECG tracing, at visits where required (see Study Schedule, Attachment 1), and before collection of blood samples for laboratory testing.**

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). At all subsequent study visits, 3 HR and 3 BP measurements should be taken at least 1 minute apart using the same arm.

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 ECG 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. **An ECG must be**

recorded *after* vital sign measurements are obtained and before collecting blood samples for laboratory testing.

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. 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).

Twelve-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 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 an external independent Data Monitoring Committee (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. For locally performed laboratory testing, maximum amount per sample and maximum number of samples will be determined locally. Fewer invasive sampling may actually occur, but more samples will be collected if patient participates beyond 84 months, this will not require a protocol amendment.

10.3.1. Samples for Standard Laboratory Testing

Fasting blood and urine samples will be collected at the times specified in the Study Schedule ([Attachment 1](#)). Standard laboratory tests, including HbA_{1c}, ALT, lipids, serum creatinine, and urine albumin/creatinine ratio, will be performed locally. Pregnancy tests will be performed locally, if applicable. Calcitonin will be analyzed by a central laboratory.

Investigators must document their review of each laboratory safety report.

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

10.3.2. Samples for Exploratory Work

10.3.2.1. Nonpharmacogenetic Biomarker Stored Samples

Collection of samples for nonpharmacogenetic biomarker research is a part of this trial unless dictated otherwise by local regulations. Blood samples will be collected at the times 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 LY2189265, or for validating diagnostic tools or assay(s) related to type 2 diabetes.

The sample will be identified by the patient number (coded) and may be stored for a maximum of 15 years after the last patient visit for the study at facility selected by the sponsor.

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 consents on a separate form, a blood sample may be collected for pharmacogenetic analysis. It is a 1-time collection, as noted in the Study Schedule ([Attachment 1](#)).

In addition, 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 LY2189265 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 LY2189265. 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 a maximum of 15 years after the last patient visit for the study. 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 9622 patients is required to show superiority of LY2189265 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. The following assumptions were used: (1) two-sided significance level of 0.05; (2) 90% power for the primary endpoint; (3) uniform 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 hazard ratio of 0.82 between LY2189265 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. After database lock at the conclusion of the study, analyses for the major key manuscripts will be conducted by an 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. An ISAC will perform analyses for the IDMC prior to unblinding.

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 conducted using all randomized patients. The primary efficacy analyses and safety analyses will be conducted using the ITT population. Selected 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 $\geq 75\%$, 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 Population for Study H9X-MC-GBDJ

Population	Definition
All Entered	All patients who signed informed consents
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 <ul style="list-style-type: none"> • have not permanently discontinued study drug • no important protocol deviations • have completed the study • have an overall adherence with study drug of $\geq 75\%$

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. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10. No adjustment for multiplicity will be performed unless otherwise specified.

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, minimum, and maximum 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 LY2189265 and placebo will be reported.

For categorical measures, summary statistics will include sample size, frequency, and percentage. Frequencies will be analyzed using Chi-square test 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 up to 2 interim and 1 final analyses. The 2 interims will be performed when approximately 50% (533) and 75% (800) primary endpoint events have occurred and have been adjudicated as such. The final analysis will be performed at 100% (approximately 1067 adjudicated primary endpoint events) if the study is not stopped early for superiority. These analyses will be performed on unblinded study data. If an interim analysis shows clear benefit of LY2189265 over placebo for the primary endpoint, the IDMC may recommend early termination of the study. Alternatively, if the boundaries are crossed at an interim analysis, the IDMC may still recommend the trial continue and not stop for early efficacy. Anytime over the course of the trial, the IDMC could recommend stopping the trial for safety reasons. The alpha spending across the analyses will be monitored by a generalized Haybittle-Peto boundary of 4 standard errors (2-sided alpha = 0.000063) at the first interim and 3.5 standard errors (2-sided alpha = 0.000465) at the second interim analysis (Jennison and Turnbull 2000). The alpha spent 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 each of the interim analyses. At the final analysis, superiority will be tested. The adjusted 95% CI for the hazard ratio will be calculated.

The median unbiased estimator for the hazard ratio will be reported if the trial is stopped early for efficacy at an interim analysis.

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 test or Fisher's exact test.

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, maximum, minimum and standard deviations. Mean will be analyzed using ANOVA. For categorical measures, summary statistics will include sample size, frequency, and percentage. Frequencies will be analyzed using Chi-square test or Fisher's exact test.

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 ITT population. All concomitant therapies that originally mapped using the WHO DRUG dictionary in the clinical trial database will be further classified using ATC code for reporting purpose. Frequencies will be analyzed using Chi-square test or Fisher's exact test.

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 Chi-square test or 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, maximum, minimum, 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 LY2189265 versus placebo. If the superiority test fails, then a noninferiority test with a 1.3 margin will be performed. The margin of 1.3 is required by regulatory guidance for CV safety. If the upper limit of the 95% CI is below 1.0 (after adjustment for interim looks), LY2189265 will be declared superior to placebo in reducing the incidence of CV events. If the

upper limit of the adjusted 95% CI of LY2189265 versus placebo is above 1.0 but below 1.3, LY2189265 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. A sensitivity analysis will be performed using a Cox model stratified by country.

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 LY2189265 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 the secondary endpoints of HF requiring hospitalization, hospitalization for unstable angina, and the composite of diabetic retinopathy requiring laser therapy, vitrectomy for diabetic retinopathy, development of clinical proteinuria, a 30% decline in eGFR from baseline, or need for renal replacement therapy. The eGFR values will be calculated using the MDRD equation [$eGFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times \text{standardized Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ [if black]} \times 0.742 \text{ [if female]}$] (Levey et al. 2006). The percentage change from baseline in eGFR will be calculated using the postrandomization values and the values calculated at Visit 3 (randomization) as baseline, and compared to -30%.

12.2.8.1. 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 the measurements of AEs, SAEs, severe hypoglycemic episodes, laboratory analytes, vital signs, and ECGs.

12.2.8.2. 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), defined as an event that first occurs or worsens (increases in severity) after baseline (Visit 3). 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 test or Fisher's exact test.

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 test or Fisher's exact test.

Permanent discontinuations of study drug due to AEs and deaths 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 fixed effects. 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 using the categories 1, 2, and ≥ 3 discontinuations.

12.2.8.3. 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 log-rank tests 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.

12.2.8.4. 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, 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 (acute, chronic, and unknown) 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.

12.2.8.5. 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 is Visit 1 and for lipids 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 laboratory measures will be analyzed using Chi-square test or Fisher's exact test. For lipids that include total cholesterol, LDL-C, HDL-C, triglycerides, and non-HDL-C the summary analysis will be conducted based on 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.

12.2.8.6. Vital Signs

Vital signs (SBP, DBP, and heart rate) will be collected in the sitting position at each office 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 Chi-square test or Fisher's exact test.

12.2.8.7. 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.

12.2.9. Analysis for the Additional Objectives

For HbA_{1c}, 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 fixed effects 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; any hospitalization; fractures; and development of cholelithiasis. A Cox proportional hazards regression model for the time to the first occurrence of the event, with treatment as fixed effects will be performed for the ITT population.

Cognitive function will be assessed in all randomized 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 only all male randomized patients. The International Index of Erectile Function (IIEF) scores will be used to assess for degree of erectile dysfunction. 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.

12.2.10. Subgroup Analyses

The effects of LY2189265 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 \geq 65 years)
- Duration of diabetes (Duration <5 years, 5 years \leq Duration <10 years, and Duration \geq 10 years)
- Body mass index (< median and \geq median)
- Baseline HbA_{1c} (< median and \geq median)
- Ethnicity (Caucasian vs. non-Caucasian)
- 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.

12.2.11. Interim Analyses

The independent data monitoring committee (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 for the safety of their patients.

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

There will be up to 2 interim and 1 final analyses for this study. The 2 interim analyses will occur when approximately 50% (533 events) and 75% (800 events) of the expected number (1067) 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 could recommend stopping, pausing, or modifying the trial if it determines from its periodic safety reviews of data from this trial that harm or clear benefit exists.

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 is being conducted under an active US investigational drug application (IND) at clinical sites within the United States. 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	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	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
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
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																						
Serum 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
Urine albumin/creatinine ratio ^f			X						X				X				X				X	X
Lipids (fasting)			X						X						X							

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	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
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	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; 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 An ECG must be recorded after vital sign measurements are obtained and before collecting blood samples for laboratory testing.
- c Solicitation of new CV events, hospitalizations, fractures, cholelithiasis, or severe hypoglycemia episodes 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 only. 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.
- 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 not be dispensed at Visit 4. Study drug will be dispensed at visit 2, at randomization, and every 3 months thereafter with a maximum dispensing window of +/-1 week. See [Attachment 2](#).
- 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 be discontinued from 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 = interactive voice response system.

^a Study drug will be dispensed at Visit 2, at randomization, and every 3 months thereafter with a maximum dispensing window of +/-1 week. A study drug dispensing visit occurring after a scheduled clinic visit number (referred to as Visit X) will be called Visit “XB” on the IVRS. Sites will need to call IVRS 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)

HbA_{1c}

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: HbA_{1c} = 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 will be calculated.

^d A serum pregnancy test will be performed at Visit 1 for women of childbearing potential. 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 amount per sample and maximum number of samples will be determined locally. Fewer samples may actually be taken, but more samples will be collected if patient participates beyond 84 months. This will not require a protocol amendment.

Protocol H9X-MC-GBDJ (REWIND) Sampling Summary ^a

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples ^b	Maximum Total Amount
Calcitonin testing (Central) ^b	Blood	5 mL	8	40 mL
Pharmacogenetic samples	Blood	10 mL	1	10 mL
Nonpharmacogenetic biomarkers	Blood (Serum and Plasma)	14 mL	5	70 mL
Total [Blood]	Blood	29 mL	14	120 mL

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

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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)**

Confidential Information

The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of dulaglutide (LY2189265), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries. This document and its associated attachments and appendices are subject to United States Freedom of Information Act Exemption 4.

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.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol Signed and Approved by Lilly

Protocol Electronically Signed and Approved by Lilly: 02 March 2011
Amendment (a) Electronically Signed and Approved by Lilly: 03 June 2011
Amendment (b) Electronically Signed and Approved by Lilly: 27 February 2012
Amendment (c) Electronically Signed and Approved by Lilly: 19 May 2015
Amendment (d) Electronically Signed and Approved by Lilly
on approval date provided below.

Approval Date: 05-Oct-2016 GMT

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	
<p>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.</p> <p>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:</p> <ul style="list-style-type: none"> • 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 <p>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:</p> <ul style="list-style-type: none"> • acute pancreatitis • serious gastrointestinal events • any cancer (excluding basal or squamous cell skin cancer) and specific categories of <ul style="list-style-type: none"> ○ 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 $\leq 9.5\%$) 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.

<p>Reference Therapy, Dose, and Mode of Administration: Placebo, administered subcutaneously once weekly</p> <p>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.</p> <p>Secondary efficacy measures include:</p> <ul style="list-style-type: none"> • time (after randomization) to: <ul style="list-style-type: none"> ○ 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 <p>The prespecified safety measures include the incidence of:</p> <ul style="list-style-type: none"> • acute pancreatitis • serious gastrointestinal events • any cancer (excluding basal or squamous cell skin cancer) and specific categories of <ul style="list-style-type: none"> ○ 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 <p>Safety will be also assessed based on other data collected in the trial.</p>
<p>The additional measures include:</p> <ul style="list-style-type: none"> • change from baseline in: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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

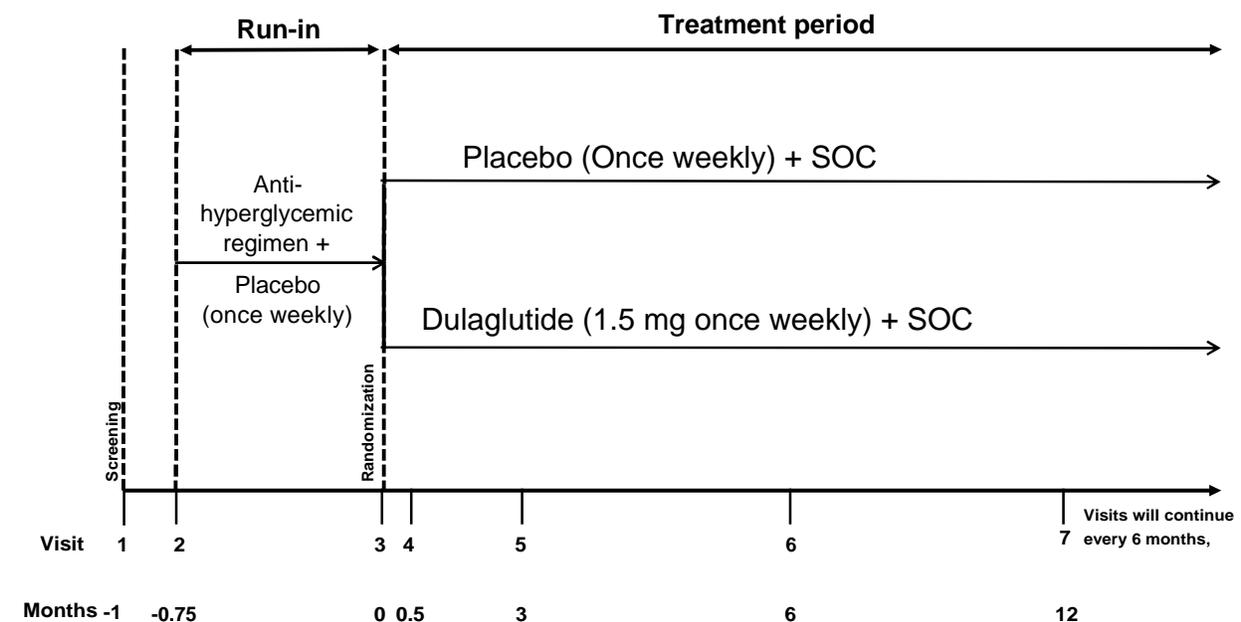
The additional objectives are to assess the effects of add-on therapy with 1.5-mg dulaglutide compared to placebo on the following:

- 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 $\leq 9.5\%$ 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). ICON will be the CRO for this study. 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 $\geq 6.5\%$ (≥ 48 mmol/mol)
- [2] HbA1c value of $\leq 9.5\%$ (≤ 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 $eGFR < 60 \text{ mL/minute/1.73m}^2$
- 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) $\geq 3.4 \text{ mmol/L}$ (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 \geq 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) \geq 140 mm Hg or diastolic blood pressure (DBP) \geq 95 mmHg
 - measured waist-to-hip ratio >1.0 for men and >0.8 for women
- [6] Body mass index \geq 23 kg/m²
- [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/1.73m²) 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 \geq 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 2°C to 8°C 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 drug but

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

10.2.2.3.2. 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 $\geq 30\%$ above baseline in serum creatinine level reported in two consecutive laboratory results obtained on different days.
- A sustained decline $\geq 30\%$ 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/1.73m²
- 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 $\geq 75\%$, 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: <ul style="list-style-type: none"> • have not permanently discontinued study drug • no important protocol deviations • have completed the study • have an overall adherence with study drug of $\geq 75\%$

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, 10th and 90th 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.

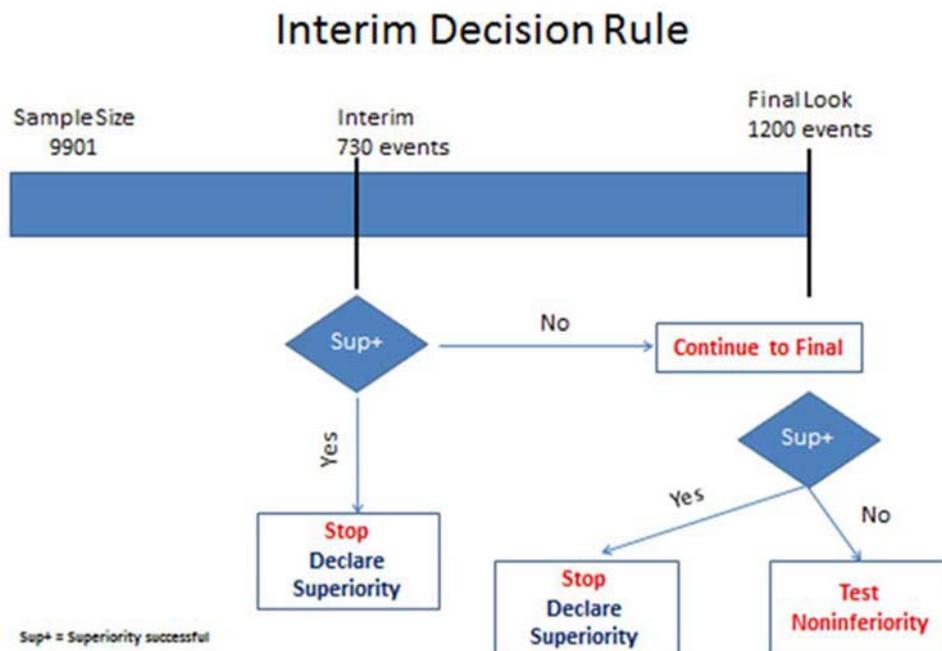


Figure GBDJ.2. Interim decision rule.

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, 10th and 90th 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, 10th and 90th 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 [$eGFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times \text{standardized Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ [if black]} \times 0.742 \text{ [if female]}$] (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 percent age 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 percent age 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 laboratory 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 percent age 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 \geq 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 \geq 65 years)
- Prior CV event
- Duration of diabetes (Duration <5 years, 5 years \leq Duration <10 years, and Duration \geq 10 years)
- Body mass index (<median and \geq median)
- Baseline HbA1c (<median and \geq 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	1j	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19k	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
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	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 probability for superiority (CpSup) at the end of the trial will be calculated; b) removed the text that indicated if the CpSup is $\geq 10\%$, 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

<p>Note: Deletions have been identified by strikethroughs. Additions have been identified by the use of <u>underscore</u>.</p>
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Global changes:

- Page headers: H9X-MC-GBDJ(~~d~~) (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	
<p>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.</p> <p>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 :</p> <ul style="list-style-type: none"> • 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 <p>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:</p> <ul style="list-style-type: none"> • acute pancreatitis • serious gastrointestinal events • any cancer (excluding basal or squamous cell skin cancer) and specific categories of <ul style="list-style-type: none"> ○ 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 $\leq 9.5\%$) 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.

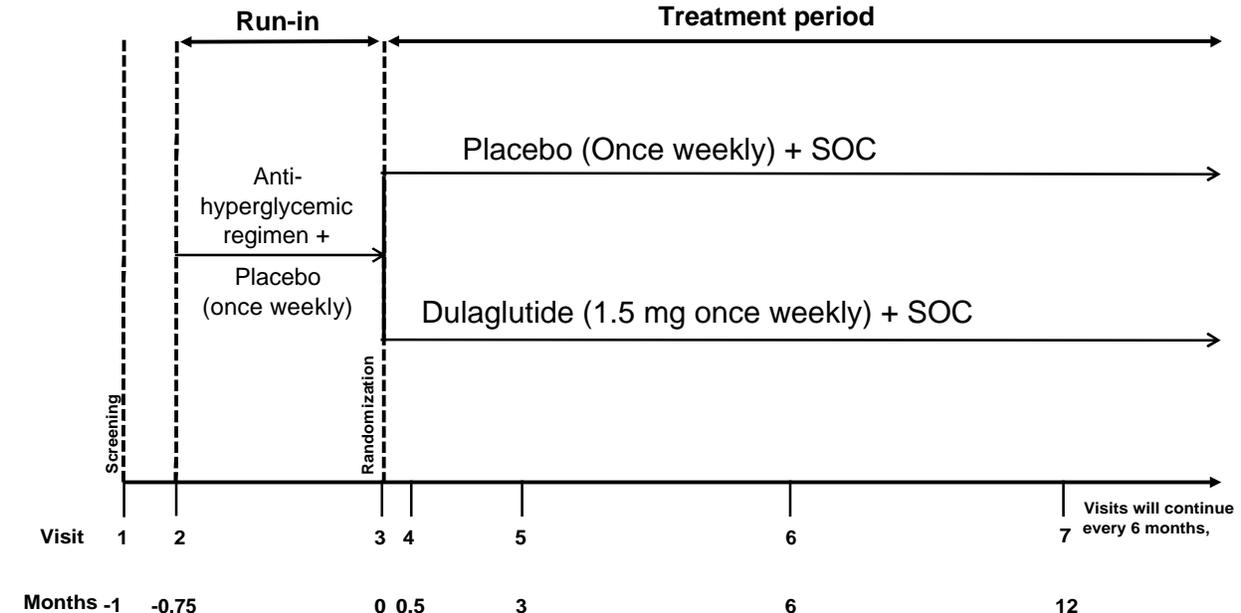
For other analyses, including analyses of prespecified safety measures, the number and proportion of patients will be calculated for binary data and summary statistics (mean, median, standard deviation, 10th and 90th percentiles) will be presented for continuous data. Summary statistics of change from 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 ~~12004067~~ 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 $\geq 10\%$, 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; 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 ~~1200~~1067 events at the final analysis, 2-sided alpha = ~~0.04750~~0.0458; 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.

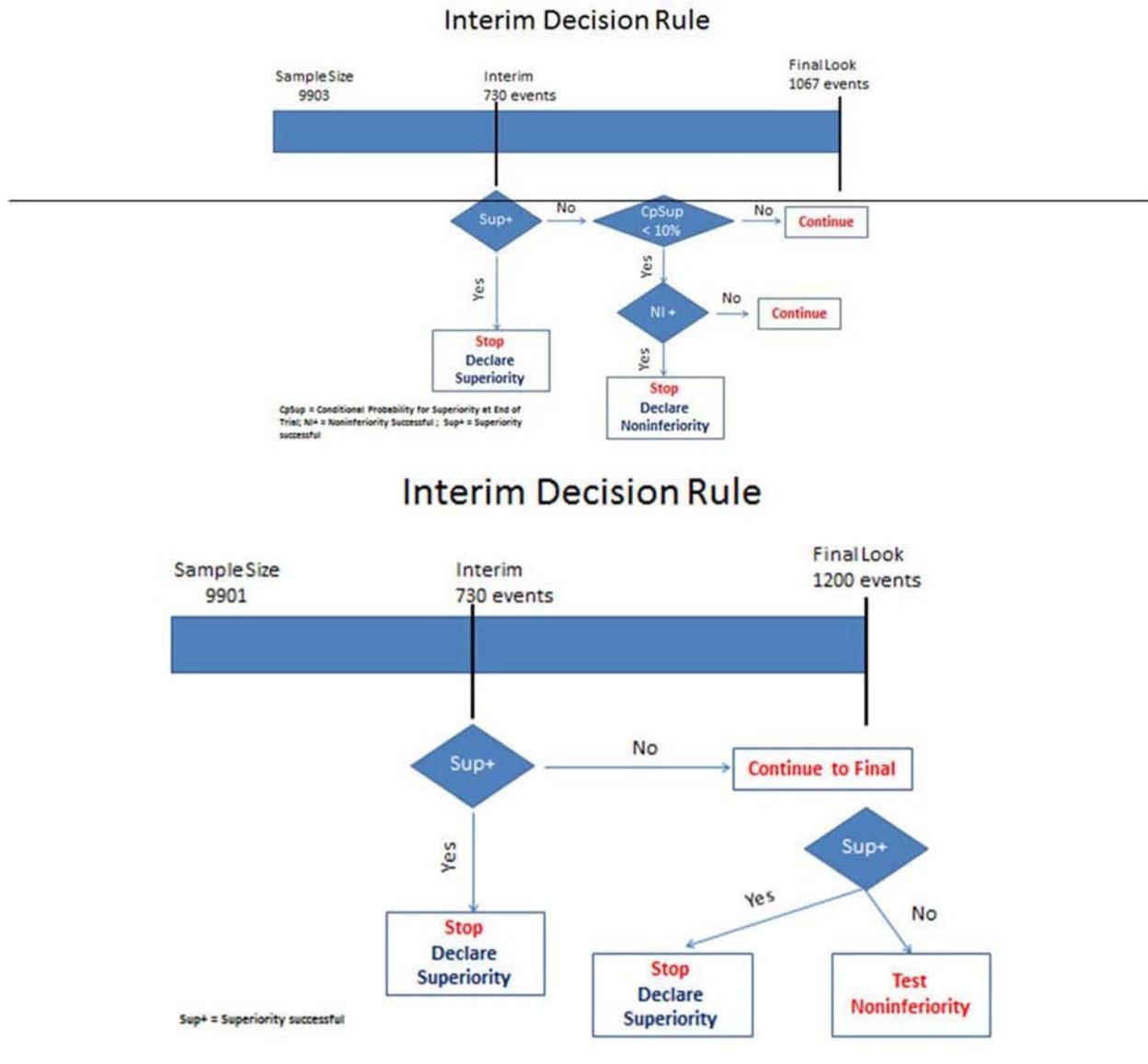


Figure GBDJ.2. Interim decision rule.

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	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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Summary of Changes to the REWIND Protocol

Changes from Initial Protocol to Amendment a

Protocol H9X-MC-GBDJ [**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 protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- LY2189265 was replaced with the word “dulaglutide” in the study title and throughout the protocol. Dulaglutide became the approved generic name of the compound after the protocol was originally approval.
- The word “Reducing” in the study title/REWIND acronym was replaced with the word “Researching” because the word reducing might be misinterpreted as an implied claim and the study is designed to test the hypothesis that dulaglutide reduces major CV events.
- Minor editorial and typographical corrections were made throughout the protocol.
- Minor edits were made in the Section 5.2, Study Rationale, for clarification.
- The secondary efficacy objectives were reordered (in the synopsis and Sections 6 and 10) to reflect the frequency of expected events and thus the potential to detect a difference in these events between treatment groups.
- Text was revised in Sections 7 and 9 to clarify that management of glycemic control will be at the discretion of the study investigator and that management of CV risk factors and other comorbid conditions will be at the discretion of the study investigator or the patient’s usual physician(s), depending on local arrangements. This revision was made to accommodate the pragmatic nature of this trial and because physicians in different therapeutic areas will serve as primary investigators in this trial but may not serve as the primary physician responsible for the patient’s CV care (based on their medical specialty). This clarification was made at the request of the US FDA.
- The number of patients to be entered/enrolled/completed and the number of events needed to conclude the trial were considered too specific, given these numbers may vary depending on the observed annual CV event rate. Therefore minor revisions to these estimates were made throughout the protocol (synopsis, Section 7 and 12).
- Minor edits were made throughout Section 7 for clarification and readability.
- The following sentence was removed from Section 7.1 because this same information is covered in detail in Section 7.1.5, “When the number of adjudicated primary endpoint events has occurred, a final visit will be completed for all patients.”
- In Section 7.1.2 several sentences were moved to improve readability. No changes were made to sentence content.
- Text was added to in Section 7.1.4.1 to clarify that patients will not return any unused study drug at Visit 4.
- In Section 7.1.3 text was added to reflect the need to reduce the mealtime dose of or discontinue meglitinide to reduce the risk of hypoglycemia when study drug is initiated. Several sentences were added for clarity to ensure patients contact the site if they have difficulty injecting study medication. A clause stating patients are to return unused study

drug at the next visit was removed because patients will not return unused study drug until Visit 5.

- Inclusion criterion [1] was revised to reflect the criteria for diagnosis of diabetes in accordance with the 2011 ADA Clinical Practice guidelines. Specifically clarification was added to reflect the need to confirm the diagnosis by repeat testing. This revision was done in response to a request from the US FDA. The SI unit equivalent (≥ 48 mmol/mol) for HbA1c $\geq 6.5\%$ was added.
- Inclusion criterion [2] was revised. The lower boundary for HbA1c was removed and the SI unit equivalent (≤ 81 mmol/mol) for an HbA1c $\leq 9.5\%$ was added. This study is assessing the effect of dulaglutide on major CV outcomes and the protocol stipulates the reduction of concomitant baseline diabetes medications to reduce the risk of hypoglycemia at the time of randomization.
- Exclusion criterion [10] was revised for clarification to ensure that patients with uncontrolled diabetes requiring immediate therapy at the time of randomization are not enrolled into the study
- Exclusion criterion [18] was revised for clarification at the request of the US FDA who expressed that the MEN exclusion criteria was not clear and that it did not appropriately exclude patients from families with MEN-2 whose affected members do not have a known RET mutation.
- Exclusion criterion [24] was revised for safety purposes to denote that women of childbearing potential must agree to use a reliable method of birth control for one month following the last dose of study drug.
- Section 8.3.1, Discontinuation of Patients, was revised for clarity. The following sentence was removed “Scientific design (included in the protocol) requires follow-up data from the entire intent-to-treat population”. This sentence reflects the REWIND study design and is an inherent requirement so there was no need to explicitly state this as a reason why a patient who is inadvertently randomized into the protocol may continue in the study.
- Section 8.3.2, Temporary Discontinuation of Study Drug, was revised. A paragraph was inserted to reflect that women of childbearing potential who become pregnant during the study must temporarily discontinue study drug but will remain in the trial for follow-up. After the pregnancy, study drug may be resumed when it is safe to do so, in the opinion of the investigator.
- Section 8.3.3, Permanent Discontinuation of Study Drug, was revised. The requirement that women of childbearing potential who become pregnant during the study must permanently discontinue study drug was removed. Such circumstances will only require temporary discontinuation of study drug given the anticipated duration of follow-up in this study (up to 8 years).
- Minor edits were made throughout Section 9 for clarification and readability.
- Section 9.3, Method of Assignment to Treatment, was revised to reflect that randomization will be stratified by site and not by country.
- In Section 9.9, Treatment Adherence, a few sentences were added to denote the expectation regarding assessment of study drug compliance at each visit.
- Minor edits were made throughout Section 10 for clarification and readability.
- In Section 10.1.2, Secondary Efficacy Measures, revisions were inserted to clarify how a 30% decline in eGFR will be calculated and how the components of the composite

microvascular endpoint will be collected. These clarifications were inserted at the request of the US FDA.

- Section 10.1.3 and the synopsis were revised to denote that the measure will be incidence, not time to first occurrence, for the additional measures of any fracture and the development of cholelithiasis.
- In Section 10.1.3.1, Cognitive Function, the time to administer the DSST was revised from 90 to 120 seconds.
- The order of sentences in Section 10.1.3.3, were modified to improve readability.
- In Section 10.1.3.4, Other Measures, the definition of a fracture was revised to also include radiologically apparent fractures, not just clinically apparent fractures.
- Section 10.2.2.3.1, Calcitonin Monitoring Algorithm, was revised and simplified for ease of patient safety management. This reassessment occurred in response to feedback from the US FDA who expressed that the discontinuation criteria for elevations in serum calcitonin may be too conservative and that trial integrity may be impacted if study medication is discontinued for too many patients due to minor elevations in calcitonin.
- Section 10.2.2.6, Adverse of Interest: Allergic/Hypersensitivity Adverse Events, is newly added text in response to the US FDA request to amend the protocol to include hypersensitivity reactions as an adverse event of interest. Allergic/hypersensitivity reactions were also added as a prespecified safety objective in the synopsis and Section 6, Study Objectives.
- Sections 10.3 through 10.3.2.2 were revised to clarify requirements pertaining to blood samples collected for central versus local laboratory processing; that only DCCT or IFCC standardized HbA1c assays may be used to measure HbA1c values (point of care assays will not be accepted); and to meet requirements for collection of blood samples for exploratory work at US Veteran’s Affairs study sites.
- Section 12, minor edits were made throughout the whole section for consistency with revisions incorporated in other sections.
- Section 12.1, assumptions for estimating sample size were revised for more accuracy; “uniform patient accrual over 3 years” is revised to “patient accrual over 3 years” and “a hazard ration of 0.82” was revised to “a detectable hazard ratio of 0.82”.
- Section 12.2.1, a statement was added to indicate that analyses for the major key manuscripts will be conducted by the same or another ISAC that will perform analyses for the IDMC prior to unblinding. A statement was added to clarify definition of the ITT population. A statement was added following the US FDA suggestion to perform an “as treated analysis” of the primary endpoint events that occurred while patients were on study drug irrespective of protocol deviations. For this analysis, patients will be analyzed in the group of the treatment they actually took, not the one they were randomized to, and irrespective of protocol deviations. In addition this analysis will only include events that occur when patients were on treatment, and will be censored when they permanently discontinue study drug. A statement was revised to indicate that additional analyses will be conducted using the Per-protocol population. The additional analyses are fully detailed in the SAP. A statement was added to indicate that summary statistics will also include “10th and 90th “percentiles instead of “minimum and maximum” since the latter may be outliers and may not represent the true pattern of the data.

- Section 12.2.6 was revised to denote that 10th and 90th “percentiles will be presented instead of “minimum and maximum” since the latter may be outliers and may not represent the true pattern of the data.
- Section 12.2.9, a statement was added to indicate that frequency counts and percentages of patients with fractures and patients who develop cholelithiasis, will be presented for each treatment group and compared across treatment groups using Chi-square tests or Fisher’s exact tests.
- Section 12.2.10, subgroup limits were revised for body mass index ($<30 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$) and Baseline HbA1c ($<8.0\%$ and $\geq 8.0\%$).
- Attachment 1, Study Schedule, was updated to indicate that waist/hip circumference will be measured at Visit 1. Footnote “c” was revised to reflect all events that are being prospectively collected and footnote “e” was revised to indicate that point of care HbA1c assays will not be acceptable.
- Minor revisions were inserted in Attachment 3, Clinical Laboratory Tests, for clarity.
- In Attachment 4, Sampling Summary, the sampling volumes were revised because 6 samples instead of 5 will be collected for nonpharmacogenetic biomarkers.

Changes from Amendment a to b

Protocol H9X-MC-GBDJ(a) [**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 protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Intravitreal anti-vascular endothelial growth factor (VEGF) therapy for the treatment of diabetic retinopathy was added as an event to the composite microvascular endpoint, a secondary efficacy measure. Currently, anti-VEGF injections are used clinically in the management of diabetic retinopathy; however, the role for this therapy in diabetic retinopathy is evolving and is likely to be clarified while the trial is under way. Having these data in the database will enable the ability to make an evaluation about the effect of the study therapy on this outcome. Revisions were included in various sections of the protocol where appropriate.
- Urgent heart failure (HF) visit was added to the secondary efficacy endpoint of HF requiring hospitalization. The management of HF is evolving and an increasing number of patients are now being treated for HF in the office or emergency department rather than in the hospital. The availability of this data in the database will enable the ability to make a more informed assessment about the effect of dulaglutide versus placebo on HF. Revisions were included in various sections of the protocol where appropriate.
- Sections 7.1.1 and 7.1.2: Text was modified for consistency with revisions to Inclusion Criterion [3], Section 8.1. Patients taking a dipeptidylpeptidase-IV (DPP-IV) inhibitor or glucagon-like peptide-1 (GLP-1) analog at screening must discontinue these therapies after eligibility is confirmed; this should occur no later than the start of the run-in period.
- Section 7.1.6, Missed Visit. This section was added to clarify for investigative sites what to do in the event that a patient misses a study visit.
- Section 8.1, Inclusion Criterion [3]. The need to discontinue a DPP-IV inhibitor or a GLP-1 analog at the time of screening was revised to clarify that these agents should be discontinued only after eligibility is confirmed.
- Section 8.1, Inclusion Criterion [3]. The inclusion criterion was modified to enable patients who may be taking a combination of a GLP-1 analog plus basal insulin to participate in the study. This reflects changes in current practice standards and scientific evidence of efficacy of this combination.
- Section 8.1, Inclusion Criterion [3]. The text “one injection of basal insulin” was revised to “basal insulin daily” and criteria for what defines basal insulin daily was added. This change was made to reflect how basal insulin is usually administered in clinical practice.
- Section 8.1, Inclusion Criterion [4] was revised for clarity
- Section 8.1, Inclusion Criterion [5], established clinical vascular disease. A sentence was added to clarify that a carotid or peripheral artery revascularization should have been

performed >2 months prior to randomization to be eligible for the study. The rationale for this is that a patient who has experienced an acute coronary or cerebrovascular event within 2 months prior to randomization is not eligible for the study (Exclusion Criterion [12]) and such an acute event may have precipitated the need for revascularization.

- Section 8.1, Inclusion Criterion [5], subclinical vascular disease. Text was added to the requirements for estimated glomerular filtration rate (eGFR) and albuminuria to clarify that patients should have evidence of persistent (ie, not acute or transient) impaired renal function to be eligible for the trial.
- Section 8.1, Inclusion Criterion [5], cardiovascular risk factors. Text was added to clarify that patients with treated hypercholesterolemia may be eligible for the trial to account for the fact that many patients with diabetes already will be on therapy to manage lipids.
- Section 8.2, Exclusion Criterion [24]. The criteria for women of childbearing potential and menopause were clarified.
- Section 9.2, Materials and Supplies. Text specific to the actual number of prefilled syringes to be dispensed was removed, as this may be subject to change during the study. Revisions were made to simply state that study drug will be dispensed to a patient at Visit 2 or beyond, as per the Study Schedule.
- Section 10 - Minor revisions were made in this section to clarify that all suspected or potential endpoint events are expected to be submitted for adjudication.
- Section 10.1.3.1, Cognitive Function - The instructions on how to administer the Digit Symbol Substitution Test (DSST) were corrected. A patient is to draw the symbol that matches the number. The DSST score will reflect the number of correct symbol-number matches.
- Section 10.2.2.6, Allergic/Hypersensitivity Reactions. The text was revised to clarify that all allergic/hypersensitivity reactions are to be reported as adverse events (AEs) or serious adverse events (SAEs) and that additional data will be prospectively collected only for those events that an investigator deems related to study drug.
- Section 10.3.2.2, Sample for Pharmacogenetic Analysis. The text stating that a patient has to provide consent “on a separate form” was removed because not all countries or sites require the use of a separate consent form for pharmacogenetic testing.
- Section 12.2.10, Subgroup Analyses. “Ethnicity” was revised to “Race” to align with what is being collected on the case report form.
- Attachment 1, Study Schedule – Allowable Deviation (days). The allowable deviation was increased from 7 to 15 days beginning at Visit 7 and every clinic visit thereafter to allow increased scheduling flexibility. However at the final visit, the allowable deviation was removed as this will not apply.
- Attachment 1, Study Schedule - Footnote ‘d’ and Attachment 3, Clinical Laboratory Tests – Footnote ‘d’ were revised to reflect that women of childbearing potential should have a serum pregnancy test at screening unless this form of testing is not available locally, then a urine pregnancy test will be acceptable.

- Attachment 1, Study Schedule – Serum creatinine and urine albumin/creatinine ratio will be measured at screening instead of randomization and will be measured annually thereafter to reflect standards of medical care.
- Attachment 1, Study Schedule – Footnote ‘i’ was revised for clarity.
- Attachment 2, Additional Study Drug Dispensing Schedule – Footnote ‘a’ was revised for clarity.
- Attachment 4, Sampling Summary - The number of the nonpharmacogenetic biomarker stored samples was corrected from 6 samples to 3 samples (to reflect the actual number of samples being collected) and the maximum total volume of the samples collected was updated accordingly.

Changes from Amendment b to c

Protocol H9X-MC-GBDJ(c) [**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 (c)** 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 and Sections 5.3, and 13.3:** Text has been added to indicate dulaglutide has received regulatory approval in some countries and is under current regulatory review in other countries.
- **Sections 7.1.4.1. Additional Study Drug Dispensing Visits, Section 9.7. Blinding, and the Study Schedule:** Text specific to future use of the Interactive Voice Response System (IVRS) has been changed to Interactive Web Response System (IWRS). The IWRS will replace the IVRS in February 2015.
- **Section 7.1.5. Final Visit:** Text has been clarified to indicate that all tests and procedures listed in the Study Schedule should be completed for all visits.
- **Section 9.9. Treatment Adherence:** The definition of study drug overdose has been provided to clarify definition to investigative staff.
- **Sections 10.2.3.1. Vital Sign Measurements and Section 10.2.3.3. ECGs:** Text that had specified the order in which the following procedures were to be completed
 - vital sign measurements,
 - ECG tracing,
 - collection of blood samples for laboratory testinghas been removed. The order of conduct of these procedures will now be determined at the investigative site. Investigative staff will continue to follow the procedural instructions contained in the protocol for the measurement of vital signs and ECGs.
- **Section 10.2.2. Prespecified Safety Measures:** The heading text has been changed to “**Adverse Events of Interest**” and additional items included to fulfil a post marketing commitment between Lilly and FDA. The additional items included in the list are serious gastrointestinal events, specific categories of cancer including pancreatic cancer, and other thyroid carcinomas, immune mediated reactions, serious hepatic events, clinically significant supraventricular arrhythmias and cardiovascular conduction disorders and serious renal events. Each of these items is included as an adverse event of interest in the following subsection and a description provided. The order of the section has been modified to incorporate the items in a logical manner. The **Synopsis** and the **Objectives** sections of the protocol document have been modified to reflect the changes made in Section 10.2.2.

- **Sections 12.2.2. Trial Design and Section 12.2.12. Interim Analyses:** The protocol previously stated that up to two interim analyses could be conducted. The primary efficacy objective of superiority was unlikely to be proven at the first interim at 533 endpoint events, even at the protocol assumed 18% risk reduction. Therefore, the plan was modified to conduct one single interim when a sufficient number of 730 endpoint events have accrued, to test superiority and assess the futility of the primary objective at the end of the study. The alpha spending function has been changed accordingly to the O'Brien Fleming method to enable this goal. The timing of the interim analysis at 730 events would provide enough events to assess evidence of efficacy, harm, or futility, and to potentially stop the study if warranted. The DMC could recommend stopping the trial for safety reasons at any of its periodic reviews of the totality of the trial data. These changes do not affect the original intent of the trial and the scientific value of the trial is preserved.
- **Section 12.2.2. Trial Design:** The decision rule at the interim analysis time point for stopping or continuing the trial has been modified to include testing futility for superiority. The trial should be stopped if the regulatory requirements are met at the interim and it is unlikely that the primary objective of superiority would be met at the end of the trial.
- To justify any potential claim of the secondary objectives, a graphical testing strategy has been introduced to test the secondary hypotheses and to control the family-wise error rate across the testing of the secondary objectives. This text is included in the **Synopsis and Section 12.2.1. General Considerations**.
- **Synopsis and Section 12.2.11.1. Subgroup Analyses:** The subgroup of “prior CV event” has been added to the pre-specified variables for subgroup analyses. The thresholds for the subgroup variables of BMI and HbA1c have been changed to their baseline medians to allow for balanced subgroups.

Changes from Amendment c to d

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 probability for superiority (CpSup) at the end of the trial will be calculated; b) removed the text that indicated if the CpSup is $\geq 10\%$, 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.

**1. Statistical Analysis Plan:
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)
Type 2 Diabetes Mellitus

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 anti-diabetic regimen.

Eli Lilly and Company
Protocol H9X-MC-GBDJ
Phase 3
[SAP] Version 1

Confidential Information

The information contained in this Statistical Analysis Plan (SAP) is confidential and the information contained within it may not be reproduced or otherwise disseminated without the approval of Eli Lilly and Company or its subsidiaries.

Approval Date: 21-Nov-2011 GMT

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3. Revision History

The protocol for this study was approved on 02 March 2011. Protocol amendment (a) was approved on 03 June 2011. The SAP a Priori Analyses addresses the planned statistical analyses prior to the first unblinding of treatment codes.

4. Study Objectives

4.1. 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 the glucose-lowering regimen of patients with type 2 diabetes, compared to the addition of a once-weekly placebo injection.

4.2. Secondary Objectives

4.2.1. 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 for diabetic retinopathy, 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

4.2.2. Prespecified Safety Objectives

The pre-specified 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.
- any cancer (excluding basal and squamous cell skin cancer).
- medullary thyroid carcinoma (MTC).
- C-cell hyperplasia.
- discontinuation of study drug for any reason.
- severe hypoglycemia.
- allergic/hypersensitivity reactions.

4.2.3. *Additional Objectives*

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

- hemoglobin A_{1c} (Hb A_{1c}) 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.

5. A Priori Statistical Methods

REWIND will be a randomized, double-blind, placebo-controlled, international, multicenter, parallel trial to determine whether the addition of the once weekly GLP-1 analog dulaglutide to the diabetes regimen of patients with type 2 diabetes at high cardiovascular (CV) risk reduces major adverse CV and other serious outcomes. There will be a single-blind placebo run-in period to test a prospective participant's behavior and willingness to inject study drug on a weekly basis, given that patients will be expected to inject study therapy for 5 or more years.

There will be up to 2 interim and 1 final analyses. The 2 interims will be performed when approximately 50% (533) and 75% (800) of the expected total number of primary endpoint events have occurred and have been adjudicated as such. The final analysis will be performed at 100% of the total information (approximately 1067 adjudicated primary endpoint events) if the study is not stopped early for superiority. These analyses will be performed on unblinded study data. If an interim analysis shows clear benefit of dulaglutide over placebo for the primary endpoint, the independent data monitoring committee (IDMC) may recommend early termination of the study. Alternatively, if the boundaries are crossed at an interim analysis, the IDMC may still recommend the trial continue and not stop for early efficacy. Anytime over the course of the trial, the IDMC could recommend stopping the trial for safety reasons. The alpha spending across the analyses will be monitored by a generalized Haybittle-Peto boundary of 4 standard errors (2-sided alpha = 0.000063) at the first interim and 3.5 standard errors (2-sided alpha = 0.000465) at the second interim analysis. The alpha spent at the final analysis will be adjusted to maintain the overall type I error control at a two-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 each of the interim analyses. At the final analysis, superiority will be tested. The adjusted 95% confidence interval for the hazard ratio will be calculated.

The median unbiased estimator for the hazard ratio will be reported if the trial is stopped early for efficacy at an interim analysis.

5.1. Determination of Sample Size

A minimum of 1067 unique primary endpoint events will be required to provide 90% power to demonstrate the superiority of dulaglutide over placebo at a true hazard ratio of 0.82 and 2-sided significance level of 0.05. To calculate the sample size, the following assumptions were used and yielded a sample size requirement of approximately 9600 patients: (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%.

The calculations were performed 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.

5.2. General Considerations

All entered data will be verified, and archived at a contract research organization (CRO) external to Lilly and/or at Lilly. An independent statistical analysis center (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 the CRO and/or by Lilly for the purpose of the final clinical study report.

Efficacy and safety analyses will be conducted using the intent-to-treat (ITT) population. This population will include 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.

Additional analyses will be conducted using the per-protocol (PP) population. The PP population is a subset of the ITT population defined as all randomized patients who have not permanently discontinued study drug, discontinued from the study, have an overall adherence of $\geq 75\%$, and have no important protocol deviations. The primary efficacy analysis will be repeated using the PP population. Important protocol deviations are defined in Section 5.5.

The analysis populations used in this study are defined in Table GBDJ.5.1.

Unless otherwise specified, listings will be conducted using all randomized patients. The data collected will be presented as listings by investigator site, patient, and treatment.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and confidence intervals (CI) will be calculated at a 2-sided 95% confidence level. All tests of interactions between treatment groups and other factors will be conducted at a nominal 2-sided alpha level of 0.10 and will be deemed to be exploratory. No adjustment for multiplicity will be performed unless otherwise specified.

Countries in similar geographic regions with < 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. If baseline data are missing, the last measurement taken prior to this visit will be used for the baseline measurement.

The primary analysis and key secondary CV endpoint analyses will be based on adjudicated events that occurred after randomization (Visit 3). Sensitivity analyses may be conducted

including events reported by investigators or events identified through safety reviews, to assess their impact on the primary analysis results.

The endpoint for the primary analysis is defined as the first occurrence after randomization of death due to a CV cause, nonfatal myocardial infarction (MI), or nonfatal stroke (adjudicated as such). 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 fixed effects.

Treatment comparisons will be based on the hazard ratio and its 95% confidence interval from the Cox model.

For continuous measures, analysis of covariance (ANCOVA) with multiple imputation or a 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, SD, median, 10th and 90th percentiles for both the actual and the change from baseline measurements. Least-squares mean (LS Mean) and standard error (SE) 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 dulaglutide and placebo will be reported, unless stated otherwise.

Covariates of interest that may be included in analyses include sex, age, duration of diabetes, existing diabetes regimen at Visit 1, race and/or ethnicity, and BMI.

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

5.3. Default Analysis Methods

A default analysis method will be defined for certain types of variables (for example, baseline continuous, baseline categorical and time-to-event) that will be commonly encountered in this study. If a specific analysis requires a methodology other than the default for that variable type, the methodology will be described in the appropriate sections of this SAP.

5.3.1. Baseline Analyses

Measurements collected at Visit 3 will be considered the baseline values. If data from Visit 3 are missing, measurements from the screening/run-in period (between Visit 1 and Visit 3) will be used. If a patient has no information for a variable prior to randomization, data will not be imputed and the patient will not be included in the analysis. Baseline analyses will be conducted using all randomized patients with baseline data.

The default analysis method for continuous baseline variables will be an ANOVA model with only a fixed effect for treatment; however, in situations where the baseline variable will be expected to violate the assumption of normality, Wilcoxon's rank sum test will be used. Such

situations will be appropriately identified throughout this SAP. Summaries for continuous variables will include descriptive statistics (i.e., number of patients, mean, standard deviation, sample size, median, 10th percentile, 90th percentile, and interquartile range).

Categorical variables will be compared between treatments using Pearson's chi-square test if the expected count is at least 5 in at least 80% of the cells; otherwise, Fisher's exact test will be used. Summary statistics for categorical variables will include sample size, number, and proportion of patients.

5.3.2. Post-Baseline Analyses of Continuous Variables

For each continuous response variable, visit-specific analyses will be performed for the visits where the variable was scheduled to be measured. If a patient has no post-baseline measurements of a variable, the patient will not be included in the visit-specific analyses of that variable. Analyses of change and percent change from baseline to specific visits will have the same requirements plus the additional constraint that the patient has a baseline measurement of the variable.

The default analyses for continuous response variables will be an analysis of covariance (ANCOVA) with multiple imputation or an MMRM.

The ANCOVA model will consist of a response variable (the value at the visit, change from baseline, or the percent change from baseline), the respective baseline value of the variable being analyzed as the covariate, and a fixed effect for treatment. No interaction term will be included in the model. Between-treatment comparisons will be assessed using the p-value corresponding to the treatment term in the model using type III sums of squares. The corresponding estimate of the treatment contrast (dulaglutide/placebo) and its 95% CI will also be presented. For the within-treatment analyses, the model-adjusted mean, associated standard error, and within-treatment p-value will be presented for each treatment. Summaries will also include the number of patients in each treatment group analyzed.

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, SD, median, 10th percentile, 90th percentile, and interquartile range for both the actual and the change from baseline measurements. Least-squares mean (LS Mean) and SE derived from the model will also be presented for the change from baseline measurement. Between-treatment comparisons will be assessed with the treatment difference in LS Means and the 95% confidence limits along with the p-value.

In situations where the continuous response variable will be expected to violate the assumption of normality, Wilcoxon's rank sum test will be used. Such situations will be appropriately identified throughout this SAP. Between-treatment comparisons will be assessed using the p-value, and within-treatment changes will be assessed using the p-value from the signed rank test. Summaries for these variables will include descriptive statistics: number of patients, median, and 25th and 75th percentiles. In addition, the Hodges-Lehman estimator of the treatment contrast will be provided.

5.3.3. Post-baseline Analyses of Categorical Variables

Categorical variables will be compared between treatment groups using the Pearson chi-square test if the expected count is at least 5 in at least 80% of the cells; otherwise, Fisher's exact test will be used. Summaries for these variables will include the between-treatment p-value and the descriptive statistics: number and proportion of patients. For post-baseline outcome variables, the relative risk estimate and the associated 95% CI will be provided, if there are at least 10 patients with the outcome.

If the categorical variable is a scheduled post-baseline measurement, then a patient must have a measurement of the variable to be included. However, when the categorical variable is an outcome, such as development of an adverse event, then all randomized patients will be included in the analysis.

5.3.4. Time-to-Event Analyses

Time-to-event analyses will be performed for each of the adjudicated outcomes. For each analysis, all adjudicated events in the locked database will be used.

Time-to-event variables will be analyzed using survival analysis methodology if the total number of outcomes is 10 or more. A Cox proportional hazards regression analysis, where the model only includes a fixed effect for treatment, will be used to derive the hazard ratio (dulaglutide/placebo) and the associated 95% CI. The between-treatment comparison will be based on the p-value from the Cox model. The proportional hazard assumption will be examined graphically. If not met, data will be analyzed using accelerated failure time models. Kaplan-Meier (KM) estimates of the survival curve for each treatment will be generated. The number and proportion of patients with the event will be provided, along with the between-treatment p-value. Tied event times will be handled by the Exact method.

If the number of outcomes is <10, survival analyses will not be performed. Instead, Fisher's exact test will be used and the summary statistics will include the number and proportion of patients with the event plus the between-treatment p-value.

For adjudicated outcomes, the incidence rate per 100 person-years of follow-up will be calculated for each treatment group. The numerator will be the number of patients with the event, and the denominator will be the event-specific total person-years of follow-up divided by 100. Total person-years of follow-up is the sum, over patients, of the time on study until the first outcome (first event time or censoring time). The absolute risk difference (ARD) will then be calculated by subtracting the incidence in the dulaglutide arm from that in the placebo arm. For some analyses, the number needed to treat (NNT) to prevent an additional event will be derived using the incidence rates, that is, $1/(\text{Placebo rate} - \text{dulaglutide rate})$. These analyses will be performed where documented in the SAP, and this statistic will only be derived if the p-value from the Cox model is statistically significant.

5.3.4.1. Time to Event

For each patient, time-to-event for an event of interest will be the number of days between the date of randomization and the onset date of the event plus 1 day if the patient experiences the event or the number of days between the date of randomization and the censoring date (Section 5.3.4.3) plus 1 day if the patient does not experience the event. If a patient experiences multiple events, for example, multiple strokes, the date of the first event will be used, unless otherwise specified.

5.3.4.2. Person-Years of Follow-up

Person-years of follow up for an event of interest will be calculated for each patient as the time to event (defined in Section 5.3.4.1) divided by 365.25.

The total person-years of study follow-up will be calculated for each patient as the number of days between the randomization date and the censoring date plus 1 day divided by 365.25. The censoring date is defined in Section 5.3.4.3 for time-to-event analyses (other than mortality analysis).

5.3.4.3. Censoring Date

For time-to-event analyses (except for mortality analyses), the censoring date for a patient is the Final Visit date if a Final Visit was conducted, the discontinuation date if the patient discontinues from the study early, or the patient's date of death if the patient dies during the course of the study. This censoring date will be used in all analyses (except the mortality analyses) to censor patients who have not experienced the event of interest.

For time-to-event analyses for mortality, the censoring date for a patient is the Final Visit date if the patient is known to be alive at the time of the Final Visit. If the patient discontinues from the study early, the censoring date will be the last date that the investigator can ascertain the patient was alive.

5.3.4.4. Handling of Missing Dates

An incomplete death date will be imputed as described below:

- If only the day of the death date is missing, the day will be imputed as follows.
 - (a) If the date of the last reported contact for the patient falls in the same month and year as the death date where the day is missing, the day will be imputed to fall halfway between the last reported contact and the end of the given month (for example, if an incomplete death date is 04-X-2012, and the date of the last reported contact is 04-22-2012, the death date will be imputed as 04-26-2012).
 - (b) If the date of the last reported contact for the patient occurs before the reported month and year of the death date, the day will be imputed as the 15th of the reported month (for example, if an incomplete death date is 04-X-2012, and the date of the last reported contact is 03-26-2012, the death date will be imputed as 04-15-2012).

- If both the month and day of the death date are missing, the month and day will be imputed as follows. (a) If the date of the last reported contact for the patient falls in the same year as the incomplete death date, the death date will be imputed as the first of the month falling halfway between the month of the last reported contact and the end of the year (for example, if an incomplete death date is X-X-2012, and the date of the last reported contact for the patient is 06-22-2012, the death date will be imputed as 09-01-2012). (b) If the year of the last reported contact date for the patient occurs before the year of the incomplete death date, the death date will be imputed as 30 June of the reported year (for example, if an incomplete death date is X-X-2012, and the date of the last reported contact is 06-22-2011, the death date will be imputed as 06-30-2012).
- If the day, month, and year of the death date are missing, the date will be imputed as the midpoint between date of last patient contact and date when the site learned about the death.

For all adjudicated events, the date the Clinical Endpoints Committee (CEC) indicates the event occurred will be used in all analyses. If this date is missing then the investigator-reported date will be used.

An incomplete endpoint event (that is, primary endpoint or secondary efficacy endpoint events) date will be imputed as outlined below:

- If only the day of the event date is missing, the day will be imputed as the 15th of the reported month.
- If both the month and day of the event date are missing, the month and day will be imputed as 30 June of the reported year.
- If only the month is missing, the month will be imputed as June.
- In the case that the imputed event date falls after the patient's censoring date as defined above, the incomplete event date will be imputed as the censoring date (for example, if an incomplete onset date of an event is X-X-2012 and the patient's censoring date is 05-22-2012, then the onset date of the event will be imputed as 05-22-2012 rather than as the date of 06-30-2012 as imputed by following the procedure stated above for missing month and day).
- If the day, month, and year of the event date are missing, the date will be imputed as the midpoint between date of last patient contact and date when the site learned about the event.

5.3.5. Subgroup and Risk-Adjusted Analyses

Subgroup analyses and analyses that account for differences in baseline risk factors will be performed and will be regarded as exploratory. The subgroup analyses will only be conducted if the number of outcomes is at least 50.

Clinically relevant baseline characteristics will be identified for the primary outcome variable and each of its components. A multivariate baseline risk factor adjusted Cox proportional hazards regression model will be obtained using a model selection process, guided by clinical review of the published literature. All these factors will be forced into the model, along with gender (female and male), age group (age <65 years, and age \geq 65 years), duration of diabetes (duration <5 years, 5 years \leq duration < 10 years and duration \geq 10 years), body mass index (BMI) (BMI <30 kg/m² and BMI \geq 30 kg/m²), baseline HbA_{1C} (HbA_{1C} <8% and HbA_{1C} \geq 8%), race (Caucasian, Non-Caucasian), and geography (North America, South America, Europe, Asia, and Other). For all factors, the significance level for remaining in the model will be 0.05. After the selection of terms into the model concludes, treatment will be added to the model. For all dichotomous terms in the final model, parameter estimates, standard errors and p-values plus the hazard ratio and its 95% CI will be reported. For the geography variable, contrasts of each region versus the other regions of the world will be presented.

All subgroup analyses will include subgroup analyses for the 7 categorical variables: gender, age group, duration of diabetes, BMI, baseline HbA_{1C}, race, and geography. In addition, any factors remaining in the final multivariate proportional hazards model will also be used for subgroup analyses.

5.3.6. Multiple Comparisons/Multiplicity

The primary objective of this study is to demonstrate with statistical significance a clinically meaningful reduction in the incidence of primary endpoint events. There will be up to 2 interim and 1 final analyses. The 2 interims will be performed when approximately 50% (533) and 75% (800) primary endpoint events have occurred and have been adjudicated as such. The final analysis will be performed at 100% of the total information (approximately 1067 adjudicated primary endpoint events) if the study is not stopped early for superiority. Appropriate adjustments for multiplicity will be made to maintain an overall type I error rate of <0.05 (Section 5).

No adjustments will be made for multiple comparisons on secondary and other endpoints.

5.4. Multicenter Study

Patients will be enrolled at approximately 486 investigational sites in approximately 27 different countries. To control for differences between sites and assure that treatment allocation is balanced within site, randomization will be stratified by site. Randomization blocks of size 4 will be dynamically allocated to sites. Patients will be assigned in a 1:1 ratio to the next available treatment (either dulaglutide 1.5 mg/week or placebo) from the block currently allocated to their site at the time the call was made to the interactive voice response system (IVRS). The number of patients randomized at each site in each country will be provided.

5.5. Patient Populations/Analysis Subsets

The patient populations and analysis subsets used in the study are described below.

Table GBDJ.5.1. Analysis Population for REWIND

Population	Definition
All Entered	All patients who signed informed consents
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 <ul style="list-style-type: none"> • have not permanently discontinued study drug • no important protocol deviations • have completed the study • have an overall adherence with study drug of $\geq 75\%$

5.6. Patient Disposition

A listing of patient discontinuations will be presented for all randomized patients. Summary analyses will be conducted for the ITT and PP populations.

Number and proportions of patients will be presented for each treatment group and compared across treatment groups using a Chi-square test or Fisher's exact test.

5.7. Important Protocol Deviations

Important protocol deviations will be listed for all randomized patients. The following protocol deviations will be considered important:

- Not meeting an inclusion criterion or meeting any of the exclusion criteria [10], [11], [12], [13], and [21] (REWIND study protocol) that affect the primary endpoint analysis
- Unblinding of treatment assignment for any reason
- Using prohibited concomitant medications (ie, non-study GLP-1 analogs, pramlintide, or weight loss drugs (OTC or prescription))

5.8. 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, 10th percentile, 90th percentile, and standard deviations. Mean will be analyzed using ANOVA. For categorical measures, summary statistics will include sample size, number, and proportion. Treatment group comparisons will be performed using a Chi-square test or Fisher's exact test.

5.9. Concomitant Medications

Concomitant medications will be summarized by different categories and treatment group using ITT population. All concomitant therapies originally mapped using the WHODRUG dictionary in the CLinTrial database will be further classified using ATC code for reporting purpose. The number and proportion of patients will be analyzed using a Chi-square test or Fisher's exact test.

5.10. Historical Illnesses

A limited number of historical illnesses collected at Visit 1 will be listed using all randomized patients. Summary reports will be conducted by treatment group using the ITT population. Historical illnesses will be reported using the terms in the medical history questions on the case report forms. The number and proportion of patients will be analyzed using a Chi-square test or Fisher's exact test.

5.11. Treatment Adherence

Treatment adherence will be assessed for each visit interval. Patients will be instructed to return any unused study drug syringes at each study visit for the purposes of study drug accountability. Study drug adherence will be calculated at each visit after baseline when study drug is dispensed based on the percentage of syringes used, specifically it will be calculated as follows:

$$\text{Study drug adherence for each visit} = \frac{[(\text{no. of syringes dispensed} - \text{no. of syringes returned}) / (\text{no. of weeks between the 2 consecutive visits})] * 100\%.$$

Adherence for each visit interval will be defined as using 75% to 120% of the study drug syringes dispensed for that interval.

Treatment adherence will be listed and summarized using the ITT population. The number and proportion of patients who are compliant at each visit by treatment group will be summarized and compared using a Chi-square test unless the total count is <10.

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 compliant divided by the total number of visits with non-missing adherence data for this patient (that is, the proportion of visits at which the patient was compliant among visits with nonmissing adherence data for the patient). The overall adherence will be summarized and presented in descriptive statistics that include the sample size, mean, median, 10th and 90th 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.

5.12. Treatment Exposure and Study Duration

Patients may temporarily or permanently discontinue study treatment but remain in the study.

Treatment exposure will be the period of time over which the patient is receiving or is temporarily off study drug. This time period will be derived by subtracting the randomization date (Visit 3) minus 1 day from the last visit date for patients actively participating in the study at the time of database lock (at the conclusion of REWIND) or the discontinuation date for patients who permanently discontinue study drug. The duration of treatment exposure will be reported in months and will be compared between treatments using nonparametric methods (Wilcoxon rank-sum tests). The duration of treatment exposure will be summarized by treatment group using the ITT population. The duration of exposure will be categorized into the following groups: ≥ 2 weeks, ≥ 3 months (13 weeks), ≥ 6 months (26 weeks), ≥ 1 year (52 weeks), ≥ 2 years, ≥ 3 years, ≥ 4 years and ≥ 5 years, etc. These categories will be summarized by the number and proportion of patients in each category by treatment group.

Keeping with the ITT principle, the study duration for a patient will commence on the date of randomization to the time of last participation in the study. This will be the patient's safety reporting period. At the time of datalock (at the conclusion of REWIND), the time of last participation will be the Final Visit date for patients still actively participating in the study; the date of discontinuation if the patient discontinued from the study early; or the date of death if the patient dies during the study. The study duration will be reported in months and will be compared between treatments using nonparametric methods (Wilcoxon rank-sum tests). In addition, a categorical breakdown of the study duration will be provided using the same categories as the duration of treatment exposure.

The number and proportion of patients who permanently discontinue study drug will be compared between treatment groups with separate analyses for the reasons for the discontinuation, e.g., adverse event, protocol, or patient decision. Similar analyses will be performed for patients who temporarily discontinue study drug. The number of temporary discontinuations will be descriptively summarized by treatment groups using the categories 1 temporary discontinuation, 2 temporary discontinuations, and ≥ 3 temporary discontinuations. The length of time patients are off study drug and the number and proportion of patients who went from temporary to permanent discontinuation of study drug, will be summarized by treatment group. The analyses for permanent and temporary discontinuations will also be performed by visit.

5.13. Primary Efficacy Measure

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.

An independent Clinical Endpoints Committee (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 Cardiovascular Causes** will be defined as a death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, 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 MI 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. Myocardial infarction 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 TIA will be defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, *without* acute infarction.

The analysis for the primary efficacy measure will be based on the ITT population.

5.13.1. Primary Analysis Model

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

5.13.2. Analysis of Primary Endpoint

The analyses for the primary efficacy measures will be based on the ITT population.

Time-to-event analyses will be performed for the composite primary endpoint. Counts and proportions of patients who experience a primary endpoint event will be calculated. Person-years of follow-up for the primary endpoint, and the incidence rate, calculated by dividing the number of patients who developed the event during the study period by the event-specific person-years of follow-up, will be provided. The ARD for an endpoint will be calculated based on the difference in cumulative incidence between the 2 treatment groups at the end of the study period. ARD will be calculated for the primary endpoint. The 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. An adjusted 95% CI for the hazard ratio (Dulaglutide/Placebo) from the Cox proportional hazards regression model will be provided.

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.

5.13.3. Subgroup Analysis of Primary Endpoint

The effects of dulaglutide compared to placebo on the incidence of the composite primary endpoint events will be examined across the following subgroups of interest:

- Gender (Female vs Male)
- Age (age <65 years, and age ≥65 years)
- Duration of diabetes (Duration <5 years, 5 years ≤Duration <10 years and Duration ≥10 years)
- Body mass index (<30 kg/m² and ≥30 kg/m²)
- Baseline HbA_{1C} (<8% and ≥8%)
- Race (Caucasian versus non-Caucasian)
- Geography (North America, South America, Europe, Asia, Other)

These subgroup variables will be considered as default variables to be included in all multivariable-adjusted analyses and subgroup analyses.

The clinically relevant baseline characteristics for the primary endpoint include: prior MI, prior history of stroke or TIA, prior hospitalization for unstable angina, prior myocardial revascularization, existing microalbuminuria (defined as a urine albumin/creatinine ratio (ACR) >30 mg/g and <300 mg/g) or macroalbuminuria (see Section 5.17.3), current smoker, hypertension, hyperlipidemia, aspirin use, beta-blocker use, calcium channel blocker use, ACE inhibitor or angiotensin receptor blocker use, diuretic use, and antithrombotic (nonaspirin antiplatelets, vitamin K antagonists, heparin, direct thrombin inhibitor, or other antithrombotics).

A risk-adjusted analysis will be performed using these baseline characteristics, the default subgroups, and a multivariate proportional hazards model. The baseline characteristics remaining in the final multivariate proportional hazards model plus the default subgroup variables will be used for subgroup analyses.

The risk-adjusted and subgroup analyses will be performed using the ITT population.

5.13.4. Sensitivity Analyses of Primary Endpoint

The time-to-event analysis for the primary endpoint will be repeated using the PP population, but NNT will not be calculated.

Randomization was stratified by site. To account for the stratification, a time-to-event analysis of the primary endpoint stratified by site will be performed.

5.14. 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 for diabetic retinopathy, 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

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.
- 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.

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** will be defined as a surgical procedure, for the treatment of diabetic retinopathy, 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) **Clinical proteinuria (macroalbuminuria)** will be defined as an albumin-creatinine ratio (ACR) >300 mg/g (>33.9 mg/mmol).
- 4) **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.
- 5) **A sustained 30% decline in eGFR** will be based on a 30% reduction from the baseline value (Visit 3) in 2 consecutive calculations of postrandomization eGFR, using the MDRD equation.

Events of laser therapy, vitrectomy, 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.

An event of the composite microvascular endpoint is the first occurrence after randomization of an event of diabetic retinopathy requiring laser therapy, vitrectomy for diabetic retinopathy, development of clinical proteinuria (macroalbuminuria, see Section 5.17.3), a 30% decline in eGFR (see Section 5.17.3) from baseline, or need for renal replacement therapy.

Time-to-event analyses will be performed for each of the secondary efficacy measures including the individual components of the composite primary endpoint using the ITT population. The analyses of death from CV causes, nonfatal MI, nonfatal stroke, HF requiring hospitalization or hospitalization for unstable angina will be based on adjudicated events. The NNT statistic will be provided for each analysis provided that the p-value from the Cox model is statistically significant. The incidence rate per 100 person-years of follow-up will also be calculated for each type of event.

5.14.1. Additional Analyses of All Cause Mortality

Deaths will be analyzed on the basis of the adjudicated cause of death which will be categorized into CV death and non-CV death. Deaths with an undetermined cause will be included in CV deaths for analysis purposes. Time-to-event analyses will be performed for all deaths as well as for each adjudicated cause of death (CV death vs Non CV death and the subcategories under CV death). Incidence rates per 100 person-years of follow-up will be calculated for each type of death for each treatment group. The NNT statistic will not be provided for these analyses. These analyses will be performed using the ITT population.

A by-patient listing of all deaths and the adjudicated outcome, will be provided.

5.14.2. Additional Analyses of MI Endpoint

The additional analyses of the MI endpoint will be performed using the ITT population.

5.14.2.1. Analyses of Classifications MI Endpoint

5.14.2.1.1. Universal MI Definition

For each MI event, the adjudicators will classify the MI type using the universal MI definition (Thygesen 2007) as follows:

Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply, for example, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4: MI associated with PCI or MI associated with stent thrombosis as documented by angiography or at autopsy

Type 5: MI associated with CABG

Each type of MI (using the universal MI definition) will be further summarized in categories of multiples (1-2X, 2-3X, 3-5X, 5-10X, and >10X) of the 99th percentile of the upper reference limit (URL) of cardiac biomarkers creatine kinase-MB (CK-MB) or troponin, and compared between treatment groups.

5.14.2.1.2. Other Classifications of MI

The adjudicators will also classify MI type as STEMI vs NSTEMI and by subtypes of MI (Spontaneous, Periprocedural [PCI or CABG related], or Silent). MI types will be summarized using number, and proportion of patients for both treatment groups using these different classification schemes. For these analyses, the denominator will be the total number of patients having an MI. If a patient has >1 MI, only the first MI will be included in the analysis.

5.14.2.2. Subgroup Analysis of Non-Fatal MI Endpoint

For subgroup analyses all adjudicated nonfatal MI outcomes will be included, and the analyses will be performed for the ITT population. The potentially clinically relevant baseline risk factors and medication use for the MI events will include: prior MI, prior hospitalization for unstable angina, prior myocardial revascularization, current smoker, alcohol abuse, hypertension, hyperlipidemia, aspirin use, beta-blocker use, calcium channel blocker use, ACE inhibitor or angiotensin receptor blocker use, diuretic use, and antithrombotic use (excluding aspirin).

The risk-adjusted analysis will be performed using these risk factors, medication use, the default subgroups (Section 5.13.3), and a multivariate proportional hazards model. The risk factors and medication use remaining in the final model plus the default subgroup variables will be used for subgroup analyses.

5.14.3. Additional Analyses of All Stroke Endpoint

Time-to-event analyses will be performed for each subtype of stroke (hemorrhagic, ischemic, or unknown) in the ITT and per-protocol populations. Incidence rates per 100 person-years of follow-up will be calculated for each type of stroke for each treatment group. The NNT statistic will not be provided for these analyses.

Stroke disability, as measured using the modified Rankin scale (Farrell B, Godwin J, Richards S, Warlow C, *et al.*, 1991), will be assessed at approximately 30 days after the diagnosis. The

number of patients in each of the following categories of the scale will be summarized and compared between treatment groups using a Chi-square test Fisher's exact test:

- 0: No symptoms at all
- 1: No significant disability despite symptoms (Able to carry out all usual activities)
- 2: Slight disability
- 3: Moderate disability (Requiring some help but able to walk without assistance)
- 4: Moderate to severe disability (Unable to walk without assistance and unable to attend to own bodily needs without assistance)
- 5: Severe disability (Bedridden, incontinent and requiring constant nursing care and attention)
- 6: Death.

5.14.4. Subgroup Analysis of Nonfatal Stroke Endpoint

For subgroup analyses all adjudicated nonfatal stroke outcomes will be included, and the analyses will be performed for the ITT population. The potentially clinically relevant baseline risk factors and medication use for the stroke events will include: prior MI, prior hospitalization for unstable angina, prior history of stroke or TIA, carotid or other artery disease, current smoker, hypertension, hyperlipidemia, aspirin use, beta-blocker use, calcium channel blocker use, ACE inhibitor or angiotensin receptor blocker use, diuretic use, history of atrial fibrillation, and antithrombotic use (excluding aspirin).

The risk-adjusted analysis will be performed using these risk factors and the default subgroups, and a multivariate proportional hazards model. The risk factors and medication use remaining in the final model plus the default subgroup variables will be used for subgroup analyses.

5.14.5. Other Exploratory Analyses: Analyses of Multiple Cardiovascular Events

A patient may experience more than one CV event during the course of the study. For example, a patient may be hospitalized for an unstable angina and later experience a nonfatal MI which may be followed by death from a CV cause, or a patient may experience 3 nonfatal MIs or 2 nonfatal strokes. In each case, the patients will be considered as having multiple CV events. To assess the effects of dulaglutide on multiple cardiovascular events compared to placebo, analyses accounting for multiple CV events will be performed. The analyses will be performed separately for the composite primary endpoint; acute coronary syndrome (ACS) events which include nonfatal MI and hospitalization for unstable angina; and heart failures requiring hospitalization. In each of these analyses, a patient who experiences multiple events of the endpoint will be considered as having recurrent events of the endpoint. The conditional Gap Time model of Prentice, Williams, and Peterson (PWP-GT) (Prentice et al. 1981) will be used to analyze

recurrent CV events. The hazard ratio with 95% CI will be reported for time to the first event, second event, etc. The mean time between successive events will also be reported by treatment group. Baseline characteristics will be compared between groups of patients with no event, only one event, and multiple events (2 or more) regardless of treatment assignment and between treatments within each group. Counts and proportion for categorical variables will be compared using a Chi-square or Fisher's Exact test and means for continuous variables will be compared using ANOVA.

5.15. 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 dysfunction 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

An independent CEC will adjudicate coronary, carotid, and peripheral revascularizations. Detailed event definitions and specifics regarding endpoint determination are provided in the CEC Charter.

- 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 guidewire 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 guidewire through a guide catheter into a peripheral artery.

- **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).

5.15.1. Analyses of Hemoglobin A1c, Weight, and Waist/Hip Ratio

For hemoglobin A1c, weight, and waist/hip ratio, an analysis of covariance (ANCOVA) for the change from baseline to each visit will be performed for the ITT population. The model includes pooled country and treatment as fixed effects and the baseline value as a covariate. Baseline for hemoglobin A1c and weight will be Visit 1 (Screening). Missing post-baseline values will be imputed using multiple imputation on available post-baseline observations. Five datasets will be generated with the missing post-baseline data imputed at each visit were data was missing. Missing post-baseline data will be assumed to be missing at random. If there are no data after the date of randomization, the post-baseline value will be considered missing. The baseline data will not be used as a post-baseline observation.

A correction factor will be used to standardize the Hemoglobin A1c values reported depending on whether the measurement method was IFCC or DCCT.

MMRM models will also be used to analyze the change from baseline in Hemoglobin A1c and weight.

5.15.2. Analyses of Cognitive Function and Erectile Dysfunction

Cognitive function will be assessed in all randomized patients using the Montreal Cognitive Assessment (MoCA) instrument and the Digit Symbol Substitution Test (DSST) at baseline (Visit 3) and after 24, and 60 months of treatment and at the final visit.

The DSST is an attention-demanding psychomotor component of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler D. 1997). The patient is 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 are presented in an irregular order. The patient is instructed to write the number that is appropriate for each symbol in the space below each symbol and to complete as many correct digits as possible within a 90-second test period. The DSST score is the number of correct number–symbol matches. The number attempted will also be recorded.

Analyses of the last score for the MoCA and the DSST, and visit-specific analyses will be performed using ANCOVA for each of these continuous test scores. The analysis will be based on change from baseline. Patients will be required to have a baseline and at least one post-baseline score to be included in these analyses.

The MoCA score is a continuous variable with a range of [0, 30]. It will also be analyzed as a categorical variable using the categories: below the threshold for normal cognitive function (i.e. mild cognitive dysfunction, MoCA score < 23 for Korea and MoCA score < 26 for all other countries), and above the evaluation threshold (i.e., normal cognitive function, MoCA score \geq 23 for Korea and MoCA score \geq 26 for all other countries). The number and proportion of patients in each category at each visit will be compared between treatment group using a Chi-square test or Fisher's Exact test.

5.15.3. Analyses of Erectile Dysfunction

Another additional objective is to evaluate the effect of dulaglutide compared to placebo on the International Index of Erectile Function (IIEF) scores in men. This objective will be assessed using the measure of change from baseline to each visit in total IIEF scores from the 15-item questionnaire in the erectile function (EF), orgasmic function, sexual desire, overall satisfaction (OS), and intercourse satisfaction (IS) domains. The analysis will use an ANCOVA model that includes terms for treatment and the baselines values minus their mean as covariate. The population for these analyses will be all randomized male patients.

5.15.4. Analyses of Other Additional Measures

Time-to-event analyses will be performed for each of the following endpoints: the composite endpoint of death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina; the composite endpoint of coronary, carotid, or peripheral revascularization and each of the components; any hospitalization; any fracture; and the development of cholelithiasis. A Cox proportional hazards regression model for the time to the first occurrence of the event, with treatment as fixed effects will be performed for the ITT population. Kaplan-Meier curves, hazard ratios and associated 95% confidence intervals will be provided. Treatment groups will be compared using the p-value from the Cox model. The population for the analysis of cholelithiasis will be all randomized patients who have not had a cholecystectomy before randomization.

Revascularizations are classified as elective or non-elective and as successful or not successful. The number and proportion of revascularizations falling in each category will be compared between treatment groups using a Chi-square or Fisher's Exact tests. Reasons for hospitalization (Adverse Event, endpoint, or other) will also be compared between treatment groups.

5.16. Other Exploratory Analyses

5.16.1. Analyses of Time to Glycemic Intervention

Additional therapeutic intervention may be considered (with the exception of a GLP-1 analog 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. According to the protocol, patients should continue to inject their allocated study drug and will remain in the study.

Time-to-event analyses will be performed for the time to the first glycemic intervention after randomization. The incidence of glycemic interventions will be summarized using number and proportion of patients by treatment group and by visit. The overall number and proportion will also be reported as will, Kaplan-Meier estimates of the proportion of patients having 1 or more glycemic intervention by treatment group. The number and proportion at each visit are calculated as the number of patients and proportion of patients reporting glycemic interventions at that visit. The overall number and proportion are calculated as the total number of patients and proportion of patients reporting severe glycemic interventions during the entire study treatment period. Treatment group comparison will be assessed using a Chi-square or Fisher's Exact tests or log-rank tests as appropriate. The mean time to initiation of additional therapies will be compared between treatment group using an ANOVA model with treatment and additional covariates such as baseline HbA1c and concomitant antihyperglycemic agents.

5.16.2. Analyses Stratified by Baseline Concomitant Medications

Exploratory time-to-event analyses of the primary CV endpoint will be performed stratified by the following categories of concomitant medications taken by randomized patients at baseline: antihyperlipidemic agents (Yes/No), antihypertensive agents (Yes/No), and antithrombotic agents (Yes/No). The analyses will be performed using the ITT population.

5.17. Safety Analyses

Unless otherwise noted, all listings and all summary analyses will be conducted using all randomized patients (i.e. ITT population). The routine safety analyses will include the measurements of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory analytes, vital signs, and electrocardiograms (ECGs).

5.17.1. Pre-specified Safety Measures

Pre-specified safety measures include the incidence of:

- Acute pancreatitis.
- Any cancer (excluding basal or squamous cell skin cancer).

- Medullary thyroid carcinoma (MTC).
- C-cell hyperplasia.
- Discontinuation of study drug for any reason.
- Severe hypoglycemia.

Allergic/hypersensitivity reactions

5.17.1.1. Analysis of Severe Hypoglycemia

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

The incidence of severe hypoglycemic episodes will be summarized using number and proportion by treatment group and by visit. The overall number and proportion will also be reported as will, Kaplan-Meier estimates of the proportion of patients having 1 or more events by treatment group. The number and proportion at each visit are calculated as the number of patients and proportion of patients reporting severe hypoglycemic episodes at that visit. The overall number and proportion are calculated as the total number of patients and proportion 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 tests or log-rank tests as appropriate.

Severe hypoglycemia rate per 30 days 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 pooled country, treatment, visit, visit*treatment interaction, and baseline. Other covariates of interest, including categorical, continuous and time-dependent may be included.

5.17.1.2. Analysis of Other Pre-specified Safety Measures

Each of the following events will be analyzed using the ITT population: pancreatitis, any cancer (excluding basal or squamous cell skin cancer), thyroid cancer (medullary thyroid carcinoma, papillary thyroid carcinoma, follicular thyroid carcinoma, and anaplastic thyroid carcinoma), C-cell hyperplasia, and allergic/hypersensitivity reactions (overall and by type: rash, urticaria, bronchospasm, angioedema, systemic anaphylaxis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, and other). The timing of the allergic/hypersensitivity reactions (immediate reaction - occurs within minutes [< 60 minutes], acute reaction - occurs from 1 up to 6 hours from study drug administration, > 6 hours through 7 days from study drug administration, and > 7 days from study drug administration) will also be summarized and

compared between treatment groups. Pancreatitis (acute, chronic and unknown) will be analyzed based on adjudicated events and on events as reported by investigators. The analyses of medullary thyroid carcinoma 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 number and proportion by treatment group for each of the pre-specified safety events. The overall number and proportion will be reported. The overall number and proportion will be calculated as the total number of patients and proportion of patients reporting the event during the entire study treatment period. In addition, incidence rates per 100 person-years will be calculated for each of the pre-specified safety events. Treatment group comparison will be assessed using a Chi-square or Fisher's exact tests.

5.17.2. Adverse Events

A patient's safety reporting period will commence on the date of randomization to the time of last participation in the study (Section 5.12).

An adverse event (AE) is defined as 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.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA™). Analysis of adverse events will focus primarily on those events that first occur or worsen (increase in frequency or severity) after the first injection of study drug following randomization, i.e., treatment-emergent adverse events (TEAEs); however, all conditions/events reported on the PRE-EXISTING CONDITIONS AND ADVERSE EVENTS page of the CRF will be retained in the study database and will be reported in the listings. Analyses of TEAEs will be based on all randomized patients.

The identification of TEAEs will be performed according to the following process. Each condition/event will be coded to a preferred term. For each patient, events will be divided into two groups: baseline events will include all events present prior to the date of randomization and before the first injection of study drug post randomization, and post-baseline events will include all events present on or after the date of randomization and the date of first injection of study drug. The maximum severity level (mild, moderate, or severe) reported prior to randomization and the first injection of study drug among all baseline adverse events that code to the same lower level term will be reported. If severity is missing for a particular baseline adverse event, then "mild" will be assumed. For each post-baseline event, the maximum severity reported after randomization and the first injection of study drug will be compared with the maximum baseline severity for the corresponding lower level term. If severity is missing for a particular post-

baseline adverse event, then “severe” will be assumed. When the maximum post-baseline severity exceeds the maximum baseline severity, the event will be classified as a TEAE.

The primary hierarchy (Preferred Term through System Organ Class [SOC]) associated with the lower level term will be assigned. The number of patients experiencing a TEAE will be compared between treatments at the Preferred Term and SOC levels.

A by-patient listing of all adverse events, treatment-emergent or not, will be provided.

5.17.2.1. Serious Adverse Events

A serious adverse event (SAE) is any adverse event from this study that results in one of the following outcomes (please note exceptions outlined below):

- death (except as noted below)
- 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.

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 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.

All SAEs will be compared between treatment groups at the Preferred Term level in the ITT population.

5.17.2.2. Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug or Study Withdrawal

Patients may permanently discontinue study medication but are expected to remain in the study. Separate analyses will be performed to compare the treatment groups with respect to adverse

events that led to permanent discontinuation of study medication and adverse events that led to withdrawal from the study. These analyses will be conducted for all randomized patients.

5.17.3. Laboratory Analytes

All laboratory measurements will be performed locally except calcitonin which will be performed by a central laboratory. For analyses, the laboratory measurements will be converted to SI units. The following laboratory measurements will be analyzed: calcitonin, creatinine, eGFR, serum creatinine, urine albumin/creatinine ratio, haemoglobin A1c (Section 5.15.1) and lipids (Section 17.3.1).

Laboratory measurements collected at scheduled and unscheduled visits will be listed by patient by visit using all randomized patients. An additional listing will be presented for all scheduled and unscheduled laboratory measurements that are outside the SI normal range. All summary analyses will be based on the ITT population. Laboratory measurements that fall within a visit window (± 30 days around the observed visit date) will be associated with that visit. Scheduled visits will have a ± 15 -day window around the scheduled visit date. For multiple runs of the same laboratory analyte, 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.

The eGFR values will be calculated using the MDRD equation [eGFR (mL/min/1.73 m²) = 175 X standardized Scr^{-1.154}Xage^{-0.203} X1.212 [if black] X 0.742 [if female], (Levey et al 2006)].

Unless otherwise specified, continuous laboratory measures will be analyzed using an analysis of variance (ANOVA) model on the rank-transformed data. The model includes treatment. Treatment group comparisons will be performed with no multiplicity adjustment. Categorical laboratory measures will be analyzed using Chi-square test or Fisher's exact test.

Microalbuminuria is defined as a urine albumin/creatinine ratio (ACR) greater than 30 mg/g and less than 300 mg/g) and macroalbuminuria (clinical proteinuria) as urine ACR greater than 300 mg/g). Urine ACR is calculated as the ratio of urine albumin and creatinine measured from a morning urine sample or a random urine sample if a morning sample is not available.

The proportion of patients with microalbuminuria or macroalbuminuria at baseline or during the study will be compared between treatment groups at by visit. Shift tables will be presented for urine ACR. The tables will show the proportions of patients with shifts in the laboratory results from baseline to maximum post-baseline result using categories based on the Central Laboratory reference ranges. The categories for urine ACR will be ≤ 30 mg/g, >30 mg/g to ≤ 300 mg/g and >300 mg/g. Shifts will be grouped to show the proportions of patients who experienced decreases (post-baseline category $<$ baseline category), increases (post-baseline category $>$ baseline category), or no change from baseline to maximum post-baseline result for each treatment. Baseline will be the last non-missing observation in the study period from screening to randomization (Visits 1-3). The maximum post-baseline result in the post-baseline study period (Visits 3 and beyond) will be the maximum result for the analysis. The analyses will use both scheduled and unscheduled labs and will be in all randomized patients with at least one baseline and one post-baseline urine ACR measurement.

5.17.3.1. Lipid Parameters

The following lipid parameters will be assessed for all randomized patients:

- Total cholesterol
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)
- Non-HDL-C (total cholesterol minus HDL-C)
- Triglycerides

Fasting lipids will be collected at randomization (Visit 3) and after 24 and 60 months of treatment (Visit 15). Visit 3 will be considered as baseline for these analyses. Analyses of the percent change from baseline to each visit and to last measurement will be performed separately for each marker. Analyses of change from baseline to each visit and to last measurement will be performed for the ratio of total cholesterol to HDL-C. Patients will be required to have a baseline and a post-baseline measurement of the marker to be included in these analyses.

5.17.4. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) will be collected in the seated position in triplicate at each office visit. Measurements will be averaged for each patient at each visit; the average values will be used in the descriptive summaries and analyses.

All averaged measurements will be listed by patient by visit using all randomized patients.

Descriptive statistics for the averaged measurements and change from baseline by treatment arm and visit will be presented. Summary analyses will be conducted using the ITT population. The change from baseline will be analyzed using the mixed-effects repeated-measures (MMRM) model.

5.17.5. ECG Analyses

ECGs will be performed for all randomized patients at each visit. Both scheduled and unscheduled ECGs will be qualitatively evaluated by an ECG reading center. The qualitative characteristics assessed will be summarized in the major categories and subcategories of findings: normal ECG, abnormal ECG findings and the subcategories of abnormal findings.

The number of patients in each category and subcategory will be compared between treatment groups and by visit using a Chi-square or Fishers' exact tests.

6. References

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7. Unblinding Plan

7.1. Introduction

This unblinding plan describes the organization of personnel and definition of processes that will be followed to insure integrity of the data and results throughout the trial.

7.2. Organization of REWIND Study

The 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.

Lilly will assign the obligation of study operation management to a CRO. ICON will be the CRO for this study. Medical oversight will be the responsibility of Lilly and the CRO. The CRO will be responsible for addressing medical and study operational questions, handling the data, conducting the analyses, producing all data summaries for the clinical study report as well as writing the clinical study report.

An independent data monitoring committee (IDMC) will be responsible for monitoring patient safety and will review unblinded interim and safety analyses during the study. An independent statistical analysis center (ISAC) will perform analyses for the IDMC prior to unblinding. The members of the ISAC are employees of Population Health Research Institute (PHRI).

For this unblinding plan, REWIND personnel will fall into one of the following 2 categories:

Personnel blinded until datalock

- Investigators
- Patients
- Steering Committee members*
- ICON study personnel
- Lilly personnel* except a limited number of Lilly IVRS and clinical trial material representatives
- Population Health Research Institute (PHRI) study personnel except those who are part of the ISAC

*There may be a rare exception to the blinded status of the SC Chair and Lilly personnel as noted in the IDMC charter.

At ICON, a blinded statistical team will be responsible for the production and quality assurance review of analysis datasets and their periodic transfers to Lilly and the ISAC.

Until the final database lock, no unblinded reports will be accessible to study personnel who are to remain blinded until the end of the trial.

Personnel unblinded from the time of the first unblinded analysis

- IDMC members
- ISAC
- Lilly IVRS and clinical trial material representatives

Depending on the recommendation of the IDMC, a Lilly internal review group (IRG) may be unblinded to study data. The Lilly IRG comprises a limited number of internal Lilly medical and statistical experts, who have no direct involvement in the clinical development of dulaglutide.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. This controlled access will be limited to certain IVRS or clinical trial material personnel. The IVRS representative will not be responsible for any analysis decisions or production work for the IDMC summaries and analyses that are described in the IDMC charter. The ISAC is responsible for creating and reviewing test programs and outputs for IDMC reports based on data blinded at the treatment group level (Treatment A versus Treatment B) prior to each IDMC review. The ISAC statistician is responsible for the production of the unblinded summaries and analyses for the IDMC from programs developed by the ISAC described above.

7.3. Data Handling and Storage

Transfers of data to the ISAC and to Lilly will be the responsibility of the blinded statistician and data management group at the CRO. Further details on data handling will be provided by the CRO.

The Lilly IVRS team will generate and maintain the randomization schedule and treatment group assignments. All treatment code information will be stored electronically on a secure server system directory with access only to the Lilly IVRS team members. This team will provide the treatment codes to the unblinded ISAC statistician through secure router ID at the time of the analyses for the IDMC.

7.4. Process of Producing Analyses, Summaries and Reports

Prior to each IDMC meeting, blinded data will be transferred from CRO to the ISAC unblinded statistician following the CRO internal procedures for data transfer. The ISAC unblinded statistician will then be responsible for creating and reviewing programs and outputs based on blinded data.

After completion of the blinded reports, the unblinded statistician will notify the Lilly IVRS team that the data and programs are ready and will request from IVRS the unblinded treatment assignment. The Lilly IVRS representative will provide this information by secure e-mail to the unblinded ISAC statistician. The unblinded statistician will then request that the Lilly IVRS representative who holds the randomization confirm that the randomization is a match to the IVRS version. This process will be documented for audit purposes.

The unblinded ISAC statistician will then replace the dummy treatment assignments with the correct treatment assignments (by simply changing a libname reference in the sas program), re-run the programs and validate the outputs to ensure that the actual/correct treatment assignments

have been used. The unblinded ISAC statistician will review the tables to ensure that the correct randomization codes have been used.

Once validated, the summaries and/or analyses will be produced and validated. The unblinded ISAC statistician will provide the reports to the IDMC members for review. This point is the official handover of the summaries to the IDMC, and it will now become the responsibility of the IDMC chair to insure the appropriate use of these summaries.

When the IDMC meeting is complete, it is the responsibility of the unblinded ISAC statistician to save the interim reports and all the associated programs into a separate server directory for audit trail purposes. The reports given to the IDMC members will be collected, and destroyed or stored confidentially.

Additional details about the IDMC processes can be found in the IDMC Charter.

7.5. Other Unblinding Issues

7.5.1. Unblinding of Individual Patients during the Study

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. This controlled access will be limited to certain IVRS or clinical trial material personnel. 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 IVRS. 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.

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

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 the ISAC, that provides support to the IDMC, can view group unblinded data and conduct additional analyses of the safety data.

The unblinded ISAC statistician will monitor the number of patients unblinded during the study for any trends that need to be raised to the attention of the IDMC Chair. The ISAC statistician will also maintain a list of people who received unblinded information during the trial.

Periodically and at the end of the study, the Lilly IVRS representative will provide the details of the patients and the date that they were unblinded to the unblinded ISAC statistician for review by the IDMC. Following the final review before the trial ends, the unblinded ISAC statistician will place this information into the correct server directory with all the other interim reports to be sent to the Lilly blinded statistician at the end of the trial.

7.5.2. Other Data That May Unblind Patients

It is assumed that there is no other clinical data (e.g. laboratory results, ECG findings, vital sign measurements) that might potentially disclose individual patient treatment assignment to investigators, the Steering Committee, or all other Lilly and ICON study personnel during the conduct of the study.

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Approver: Linda Shurzinske (AM\C085513)
Approval Date & Time: 21-Nov-2011 21:13:13 GMT
Signature meaning: Approved

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

Confidential Information

The information contained in this Statistical Analysis Plan (SAP) is confidential and the information contained within it may not be reproduced or otherwise disseminated without the approval of Eli Lilly and Company or its subsidiaries. This document and its associated attachments or appendices are subject to United States Freedom of Information Act Exemption 4.

Dulaglutide (LY2189265) Type 2 Diabetes Mellitus

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 anti-diabetic regimen.

Eli Lilly and Company Protocol H9X-MC-GBDJ Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly:
21 November 2011

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly:
07 August 2013

Statistical Analysis Plan Version 3 electronically signed and approved by Lilly:
08 January 2015

Statistical Analysis Plan Version 4 electronically signed and approved by Lilly on date
provided below

Approval Date: 06-Oct-2016 GMT

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Revision History

The protocol for this study was approved on 02 March 2011. Protocol amendment (a) was approved on 03 June 2011. Protocol amendment (b) was approved on 27 February 2012. The SAP a Priori Analyses addresses the planned statistical analyses. Version 1 of this SAP was approved on 21 November 2011 prior to the first unblinding of treatment codes. It was updated in Version 2 following protocol amendment (b) and prior to unblinding of the sponsor or the steering committee.

Key additions and clarifications in Version 2 include:

- the addition of anti-vascular endothelial growth factor (VEGF) therapy to the secondary efficacy objectives of composite microvascular endpoint per amendment (b)
- the addition of an urgent heart failure (HF) visit to the secondary efficacy objective of HF requiring hospitalization per amendment (b)

The replacement of race and/or ethnicity by race in the subgroup analyses due to the fact that information on ethnicity is required only of patients randomized in the United States.

Version 2 of this SAP was approved on 07 August 2013 prior to the first unblinding of treatment codes. It was updated in Version 3 and approved prior to unblinding of the sponsor or the steering committee. Key changes and additions in Version 3, as well as the rationale, include:

- The number of interim analyses was changed from 2 to 1 with the timing of the analysis set to detect a clear benefit if one was emerging. The alpha spending function was changed to the O'Brien-Fleming to also detect any emerging benefit. The timing of the interim analysis at 730 events would provide enough events to assess evidence of efficacy, harm, or futility, and to potentially stop the study if warranted.
- The decision rule at the interim analysis time point for stopping or continuing the trial was modified to include testing futility for superiority. This allows for the trial to be stopped if the regulatory requirements are met at the interim and if it is very unlikely that superiority would be demonstrated by the end of the trial
- To justify any potential claim of the secondary objectives, a graphical testing strategy was introduced to test the secondary hypotheses and to control the family-wise error rate across the testing of secondary objectives
- The heading text of Sections **4.2.2. Prespecified Safety Objectives**, and **5.17.1. Prespecified Safety Measures** were changed to **4.2.2. Prespecified Safety Objectives (Adverse Events of Special Interest)** and **5.17.1. Prespecified Safety Measures (Adverse Events of Special Interest)** and additional items were listed to fulfill Lilly's post marketing commitment to Food and Drug Administration (FDA). The additional items included in the list are serious gastrointestinal (GI) events, specific categories of cancer including pancreatic cancer, and other thyroid carcinomas, immune mediated reactions, serious hepatic events, clinically significant supraventricular arrhythmias and cardiovascular conduction disorders and serious renal events

- Keeping only a mixed-effects model for repeated measures (MMRM) for the analysis of changes from baseline for continuous measures, instead of this model and an analysis of covariance (ANCOVA) model with multiple imputations since MMRM also (implicitly) accounts for missing values
- For clarity, the inclusion of more details on the analysis of continuous laboratory measurements
- For clarity, the reordering of the variables for subgroup analyses into 2 categories: pre-specified and exploratory
- For clarity, the description of the time-to-event analysis method in only 1 section that will be referenced in subsequent sections where it is mentioned
- The addition of a criterion for a baseline factor to be included as covariate in a covariate adjusted analysis
- Clarification of the definition of treatment exposure
- Addition of a variable of “Prior cardiovascular (CV) events” for multifactor-adjusted and potential subgroup analyses, with definition consistent with the protocol
- Additions of 2 sections for the analyses of fatal myocardial infarctions (MIs) and fatal strokes
- Addition of a section for the analysis of nonfatal CV events with the competing risk of death
- The addition of a sensitivity analysis of the primary endpoint excluding silent MI
- The addition of “Ratio of total cholesterol to high-density lipoprotein-cholesterol (HDL-C) (total cholesterol divided by HDL-C)” to the lipid parameters, and the reporting of medians for triglycerides
- Substitutions of MMRM models for ANCOVA for the analyses of continuous postbaseline measurements including Montreal Cognitive Assessment (MoCA), Digit Symbol Substitution Test (DSST) and International Index of Erectile Function (IIEF) scores
- For the analysis of severe hypoglycemia rates, the change from a Generalized Estimating Equation (GEE) model to the more appropriate generalized mixed effect model with a negative binomial distribution. Yearly rates will be analyzed instead of 30-day adjusted rates. Time to first severe hypoglycemia event will also be analyzed
- Removal of race from the subgroup analyses due to the fact that patients are allowed to check multiple subcategories of race therefore making these subcategories nonindependent

- The change to the content of Section 6.4 to match the content of “Unblinded Data” in the Independent Data Monitoring Committee (IDMC) charter

Version 3 of this SAP was approved on 08 January 2015. Version 4 is being approved prior to the interim analysis, and unblinding of the sponsor or the steering committee. Key changes and additions in Version 4, as well as the rationale, include:

- The increase of the total number of events for the final analysis to 1200 following the release of the LEADER trial results in order to increase the power for the primary and key secondary analyses
- The removal of the futility threshold for superiority from the interim decision rule based on the additional information from the LEADER trial results
- The clarification of the data cut-off date for the interim analysis
- The introduction of the Whitehead method to control for type I error across the interim analysis and the final analysis that will follow an interim IDMC decision to stop the trial for efficacy. These final analyses could be used by FDA for labeling discussions
- The inclusion of 2 sensitivity analyses to explore the impact of missing data on the MACE primary endpoint findings following feedback from the FDA about the importance of addressing missing data for other dulaglutide studies
- The update to the graphical testing scheme to control type I error in the analyses of the primary and key secondary objectives, following the release of the results from the LEADER and SUSTAIN-6 trials
- The update to the definition of prior CV event
- The update to the criteria for important protocol deviation

3. Study Objectives

3.1. 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 the glucose-lowering regimen of patients with type 2 diabetes, compared to the addition of a once-weekly placebo injection.

3.2. Secondary Objectives

3.2.1. 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 (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

3.2.2. Prespecified Safety Objectives (Adverse Events 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 (GI) 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

3.2.3. Additional Objectives

The additional objectives are to assess the effects of 1.5 mg dulaglutide compared with 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

4. A Priori Statistical Methods

REWIND will be a randomized, double-blind, placebo-controlled, international, multicenter, parallel-arm trial to determine whether the addition of the once weekly glucagon-like peptide-1 (GLP-1) analog dulaglutide to the diabetes regimen of patients with type 2 diabetes at high CV risk reduces major adverse CV and other serious outcomes. There will be a single-blind placebo run-in period to test a prospective participant's behavior and willingness to inject study drug on a weekly basis, given that patients will be expected to inject study therapy for 5 or more years.

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 time point (Figure GBDJ.4.1), 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 by the Independent Data Monitoring Committee (IDMC) that will use the results and the foregoing decision rules as guidelines. Thus, 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 any time 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), (for example, with 730 events at the interim, 2-sided alpha = 0.008; power 51.3%). 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 (for example, with 1200 events at the final analysis, 2-sided alpha = 0.048; overall power = 92.8%). At the final analysis, superiority will be tested followed by noninferiority. The adjusted 95% confidence interval (CI) for the hazard ratio will be calculated.

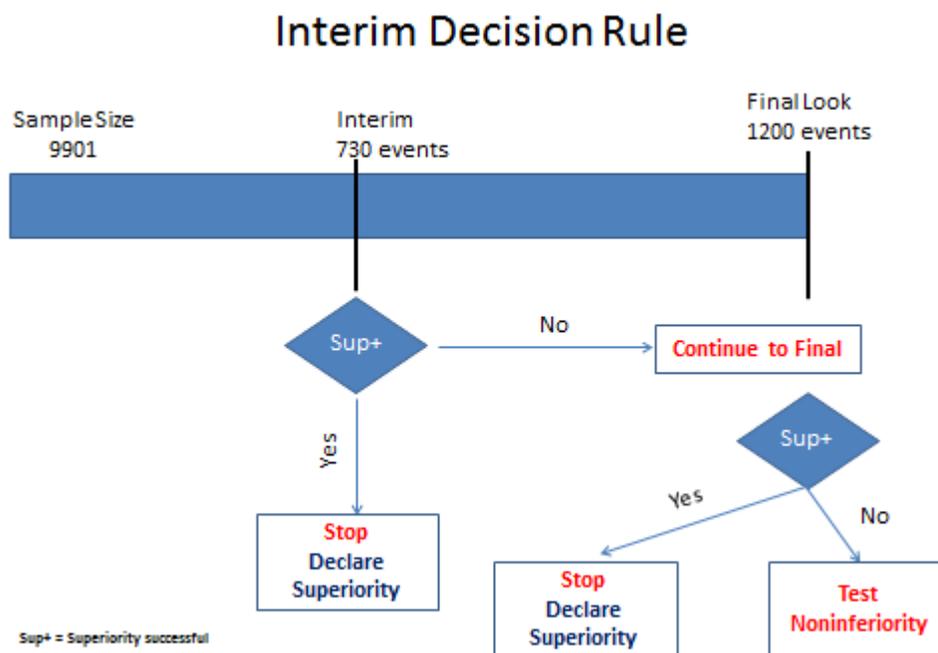


Figure GBDJ.4.1. Interim decision rule.

The median unbiased estimator for the hazard ratio will be reported if the trial is stopped early for efficacy at an interim analysis.

4.1. Determination of Sample Size

For the initial powering of the trial, a minimum of 1067 unique primary endpoint events will be required to provide 90% power to demonstrate the superiority of dulaglutide over placebo at a true hazard ratio of 0.82 and 2-sided significance level of 0.05. To calculate the sample size, the following assumptions were used and yielded a sample size requirement of approximately 9600 patients: (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%.

The calculations were performed 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.

4.2. General Considerations

All entered data will be verified, and archived at a contract research organization (CRO) external to Lilly and/or at Lilly. An independent statistical analysis center (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 the CRO and/or by Lilly for the purpose of the final clinical study report (CSR).

Efficacy and safety analyses will be conducted using the intent-to-treat (ITT) population. This population will include 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 interactive voice response system (IVRS) and a treatment is assigned at Visit 3.

Additional analyses will be conducted using the per-protocol (PP) population. The PP population is a subset of the ITT population defined as all randomized patients who have not permanently discontinued study drug, discontinued from the study, have an overall adherence of $\geq 75\%$, and have no important protocol deviations. The primary efficacy analysis will be repeated using the PP population. Important protocol deviations are defined in Section 4.7.

The analysis populations used in this study are defined in [Table 4.1](#).

Unless otherwise specified, listings will be conducted using all randomized patients. The data collected will be presented as listings by investigator site, patient, and treatment.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and CIs will be calculated at 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 nominal 2-sided alpha level of 0.10 and will be deemed to be exploratory. No adjustment for multiplicity will be performed unless otherwise specified.

Countries in similar geographic regions with <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. If baseline data are missing, the last measurement taken prior to this visit will be used for the baseline measurement.

The primary analysis and key secondary CV endpoint analyses will be based on adjudicated events that occurred after randomization (Visit 3). Sensitivity analyses may be conducted

including events reported by investigators or events identified through safety reviews, to assess their impact on the primary analysis results.

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

4.3. Default Analysis Methods

A default analysis method will be defined for certain types of variables (for example, baseline continuous, baseline categorical and time-to-event) that will be commonly encountered in this study. If a specific analysis requires a methodology other than the default for that variable type, the methodology will be described in the appropriate sections of this SAP.

4.3.1. Baseline Analyses

Measurements collected at Visit 3 will be considered the baseline values. If data from Visit 3 are missing, measurements from the screening/run-in period (between Visit 1 and Visit 3) will be used. If a patient has no information for a variable prior to randomization, data will not be imputed and the patient will not be included in the analysis. Baseline analysis for any particular variable will be conducted using all randomized patients with baseline data for that variable.

The default analysis method for continuous baseline variables will be an ANOVA model with only a fixed effect for treatment; however, in situations where the baseline variable will be expected to violate the assumption of normality, Wilcoxon's rank sum test will be used. Such situations will be appropriately identified throughout this SAP. Summaries for continuous variables will include descriptive statistics (that is, number of patients, mean, standard deviation (SD), sample size, median, 10th percentile, 90th percentile, and interquartile range).

Categorical variables will be compared between treatments using Pearson's chi-square test if the expected count is at least 5 in at least 80% of the cells; otherwise, Fisher's exact test will be used. Summary statistics for categorical variables will include sample size, number, and proportion of patients.

For the CSR, a baseline factor will be considered as a covariate for a covariate-adjusted analysis only if the baseline factor is both clinically and statistically significantly different between treatment groups.

4.3.2. Post-Baseline Analyses of Continuous Variables

For each continuous response variable, visit-specific analyses will be performed for the visits where the variable was scheduled to be measured. If a patient has no post-baseline measurements of a variable, the patient will not be included in the visit-specific analyses of that variable. Analyses of change and percent change from baseline to specific visits will have the same requirements plus the additional constraint that the patient has a baseline measurement of the variable.

The default analysis model for continuous response variables expected to be normally distributed will be a mixed-effects model for repeated measures (MMRM) using restricted maximum

likelihood (REML). The MMRM model will be used to analyze changes from baseline with the baseline value as the covariate. The model will include fixed effects for treatment, visit, treatment-by-visit interaction, the baseline as a covariate, and the patient as a random effect. An unstructured covariance structure will be used to model the within-patient errors. This analysis includes visits where the continuous response variable was scheduled to be measured.

If this analysis fails to converge, the following covariance structures will be tested in order:

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

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean (LS Mean) using Type III sum of squares.

Summary statistics will include sample size, mean, SD, median, 10th and 90th percentiles for both the actual and the change from baseline measurements. Least-squares mean (LS Mean) and standard error (SE) 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 rank-transformed data will be used and p-values for the difference between dulaglutide and placebo will be reported, unless stated otherwise. The model includes treatment. Treatment group comparisons will be performed with no multiplicity adjustment. Categorical laboratory measures will be analyzed using Chi-square test or Fisher's exact test.

In situations where the continuous response variable will be expected to violate the assumption of normality, Wilcoxon's rank sum test will be used. Such situations will be appropriately identified throughout this SAP. Between-treatment comparisons will be assessed using the p-value, and within-treatment changes will be assessed using the p-value from the signed rank test. Summaries for these variables will include descriptive statistics: number of patients, median, and 25th and 75th percentiles. In addition, the Hodges-Lehman estimator of the treatment contrast will be provided.

4.3.3. Post-baseline Analyses of Categorical Variables

Categorical variables will be compared between treatment groups using the Pearson chi-square test if the expected count is at least 5 in at least 80% of the cells; otherwise, Fisher's exact test will be used. Summaries for these variables will include the between-treatment p-value and the

descriptive statistics: number and proportion of patients. For post-baseline outcome variables, the relative risk estimate and the associated 95% CI will be provided, if there are at least 10 patients with the outcome.

If the categorical variable is associated with a scheduled post-baseline measurement, then a patient must have a measurement of the variable to be included. However, when the categorical variable is the occurrence of an event (yes/no), such as development of an adverse event (AE), then all randomized patients will be included in the analysis.

4.3.4. Time-to-Event Analyses

Time-to-event analyses will be performed for each of the adjudicated outcomes. For each analysis, all adjudicated events in the locked database will be used.

Time-to-event variables will be analyzed using survival analysis methodology if the total number of outcomes is 10 or more. A Cox proportional hazards regression analysis, where the model only includes a fixed effect for treatment, will be used to derive the hazard ratio (dulaglutide/placebo) and the associated 95% CI. The between-treatment comparison will be based on the p-value from the Cox model. The proportional hazard assumption will be examined graphically. If not met, data will be analyzed using accelerated failure time models. Kaplan-Meier (KM) estimates of the survival curve for each treatment will be generated. The number and proportion of patients with the event will be provided, along with the between-treatment p-value. Tied event times will be handled by the Exact method.

If the number of outcomes is <10, survival analyses will not be performed. Instead, Fisher's exact test will be used and the summary statistics will include the number and proportion of patients with the event plus the between-treatment p-value.

For adjudicated outcomes, the incidence rate per 100 person-years of follow-up will be calculated for each treatment group. The numerator will be the number of patients with the event, and the denominator will be the event-specific total person-years of follow-up divided by 100. Total person-years of follow-up is the sum, over patients, of the time on study until the first outcome (first event time or censoring time). The absolute risk difference (ARD) will then be calculated by subtracting the incidence in the dulaglutide arm from that in the placebo arm. For some analyses, the number needed to treat (NNT) to prevent an additional event will be derived using the incidence rates, that is, $1/(\text{Placebo rate} - \text{dulaglutide rate})$. These analyses will be performed where documented in the SAP, and this statistic will only be derived if the p-value from the Cox model is statistically significant.

4.3.4.1. Time to Event

For each patient, time-to-event for an event of interest will be the number of days between the date of randomization and the onset date of the event plus 1 day if the patient experiences the event or the number of days between the date of randomization and the censoring date (Section 4.3.4.3) plus 1 day if the patient does not experience the event. If a patient experiences

multiple events (for example, multiple strokes) the date of the first event will be used, unless otherwise specified.

4.3.4.2. Person-Years of Follow-up

Person-years of follow up for an event of interest will be calculated for each patient as the time to event (defined in Section 4.3.4.1) divided by 365.25.

The total person-years of study follow-up will be calculated for each patient as the number of days between the randomization date and the censoring date plus 1 day divided by 365.25. The censoring date is defined in Section 4.3.4.3 for time-to-event analyses (other than mortality analysis).

4.3.4.3. Censoring Date

For time-to-event analyses (except for mortality analyses), the censoring date for a patient is the Final Visit date if a Final Visit was conducted, the discontinuation date if the patient discontinues from the study early, or the patient's date of death if the patient dies during the course of the study. This censoring date will be used in all analyses (except the mortality analyses) to censor patients who have not experienced the event of interest.

For time-to-event analyses for mortality, the censoring date for a patient is the Final Visit date if the patient is known to be alive at the time of the Final Visit. If the patient discontinues from the study early, the censoring date will be the last date that the investigator can ascertain the patient was alive.

4.3.4.4. Handling of Missing Dates

For all adjudicated events, the date the Clinical Endpoints Committee (CEC) indicates the event occurred will be used in all analyses. If this date is missing then the investigator-reported date will be used.

For an incomplete endpoint event (that is, primary endpoint or secondary efficacy endpoint events) date, imputation will be performed as outlined below:

- If only the day of the event date is missing, the day will be imputed as the 15th of the reported month.
- If both the month and day of the event date are missing, the month and day will be imputed as 30 June of the reported year.
- If only the month is missing, the month will be imputed as June.
- In the case that the imputed event date falls after the patient's censoring date as defined above, the incomplete event date will be imputed as the censoring date (for example, if an incomplete onset date of an event is X-X-2012 and the patient's censoring date is 05-22-2012, then the onset date of the event will be imputed as 05-22-2012 rather than as the date of 06-30-2012 as imputed by following the procedure stated above for missing month and day).

For an incomplete death date, imputation will be performed as described below:

- If only the day of the death date is missing, the day will be imputed as follows.
 - (a) If the date of the last reported contact for the patient falls in the same month and year as the death date where the day is missing, the day will be imputed to fall halfway between the last reported contact and the end of the given month (for example, if an incomplete death date is 04-X-2012, and the date of the last reported contact is 04-22-2012, the death date will be imputed as 04-26-2012);
 - (b) If the date of the last reported contact for the patient occurs before the reported month and year of the death date, the day will be imputed as the 15th of the reported month (for example, if an incomplete death date is 04-X-2012, and the date of the last reported contact is 03-26-2012, the death date will be imputed as 04-15-2012).
- If both the month and day of the death date are missing, the month and day will be imputed as follows.
 - (a) If the date of the last reported contact for the patient falls in the same year as the incomplete death date, the death date will be imputed as the first of the month falling halfway between the month of the last reported contact and the end of the year (for example, if an incomplete death date is X-X-2012, and the date of the last reported contact for the patient is 06-22-2012, the death date will be imputed as 09-01-2012).
 - (b) If the year of the last reported contact date for the patient occurs before the year of the incomplete death date, the death date will be imputed as 30 June of the reported year (for example, if an incomplete death date is X-X-2012, and the date of the last reported contact is 06-22-2011, the death date will be imputed as 06-30-2012).

4.3.5. Subgroup and Risk-Adjusted Analyses

Subgroup analyses and analyses that account for differences in baseline risk factors will be performed and will be regarded as exploratory. The subgroup analyses for time-to-event variables will only be conducted if the number of outcomes is at least 50.

4.3.5.1. Prespecified Subgroup Analyses

Subgroup analyses will be performed for the following prespecified subgroup variables:

- gender (female and male)
- age group (age <median, and age ≥median)
- duration of diabetes (duration <5 years, 5 years ≤ duration <10 years and duration ≥10 years)

- body mass index (BMI) (BMI <median and BMI ≥median)
- baseline HbA1C (HbA1C <median and HbA1C ≥median)
- geography (region) (US/Canada, South America, Europe, and Asia Pacific)
- prior CV event (Yes, No)

For the purpose of the subgroup analyses, South Africa will be included in the geographical subgroup of Europe, Australia and New Zealand in the subgroup of Asia Pacific, and Mexico in the subgroup of South America.

A prior CV event is defined as a history of MI, or a history of myocardial ischemia by a stress test or with cardiac imaging, ischemic stroke, coronary, carotid or peripheral artery revascularization, or hospitalization for unstable angina with electrocardiogram (ECG) changes, or need for percutaneous coronary intervention (PCI).

4.3.5.2. Exploratory Subgroup Analyses

To select additional factors for subgroup analyses, clinically relevant baseline characteristics will be identified for the primary outcome variable and each of its components. A Cox proportional hazards regression model adjusted for baseline risk factors will be obtained using a model selection process, guided by clinical review of the published literature. All these factors will be forced into the model, along with the above prespecified subgroup variables. For all factors, the significance level for remaining in the model will be 0.05. After the selection of terms into the model concludes, treatment will be added to the model. For all dichotomous terms in the final model, parameter estimates, standard errors and p-values plus the hazard ratio and its 95% CI will be reported.

Any factors remaining in the final proportional hazards model will also be used for subgroup analyses.

4.3.6. Multiple Comparisons/Multiplicity Adjustments

The primary objective of this study is to demonstrate with statistical significance a clinically meaningful reduction in the incidence of primary endpoint events. There will be 1 interim analysis and 1 final analysis. The interim analysis will be performed when approximately 61% (730) of the primary endpoint events have occurred and have been adjudicated as such. The final analysis will be performed at 100% of the total information (approximately 1200 adjudicated primary endpoint events) if the study is not stopped early. Appropriate adjustments for multiplicity will be made to maintain an overall type I error rate of <0.05 (Section 4).

Multiplicity adjustments will be performed for the analyses on the primary and secondary efficacy endpoints in order to control the overall Type I error rate at a 2-sided alpha level of 0.05. For repeated testing of the primary outcome via interim analysis, an O'Brien-Fleming alpha spending function will be used to control alpha across the interim and final analyses for the testing of the primary endpoint (GBDJ Protocol Section 12.2.2). A graphical approach will be

used to control the type I error rate across the secondary endpoint analyses at the final analysis time point or at the interim analysis time-point if the decision is to stop the trial following the interim analysis (GBDJ Protocol Section 12.2.2 and Section 12.2.12 for the Interim Decision Rule).

4.3.6.1. Graphical Approach

A graphical approach using a sequentially rejective Bonferonni multiple-testing procedure to control the family wise error rate (FWER) will be used for the secondary hypotheses in this study. In general, a graphical approach is characterized by prespecifying:

- the hypotheses (or nodes) within the testing algorithm
- an initial allocation of α
- weights along the lines (edges) that connect the hypotheses tests.

The initial allocation of α is such that the sum of all α is the full alpha available for the analyses. The algorithm begins by testing all hypotheses that have α allocated to them. If any hypothesis is rejected then the graph is updated to reflect the reallocation of α where the proportion of α reallocated to other hypotheses is determined by the weights along the edges. Hence the α can be considered “recycled” as described by Bretz and colleagues (2009) as long as at least one hypothesis is rejected. This iterative process of updating the graph and reallocating the α is repeated until no further hypotheses can be tested.

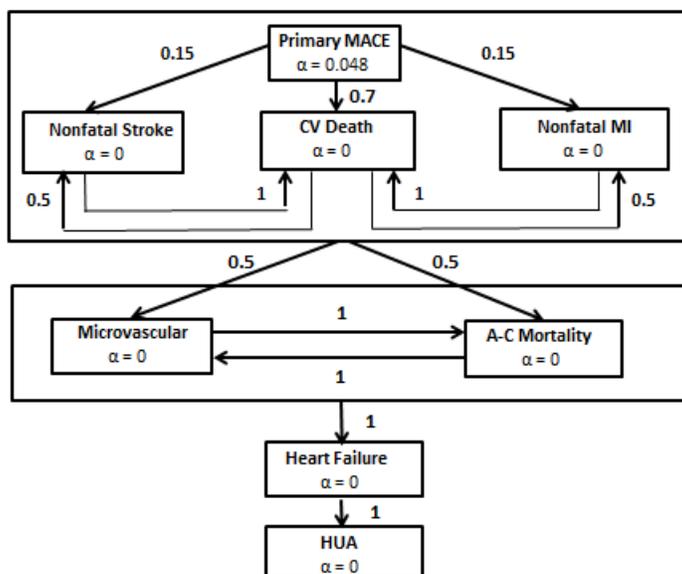
Figure GBDJ.4.2 shows the primary and secondary endpoints, the α allocation, and associated weights for the REWIND Study. Only the hypothesis test for the primary endpoint (Composite MACE) is initially allocated the full value of α at the given analysis time-point (for example, at the final analysis time-point with 1200 events, $\alpha = 0.048$, 2-sided); all other hypotheses are allocated $\alpha=0$. Additionally the weights are provided along the edges.

The first hypothesis tested will be for the primary endpoint (time to first composite MACE) which is tested at the alpha value used for the primary analysis at the given analysis time point. If that hypothesis is rejected then the graph is updated and the hypotheses for the following 3 endpoints will be tested with an α based on the weights indicated by the 3 edges (arrows) coming from the Composite MACE. Figure GBDJ.4.3 demonstrates what the graph would look like if the first test (Composite MACE primary endpoint) is rejected at the final analysis time-point with 1200 events, with α reallocated as follows:

- Time to first Nonfatal MI has a weight of 0.15 resulting in $\alpha = (0.048*0.15) = 0.0072$
- Time to CV Death has a weight of 0.7 resulting in $\alpha = (0.048*0.7) = 0.0336$
- Time to first Nonfatal Stroke has a weight of 0.15 resulting in $\alpha = (0.048*0.15) = 0.0072$.

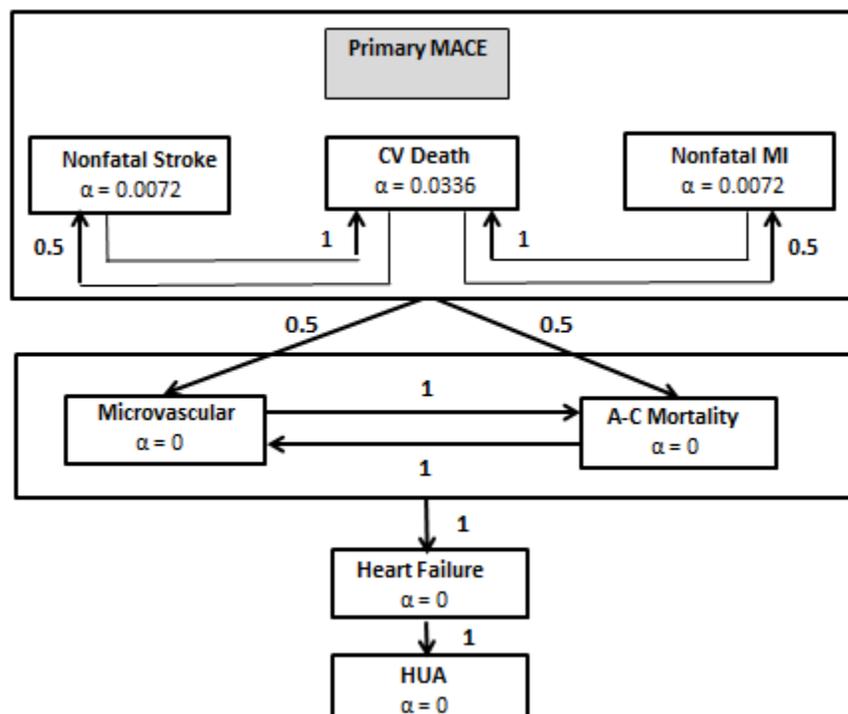
If any of the 3 hypotheses above are rejected, the graph is again updated and its alpha is reallocated to the subsequent tests according to the weights given in the figure. It should be noted it is possible for the hypothesis for a particular endpoint to fail to be rejected the first time it is tested, but subsequently receive enough α from successfully rejected hypotheses and be rejected the second time it is tested. This iterative process of updating the graph and redistribution of α is continued until no further hypotheses can be tested.

The graphical approach to multiplicity control has been evaluated in several peer reviewed publications: Bretz and colleagues (2009), Bretz and colleagues (2011); and Alosch and colleagues (2014). Because graphical approaches are closed testing procedures, they control the FWER strongly (Alosch et al. 2014). This closed testing system controls the FWER to ≤ 0.05 .



Abbreviations: A-C Mortality = all-cause mortality; CV = cardiovascular; HUA = hospitalization for unstable angina; MACE = major adverse cardiovascular event; MI = myocardial infarction.

Figure GBDJ.4.2. The graphical approach with initial α allocation and weights at the final analysis time point with 1200 primary MACE events.



Abbreviations: A-C Mortality = all-cause mortality; CV = cardiovascular; HUA = hospitalization for unstable angina; MACE = major adverse cardiovascular event; MI = myocardial infarction.

Figure GBDJ.4.3. The graphical approach reflecting α propagation after rejecting the first hypothesis at the final analysis time point with 1200 primary MACE events.

No adjustments will be made for multiple comparisons on other endpoints.

4.3.6.2. Interim Analysis and Control of Type I Error following an Efficacy Stop Decision

4.3.6.2.1. Data Cut-off Date for the Interim Analysis

The interim analysis is planned to be conducted when a minimum of 730 positively adjudicated MACE endpoint events have occurred. It is expected that there will be more than 730 events in the pool for the interim analysis, as all events that are adjudicated on the same day as the 730th positive event will also be included in the analysis. The data cut-off date for the interim analysis will be the event date, from the adjudicator's opinion, of the most recent event in this pool of unique subjects with positively adjudicated primary MACE endpoint events. In addition, all efforts will be made to adjudicate the majority of all MACE events with events dates prior to this cut-off date, and these adjudicated events will be included in the interim analysis (Figure GBDJ.4.4).

At the interim analysis, the alpha level used for the analysis will be determined based on the actual number of events included in the analysis using EAST Software (EAST 6, Cytel, www.cytel.com). If the trial continues to the end following an IDMC review of the interim

results, the final alpha will be adjusted based on the final number of primary MACE events using EAST software. If the IDMC recommends stopping the trial for efficacy following the interim analysis, analyses will be performed on this post-interim, final-lock database using the adjusted significance level alpha based on the Whitehead procedure (Section 4.3.6.2.2).

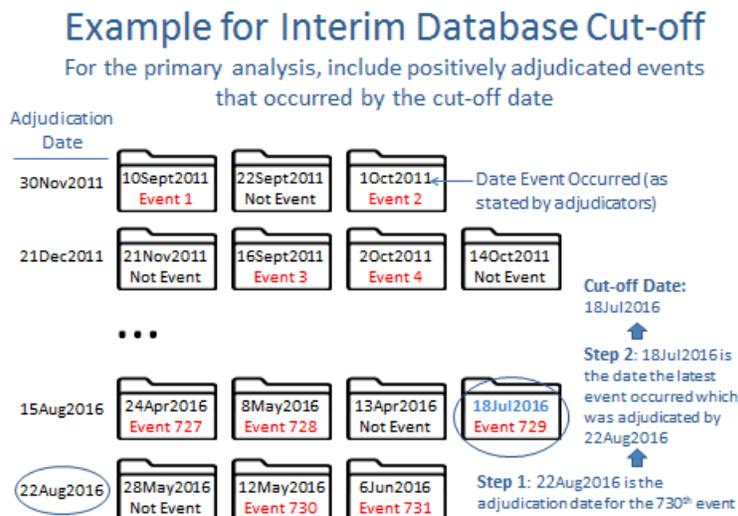


Figure GBDJ.4.4. Example of data cut-off date for the analysis of the primary MACE events.

4.3.6.2.2. Controlling Type I Error across Interim and Final Analyses Following Early Termination for Efficacy

All events until study closure will be collected and analyzed as part of the conduct of the study following a decision to stop the study early for efficacy. This post-interim, final-lock dataset will be comprised of all events, including those events collected after the interim stopping decision until final trial closure. These data are valuable in the full interpretation of the conduct of the study and will be included in the submission to Food and Drug Administration (FDA). If the study is stopped at the interim as a result of meeting the interim boundary, the interim analysis data used for making the decision will be included as part of the Common Technical Document (CTD). The post-interim final lock dataset will be the primary database to be used to support safety and efficacy in the CTD and for proposed labeling. While the Type I error rate at interim is already controlled at the interim lock, in order to control for Type I error for the post-interim final analysis, Whitehead's approach will be used to recalculate the rejection boundaries since the additional events after the interim will be included in the primary dataset (Whitehead1992). Both the interim and post-interim final data (primary and key secondary endpoints) will be included in the CTD and the CSR for efficacy.

The following is an example of the use of Whitehead's approach in the context described above. For example, with 730 events at the interim lock, the one-sided p-value boundary is 0.004. If the interim p-value is less than the stopping boundary, then the trial may be stopped early for

efficacy. If the trial is stopped early for efficacy, additional events will accrue between the interim lock and the post-interim final lock and this could range between 100 to 250 additional events. Whitehead's approach controls Type I error by recomputing the final p-value boundary based on the number of events included in the interim lock plus the additional events accrued. For example, with an additional 250 events following the interim lock (for a total of 980 events), the one-sided p-value boundary for the primary analysis is 0.013. Using Whitehead's approach, at the post-interim final analysis (following trial stop), the stopping boundary will be calculated based on the total number of primary MACE events included in the post-interim final lock (out of the 1200 events planned for the end of the trial) using the protocol-specified O'Brien-Fleming spending function. If the trial does not stop early for efficacy, Whitehead's approach will not be used.

4.4. Multicenter Study

Patients will be enrolled at approximately 486 investigational sites in approximately 27 different countries. To control for differences between sites and assure that treatment allocation is balanced within site, randomization will be stratified by site. Randomization blocks of size 4 will be dynamically allocated to sites. Patients will be assigned in a 1:1 ratio to the next available treatment (either dulaglutide 1.5 mg/week or placebo) from the block currently allocated to their site at the time the call was made to the IVRS. The number of patients randomized at each site in each country will be provided.

4.5. Patient Populations/Analysis Subsets

The patient populations and analysis subsets used in the study are described below.

Table 4.1. Analysis Population for REWIND

Population	Definition
All Entered	All patients who signed informed consents
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 <ul style="list-style-type: none"> • have not permanently discontinued study drug • no important protocol deviations • have completed the study • have an overall adherence with study drug of $\geq 75\%$

4.6. Patient Disposition

A listing of patient discontinuations will be presented for all randomized patients. Summary analyses will be conducted for the ITT and PP populations.

Number and proportions of patients will be presented for each treatment group and compared across treatment groups using a Chi-square test or Fisher's exact test.

4.7. Important Protocol Deviations

Important protocol deviations will be listed for all randomized patients. The following protocol deviations will be considered important:

- not meeting any of the inclusion criteria [1], [6], and [9], or meeting any of the exclusion criteria [10], [11], [12], [13], and [21] (REWIND study protocol) that affect the primary endpoint analysis
- nonadherence to treatment regimen (that is, overall treatment adherence <75%)
- incorrect dispensation of study drug (patient received incorrect treatment)
- unblinding of treatment assignment for any reason
- using prohibited concomitant medications (that is, non-study GLP-1 analogs, pramlintide, or prescription weight loss drugs)
- safety laboratory or measures (calcitonin and/or serum creatinine and/or ECG) not taken for 18 or more months and study drug not discontinued

4.8. Patient Characteristics at Baseline

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, 10th percentile, 90th percentile, and standard deviations. Mean will be analyzed using ANOVA. For categorical measures, summary statistics will include sample size, number, and proportion. Treatment group comparisons will be performed using a Chi-square test or Fisher's exact test.

4.9. Concomitant Medications

Concomitant medications will be summarized by different categories and treatment group using ITT population. All concomitant therapies originally mapped using the WHODRUG dictionary in the clinical trial database will be further classified using Anatomical Therapeutic Chemical (ATC) code for reporting purpose. The number and proportion of patients will be analyzed using a Chi-square test or Fisher's exact test.

4.10. Historical Illnesses at Visit 1

A limited number of historical illnesses collected at Visit 1 will be listed using all randomized patients. Summary reports will be conducted by treatment group using the ITT population. Historical illnesses will be reported using the terms in the medical history questions on the case report forms. The number and proportion of patients will be analyzed using a Chi-square test or Fisher's exact test.

4.11. Treatment Adherence

Treatment adherence will be assessed for each visit interval. Patients will be instructed to return any unused study drug syringes at each study visit for the purposes of study drug accountability. Study drug adherence will be calculated at each visit after baseline when study drug is dispensed based on the percentage of syringes used, specifically it will be calculated as follows:

$$\text{Study drug adherence for each visit} = \frac{[(\text{no. of syringes dispensed} - \text{no. of syringes returned}) / (\text{no. of weeks between the 2 consecutive visits})] * 100\%.$$

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.

Treatment adherence will be listed and summarized using the ITT population. The number and proportion of patients who are compliant at each visit by treatment group will be summarized and compared using a Chi-square test unless the total count is <10.

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 compliant 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 compliant among visits with non-missing adherence data for the patient). The overall adherence will be summarized and presented in descriptive statistics that include the sample size, mean, median, 10th and 90th 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.

4.12. Treatment Exposure and Study Duration

Patients may discontinue study treatment but remain in the study.

Treatment exposure will be defined as the total duration of time that the patient is believed to be taking study drug. This time period will be derived by subtracting the randomization date (Visit 3) minus 1 day from the last visit date for patients actively participating in the study at the time of database lock (at the conclusion of REWIND) or the discontinuation date for patients who discontinue study drug. The duration of treatment exposure will be reported in months and will be compared between treatments using nonparametric methods (Wilcoxon rank-sum tests). The duration of treatment exposure will be summarized by treatment group using the ITT population. The duration of exposure will be categorized into the following groups: ≥ 2 weeks, ≥ 3 months (13 weeks), ≥ 6 months (26 weeks), ≥ 1 year (52 weeks), ≥ 2 years, ≥ 3 years, ≥ 4 years and ≥ 5 years, etc. These categories will be summarized by the number and proportion of patients in each category by treatment group.

Keeping with the ITT principle, the study duration for a patient will commence on the date of randomization to the time of last participation in the study. This will be the patient's safety reporting period. At the time of datalock (at the conclusion of REWIND), the time of last participation will be the Final Visit date for patients still actively participating in the study; the

date of discontinuation if the patient discontinued from the study early; or the date of death if the patient dies during the study. The study duration will be reported in months and will be compared between treatments using nonparametric methods (Wilcoxon rank-sum tests). In addition, a categorical breakdown of the study duration will be provided using the same categories as the duration of treatment exposure.

The number and proportion of patients who discontinue study drug will be compared between treatment groups with separate analyses for the reasons for the discontinuation, (for example, AE, protocol, or patient decision). The length of time patients are off study drug will be summarized by treatment group. The analyses for discontinuations will also be performed by visit.

4.13. Primary Efficacy Measure

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.

An independent Clinical Endpoints Committee (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 Cardiovascular Causes** will be defined as a death resulting from an acute MI, sudden cardiac death, death due to heart failure, 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 MI 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. Myocardial infarction will include the following subtypes: spontaneous MI, 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.

The analysis for the primary efficacy measure will be based on the ITT population.

4.13.1. Primary Analysis Model

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

4.13.2. Analysis of Primary Endpoint

The endpoint for the primary analysis is defined as the first occurrence after randomization of death due to a CV cause, nonfatal MI, or nonfatal stroke (adjudicated as such). Time-to-event analyses (Section 4.3.4) will be performed for the composite primary endpoint. Treatment comparisons will be based on the hazard ratio and its 95% CI from the Cox model.

Counts and proportions of patients who experience a primary endpoint event will be calculated. Person-years of follow-up for the primary endpoint, and the incidence rate, calculated by dividing the number of patients who developed the event during the study period by the event-specific person-years of follow-up, will be provided. The ARD for an endpoint will be calculated based on the difference in cumulative incidence between the 2 treatment groups at the end of the study period. The ARD and NNT (Section 4.3.4) will be calculated for the primary endpoint. An adjusted 95% CI for the hazard ratio (dulaglutide/placebo) from the Cox proportional hazards regression model will be provided.

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.

4.13.3. Subgroup Analysis of Primary Endpoint

The effects of dulaglutide compared to placebo on the incidence of the composite primary endpoint events will be examined across the prespecified subgroups of interest listed in Section 4.3.5.

The clinically relevant baseline characteristics for exploratory subgroup analyses for the primary endpoint include: prior MI, prior history of stroke or transient ischemic attack (TIA), prior hospitalization for unstable angina, prior coronary revascularization, existing microalbuminuria (defined as a urine albumin/creatinine ratio (ACR) >30 mg/g and ≤ 300 mg/g) or macroalbuminuria (see Section 4.17.3), current smoker, hypertension, hyperlipidemia, aspirin use, beta-blocker use, calcium channel blocker use, ACE inhibitor or angiotensin receptor blocker use, diuretic use, and antithrombotic (nonaspirin antiplatelets, vitamin K antagonists, heparin, direct thrombin inhibitor, or other antithrombotics).

A risk-adjusted analysis will be performed using these baseline characteristics, the prespecified subgroups, and a multifactor proportional hazards model. The baseline characteristics remaining in the final multifactor proportional hazards model plus the prespecified subgroup variables will be used for subgroup analyses.

The risk-adjusted and subgroup analyses will be performed using the ITT population.

4.13.4. Sensitivity Analyses of Primary Endpoint

The time-to-event analysis for the primary endpoint will be repeated using the PP population, but NNT will not be calculated.

Randomization was stratified by site. To account for the stratification, a time-to-event analysis of the primary endpoint stratified by site will be performed as a sensitivity analysis.

4.13.5. Assessing the Impact of Missing Data on the Primary Endpoint Analysis

Vital status or status on the primary endpoint may not be available for patients who discontinued early from the study or patients who were lost to follow-up during the course of the study. Sensitivity analyses will be performed exploring the impact of missing data on the primary endpoint findings. Specifically, 2 analyses of the primary endpoint will be performed. The first analysis which is extreme, will assume that all such patients in the dulaglutide group have experienced MACE primary endpoint events at the time of their discontinuations from the study or their last contact dates if they were lost to follow-up, while such placebo patients did not experience an event and thus are censored at their corresponding times. The second analysis, less extreme, will assume that all these patients from both treatment groups have experienced primary MACE endpoint events at the time of their discontinuations from the study or their last contact dates if they were lost to follow-up.

4.14. 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 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 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 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 electrocardiogram (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.

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 ACR >300 mg/g (>33.9 mg/mmol).
- 5) **Renal replacement therapy (RRT)** will be defined as chronic hemodialysis or
- 6) Peritoneal dialysis used as maintenance therapy in patients with end stage renal disease (ESRD), or renal transplantation.
- 7) **A sustained 30% decline in eGFR** will be based on a 30% reduction from the
- 8) Baseline value (Visit 3) in 2 consecutive calculations of postrandomization eGFR, using the modification of diet in renal disease (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.

An event of the composite microvascular endpoint is the first occurrence after randomization of an event of diabetic retinopathy requiring laser therapy, vitrectomy for the treatment of diabetic retinopathy, anti-VEGF therapy for the treatment of diabetic retinopathy, development of clinical

proteinuria (macroalbuminuria, see Section 4.17.3), a 30% decline in eGFR (see Section 4.17.3) from baseline, or need for renal replacement therapy.

Time-to-event analyses will be performed for each of the secondary efficacy measures including the individual components of the composite primary endpoint using the ITT population. The analyses of death from CV causes, nonfatal MI, nonfatal stroke, HF requiring hospitalization or hospitalization for unstable angina will be based on adjudicated events. The NNT statistic will be provided for each analysis provided that the p-value from the Cox model is statistically significant. The incidence rate per 100 person-years of follow-up will also be calculated for each type of event.

4.14.1. Additional Analyses of All Cause Mortality

Deaths will be analyzed on the basis of the adjudicated cause of death which will be categorized into CV death and non-CV death. Deaths with an undetermined cause will be included in CV deaths for analysis purposes. Time-to-event analyses will be performed for all deaths as well as for each adjudicated cause of death (CV death versus non-CV death and the subcategories under CV death). Incidence rates per 100 person-years of follow-up will be calculated for each type of death for each treatment group. The NNT statistic will not be provided for these analyses. These analyses will be performed using the ITT population.

A by-patient listing of all deaths and the adjudicated outcome will be provided.

4.14.2. Additional Analyses of MI Endpoint

The additional analyses of the MI endpoint will be performed using the ITT population.

4.14.2.1. Analyses of Classifications MI Endpoint

4.14.2.1.1. Universal MI Definition

For each MI event, the adjudicators will classify the MI type using the universal MI definition (Thygesen et al. 2007) as follows:

Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply, for example, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new Left Bundle Branch Block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4: MI associated with PCI or MI associated with stent thrombosis as documented by angiography or at autopsy

Type 5: MI associated with CABG

Each type of MI (using the universal MI definition) will be further summarized in categories of multiples (1-2X, 2-3X, 3-5X, 5-10X, and >10X) of the 99th percentile of the upper reference limit (URL) of cardiac biomarkers creatine kinase-MB (CK-MB) or troponin, and compared between treatment groups.

4.14.2.1.2. Other Classifications of Myocardial Infarction

The adjudicators will also classify MI type as STEMI vs NSTEMI and by subtypes of MI (Spontaneous, Periprocedural [PCI or CABG related], or Silent). Myocardial infarction types will be summarized using number and proportion of patients for both treatment groups using these different classification schemes. For these analyses, the denominator will be the total number of patients having an MI. If a patient has >1 MI, only the first MI will be included in the analysis.

4.14.2.2. Subgroup Analysis of Nonfatal Myocardial Infarction Endpoint

For subgroup analyses all adjudicated nonfatal MI outcomes will be included, and the analyses will be performed for the ITT population. The potentially clinically relevant baseline risk factors and medication use for exploratory subgroup analyses for the MI events will include: prior MI, prior hospitalization for unstable angina, prior coronary revascularization, current smoker, hypertension, hyperlipidemia, aspirin use, beta-blocker use, calcium channel blocker use, ACE inhibitor or angiotensin receptor blocker use, diuretic use, and antithrombotic use (excluding aspirin).

The risk-adjusted analysis will be performed using these risk factors, medication use, the prespecified subgroups (Section 4.13.3), and a multivariate proportional hazards model. The risk factors and medication use remaining in the final model plus the pre-specified subgroup variables will be used for subgroup analyses.

4.14.2.3. Analysis of Fatal Myocardial Infarction Endpoint

A fatal MI is defined as an MI event that resulted in death within 30 days. Time-to-event analysis (Section 4.3.4) will be performed for all adjudicated fatal MI outcomes using the ITT population. Subgroup analyses will also be performed if there are enough cases of fatal MIs (Section 4.3.5 and Section 4.13.3).

4.14.3. Additional Analyses of All Stroke Endpoint

Time-to-event analyses will be performed for each subtype of stroke (hemorrhagic, ischemic, or unknown) in the ITT and PP populations. Incidence rates per 100 person-years of follow-up will be calculated for each type of stroke for each treatment group. The NNT statistic will not be provided for these analyses.

Stroke disability, as measured using the modified Rankin scale (Farrell et al. 1991), will be assessed at approximately 30 days after the diagnosis. The number of patients in each of the following categories of the scale will be summarized and compared between treatment groups using a Chi-square test Fisher's exact test:

- 0: No symptoms at all
- 1: No significant disability despite symptoms (Able to carry out all usual activities)
- 2: Slight disability
- 3: Moderate disability (Requiring some help but able to walk without assistance)
- 4: Moderate to severe disability (Unable to walk without assistance and unable to attend to own bodily needs without assistance)
- 5: Severe disability (Bedridden, incontinent and requiring constant nursing care and attention)
- 6: Death.

4.14.4. Subgroup Analysis of Nonfatal Stroke Endpoint

For subgroup analyses all adjudicated nonfatal stroke outcomes will be included, and the analyses will be performed for the ITT population. The potentially clinically relevant baseline risk factors and medication use for exploratory subgroup analyses for the stroke events will include: prior MI, prior hospitalization for unstable angina, prior history of stroke or TIA, carotid or other artery disease, current smoker, alcohol abuse, hypertension, hyperlipidemia, aspirin use, beta-blocker use, calcium channel blocker use, ACE inhibitor or angiotensin receptor blocker use, diuretic use, history of atrial fibrillation, and antithrombotic use (excluding aspirin).

The risk-adjusted analysis will be performed using these risk factors and the prespecified subgroups, and a multivariate proportional hazards model. The risk factors and medication use remaining in the final model plus the prespecified subgroup variables will be used for subgroup analyses.

4.14.5. Analysis of Fatal Stroke Endpoint

A fatal stroke is defined as a stroke event that resulted in death within 30 days. Time-to-event analysis (Section 4.3.4) will be performed for all adjudicated fatal stroke outcomes using the ITT population. Subgroup analyses will also be performed if there are enough cases of fatal strokes (Section 4.3.5 and Section 4.13.3).

4.14.6. Exploratory Analyses: Analyses of Multiple Cardiovascular Events

A patient may experience more than one CV event during the course of the study. For example, a patient may be hospitalized for an unstable angina and later experience a nonfatal MI which

may be followed by death from a CV cause, or a patient may experience 3 nonfatal MIs or 2 nonfatal strokes. In each case, the patients will be considered as having multiple CV events. To assess the effects of dulaglutide on multiple CV events compared to placebo, analyses accounting for multiple CV events will be performed. The analyses will be performed separately for the composite primary endpoint; acute coronary syndrome (ACS) events which include nonfatal MI and hospitalization for unstable angina; MIs; strokes; MACE (composite of nonfatal MI, stroke and CV death) and heart failures requiring hospitalization. In each of these analyses, a patient who experiences multiple events of the endpoint will be considered as having recurrent events of the endpoint. The conditional Gap Time model of Prentice, Williams, and Peterson (PWP-GT) (Prentice et al. 1981) will be used to analyze recurrent CV events. The hazard ratio with 95% CI will be reported for time to the first event, second event, etc. The mean time between successive events will also be reported by treatment group. Baseline characteristics will be compared between groups of patients with no event, only one event, and multiple events (2 or more) regardless of treatment assignment and between treatments within each group. Counts and proportion for categorical variables will be compared using a Chi-square or Fisher's exact test and means for continuous variables will be compared using ANOVA.

4.14.7. Exploratory Analyses: Analysis of Nonfatal Cardiovascular Events with Competing Risk of Death

The composite endpoint of nonfatal CV events (that is, the first occurrence of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, HF requiring hospitalization or an urgent HF visit, or coronary, carotid, or peripheral revascularization), will be analyzed taking into account the competing risk of death. The competing risk model of Fine and Gray will be used (Fine and Gray 1999). Covariates of interest include treatment and the baseline CV risk factors listed in Section 4.13.3.

4.15. Additional Measures

Additional measures include:

- Change from baseline in:
 - hemoglobin A1c levels
 - weight
 - waist/hip ratio
 - cognitive function as measured by the MoCA and the DSST
 - erectile dysfunction as measured by the 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

An independent CEC will adjudicate coronary, carotid, and peripheral revascularizations. Detailed event definitions and specifics regarding endpoint determination are provided in the CEC Charter.

- 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 guidewire 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 guidewire through a guide catheter into a peripheral artery.
- 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).

4.15.1. Analyses of HbA1c, Weight, and Waist/Hip Ratio

For HbA1c, weight, and waist/hip ratio, an MMRM analysis for the change from baseline to each visit will be performed for the ITT population (Section 4.3.2). Baseline for HbA1c and weight will be Visit 1 (Screening). A correction factor will be used to standardize the HbA1c values reported depending on whether the measurement method was IFCC or DCCT.

4.15.2. Analyses of Cognitive Function and Erectile Dysfunction

Cognitive function will be assessed in all randomized patients using the MoCA instrument and the DSST at baseline (Visit 3) and after 24, and 60 months of treatment and at the final visit.

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). The patient is 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 are presented in an irregular order. The patient is 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 is the number of correct symbol-number matches. The number of matches attempted will also be recorded.

Analyses of the last score for the MoCA and the DSST, and visit-specific analyses will be performed using MMRM (Section 4.3.2) for each of these continuous test scores. The analysis will be based on change from baseline. Patients will be required to have a baseline and at least one post-baseline score to be included in these analyses.

The MoCA score is a continuous variable with a range of [0, 30]. It will also be analyzed as a categorical variable using the categories: below the threshold for normal cognitive function (that is, mild cognitive dysfunction, MoCA score <23 for Korea and MoCA score <26 for all other countries), and above the evaluation threshold (that is, normal cognitive function, MoCA score \geq 23 for Korea and MoCA score \geq 26 for all other countries). The number and proportion of patients in each category at each visit will be compared between treatment group using a Chi-square test or Fisher's exact test.

4.15.3. Analyses of Erectile Dysfunction

Another additional objective is to evaluate the effect of dulaglutide compared to placebo on the IIEF scores in men. This objective will be assessed using the measure of change from baseline to each visit in total IIEF scores from the 15-item questionnaire in the erectile function (EF), orgasmic function, sexual desire, overall satisfaction (OS), and intercourse satisfaction (IS) domains. The analysis will use an MMRM model that includes among others (Section 4.3.2) terms for treatment and the baselines values minus their mean as covariate. The population for these analyses will be all randomized male patients.

4.15.4. Analyses of Other Additional Measures

Time-to-event analyses will be performed for each of the following endpoints: the composite endpoint of death from CV causes, non-fatal MI, nonfatal stroke, or hospitalization for unstable angina; the composite endpoint of coronary, carotid, or peripheral revascularization and each of the components; any hospitalization; any fracture; and the development of cholelithiasis. A Cox proportional hazards regression model for the time to the first occurrence of the event, with treatment as fixed effects will be performed for the ITT population. Kaplan-Meier curves, hazard ratios and associated 95% CIs will be provided. Treatment groups will be compared using the p-value from the Cox model. The population for the analysis of cholelithiasis will be all randomized patients who have not had a cholecystectomy before randomization.

Revascularizations are classified as elective or nonelective and as successful or not successful. The number and proportion of revascularizations falling in each category will be compared between treatment groups using a Chi-square or Fisher's exact tests. Reasons for hospitalization (adverse Event, endpoint, or other) will also be compared between treatment groups.

4.16. Other Exploratory Analyses

4.16.1. Analyses of Time to Glycemic Intervention

Additional therapeutic intervention may be considered (with the exception of a GLP-1 analog 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.

According to the protocol, patients should continue to inject their allocated study drug and will remain in the study.

Time-to-event analyses will be performed for the time to the first glycemic intervention after randomization. The incidence of glycemic interventions will be summarized using number and proportion of patients by treatment group and by visit. The overall number and proportion will also be reported as will, Kaplan-Meier estimates of the proportion of patients having 1 or more glycemic intervention by treatment group. The number and proportion at each visit are calculated as the number of patients and proportion of patients reporting glycemic interventions at that visit. The overall number and proportion are calculated as the total number of patients and proportion of patients reporting severe glycemic interventions during the entire study treatment period. Treatment group comparison will be assessed using a Chi-square or Fisher's exact tests or log-rank tests as appropriate. The mean time to initiation of additional therapies will be compared between treatment group using an ANOVA model with treatment and additional covariates such as baseline HbA1c and concomitant antihyperglycemic agents.

4.16.2. Analyses Stratified by Baseline Concomitant Medications

Exploratory time-to-event analyses of the primary CV endpoint will be performed stratified by the following categories of concomitant medications taken by randomized patients at baseline: antihyperlipidemic agents (Yes/No), antihypertensive agents (Yes/No), and antithrombotic agents (Yes/No). The analyses will be performed using the ITT population.

4.17. Safety Analyses

Unless otherwise noted, all listings and all summary analyses will be conducted using all randomized patients (that is, ITT population). The routine safety analyses will include the measurements of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory analytes, vital signs, and ECGs.

4.17.1. Prespecified Safety Measures (Adverse Events of Special Interest)

Prespecified safety measures include the incidence of:

- acute pancreatitis
- serious GI 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

4.17.1.1. Analysis of Severe Hypoglycemia

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

The incidence of severe hypoglycemic episodes will be summarized using number and proportion by treatment group and by visit. The overall number and proportion will also be reported as will Kaplan-Meier estimates of the proportion of patients having 1 or more events by treatment group. The number and proportion at each visit are calculated as the number of patients and proportion of patients reporting severe hypoglycemic episodes at that visit. The overall number and proportion are calculated as the total number of patients and proportion 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 tests or log-rank tests as appropriate.

Severe hypoglycemia rate per year (number of events per subject per year) will be summarized by yearly 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 mixed effect model with a negative binomial distribution (see SAS code below).

```
proc glimmix data=data_glm noitprint empirical initglm method=rspl;
```

```

nloptions maxiter=100 tech=NRRIDG;
class subjid trt visit country stratification variables ;
model count= baseline count country stratification variables trt visit trt*visit/dist=nb
link=log offset=log_days s ddfm=kr;
random visit/subject= subjid type=un residual;
run;

```

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 model will include pooled country, treatment, visit, visit-by-treatment interaction, and baseline. Other covariates of interest, including categorical, continuous and time-dependent may be included.

Time to the first severe hypoglycemia event per patient will also be analyzed via a Cox model described in Section 4.3.4. Incidence rates for 100 person-years will also be presented.

4.17.1.2. Analysis of Other Prespecified Safety Measures

Each of the following events will be analyzed using the ITT population: acute pancreatitis, serious GI events, any cancer (excluding basal or squamous cell skin cancer) and specific categories of pancreatic cancer, MTC and C-cell hyperplasia, and thyroid carcinomas, serious hepatic events, clinically significant supraventricular arrhythmias and cardiovascular conduction disorders, serious renal events, discontinuation of study drug for any reason, and immune mediated reactions including serious allergic and hypersensitivity reactions (overall and by type: rash, urticaria, bronchospasm, angioedema, systemic anaphylaxis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, and other). The timing of the allergic/hypersensitivity reactions (immediate reaction - occurs within minutes [<60 minutes], acute reaction - occurs from 1 up to 6 hours from study drug administration, >6 hours through 7 days from study drug administration, and >7 days from study drug administration) will also be summarized and compared between treatment groups. Acute pancreatitis will be analyzed based on adjudicated events and on events as reported by investigators. The analyses of medullary thyroid carcinoma, other thyroid carcinomas, and C-cell hyperplasia will be based on adjudicated events. The analyses of clinically significant supraventricular arrhythmias and cardiovascular conduction disorders and immune mediated reactions including serious allergic and hypersensitivity reactions will be based on SAE reports. The analysis of other cancers (excluding basal or squamous cell skin cancer) will be based on events reported by investigators.

The incidence will be summarized using number and proportion by treatment group for each of the prespecified safety events. The overall number and proportion will be reported. The overall number and proportion will be calculated as the total number of patients and proportion of patients reporting the event during the entire study treatment period. In addition, incidence rates per 100 person-years will be calculated for each of the prespecified safety events. Treatment group comparison will be assessed using a Chi-square or Fisher's exact tests.

4.17.2. Adverse Events

A patient's safety reporting period will commence on the date of randomization to the time of last participation in the study (Section 4.12).

An AE is defined as 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 AE 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.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA™). Analysis of AEs will focus primarily on those events that first occur or worsen (increase in frequency or severity) after the first injection of study drug following randomization, (that is, TEAEs); however, all conditions/events reported on the PRE-EXISTING CONDITIONS AND ADVERSE EVENTS page of the case report form (CRF) will be retained in the study database and will be reported in the listings. 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. Analyses of TEAEs will be based on all randomized patients.

The identification of TEAEs will be performed according to the following process. Each condition/event will be coded to a preferred term (PT). For each patient, events will be divided into 2 groups: baseline events will include all events present prior to the date of randomization and before the first injection of study drug post randomization, and post-baseline events will include all events present on or after the date of randomization and the date of first injection of study drug. The maximum severity level (mild, moderate, or severe) reported prior to randomization and the first injection of study drug among all baseline adverse events that code to the same lower level term will be reported. If severity is missing for a particular baseline adverse event, then "mild" will be assumed. For each post-baseline event, the maximum severity reported after randomization and the first injection of study drug will be compared with the maximum baseline severity for the corresponding lower level term. If severity is missing for a particular postbaseline adverse event, then "severe" will be assumed. When the maximum post-baseline severity exceeds the maximum baseline severity, the event will be classified as a TEAE.

The primary hierarchy (PT through System Organ Class [SOC]) associated with the lower level term will be assigned. The number of patients experiencing a TEAE will be compared between treatments at the PT and SOC levels.

A by-patient listing of all adverse events, treatment-emergent or not, will be provided.

4.17.2.1. Serious Adverse Events

A SAE is any AE from this study that results in one of the following outcomes (please note exceptions outlined below):

- death (except as noted below)

- 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.

The following primary, secondary, and additional 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
- 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.

All SAEs will be compared between treatment groups at the PT level in the ITT population.

4.17.2.2. Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug or Study Withdrawal

Patients may permanently discontinue study medication but are expected to remain in the study. Separate analyses will be performed to compare the treatment groups with respect to AEs that led to permanent discontinuation of study medication and AEs that led to withdrawal from the study. These analyses will be conducted for all randomized patients.

4.17.3. Laboratory Analytes

All laboratory measurements will be performed locally except calcitonin which will be performed by a central laboratory. For analyses, the laboratory measurements will be converted to SI units. The following laboratory measurements will be analyzed: calcitonin, creatinine, eGFR, serum creatinine, urine ACR, HbA1c (Section 4.15.1) and lipids (Section 4.17.3.1).

Laboratory measurements collected at scheduled and unscheduled visits will be listed by patient by visit using all randomized patients. An additional listing will be presented for all scheduled and unscheduled laboratory measurements that are outside the SI normal range. All summary

analyses will be based on the ITT population. Laboratory measurements that fall within a visit window (± 30 days around the observed visit date) will be associated with that visit. Scheduled visits will have a ± 15 -day window around the scheduled visit date. For multiple runs of the same laboratory analyte, 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.

The eGFR values will be calculated using the MDRD equation [eGFR (mL/min/1.73 m²) = 175 X standardized Scr^{-1.154}Xage^{-0.203} X1.212 [if black] X 0.742 [if female], (Levey et al. 2006)].

Section 4.2 describes the analysis for continuous laboratory measurements. Microalbuminuria is defined as a urine ACR >30 mg/g and ≤ 300 mg/g) and macroalbuminuria (clinical proteinuria) as urine ACR >300 mg/g). Urine ACR is calculated as the ratio of urine albumin and creatinine measured from a morning urine sample or a random urine sample if a morning sample is not available.

The proportion of patients with microalbuminuria or macroalbuminuria at baseline or during the study will be compared between treatment groups at by visit. Shift tables will be presented for urine ACR. The tables will show the proportions of patients with shifts in the laboratory results from baseline to maximum post-baseline result using categories based on the Central Laboratory reference ranges. The categories for urine ACR will be ≤ 30 mg/g, >30 mg/g to ≤ 300 mg/g and >300 mg/g. Shifts will be grouped to show the proportions of patients who experienced decreases (post-baseline category $<$ baseline category), increases (post-baseline category $>$ baseline category), or no change from baseline to maximum post-baseline result for each treatment. Baseline will be the last non-missing observation in the study period from screening to randomization (Visit 1 through Visit 3). The maximum post-baseline result in the postbaseline study period (Visits 3 and beyond) will be the maximum result for the analysis. The analyses will use both scheduled and unscheduled labs and will be in all randomized patients with at least 1 baseline and 1 post-baseline urine ACR measurement.

4.17.3.1. Lipid Parameters

The following lipid parameters will be assessed for all randomized patients:

- total cholesterol
- high-density lipoprotein cholesterol (HDL-C)
- low-density lipoprotein cholesterol (LDL-C)
- non-HDL-C (total cholesterol minus HDL-C)
- ratio of total cholesterol to HDL-C (total cholesterol divided by HDL-C)
- triglycerides

Fasting lipids will be collected at randomization (Visit 3) and after 24 and 60 months of treatment (Visit 15). Visit 3 will be considered as baseline for these analyses. Analyses of the percent change from baseline to each visit and to last measurement will be performed separately

for each marker. Analyses of change from baseline to each visit and to last measurement will be performed for the ratio of total cholesterol to HDL-C. The median will be reported for triglycerides since the data are not expected to be normally distributed; and the mean will be reported for the other lipid parameters. Patients will be required to have a baseline and a postbaseline measurement of the marker to be included in these analyses.

4.17.4. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) will be collected in the seated position in triplicate at each office visit. Measurements will be averaged for each patient at each visit; the average values will be used in the descriptive summaries and analyses.

All averaged measurements will be listed by patient by visit using all randomized patients.

Descriptive statistics for the averaged measurements and change from baseline by treatment arm and visit will be presented. Summary analyses will be conducted using the ITT population. The change from baseline will be analyzed using the MMRM model.

4.17.5. ECG Analyses

Electrocardiograms will be performed for all randomized patients at each visit. Both scheduled and unscheduled ECGs will be qualitatively evaluated by an ECG reading center. The qualitative characteristics assessed will be summarized in the major categories and subcategories of findings: normal ECG, abnormal ECG findings, and the subcategories of abnormal findings.

The number of patients in each category and subcategory will be compared between treatment groups and by visit using a Chi-square or Fisher's exact tests.

5. Unblinding Plan

5.1. Introduction

This unblinding plan describes the organization of personnel and definition of processes that will be followed to insure integrity of the data and results throughout the trial.

5.2. Organization of REWIND Study

The 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.

Lilly will assign the obligation of study operation management to a CRO. ICON will be the CRO for this study. Medical oversight will be the responsibility of Lilly and the CRO. The CRO will be responsible for addressing medical and study operational questions, handling the data, conducting the analyses, producing all data summaries for the CSR as well as writing the CSR.

An IDMC will be responsible for monitoring patient safety and will review unblinded interim and safety analyses during the study. An ISAC will perform analyses for the IDMC prior to unblinding. The members of the ISAC are employees of Population Health Research Institute (PHRI).

For this unblinding plan, REWIND personnel will fall into one of the following 2 categories:

Personnel blinded until datalock:

- investigators
- patients
- Steering Committee members*
- ICON study personnel
- Lilly personnel* except a limited number of Lilly IVRS and clinical trial material representatives
- Population Health Research Institute (PHRI) study personnel except those who are part of the ISAC

*There may be a rare exception to the blinded status of the SC Chair and Lilly personnel as noted in the IDMC charter.

At ICON, a blinded statistical team will be responsible for the production and quality assurance review of analysis datasets and their periodic transfers to Lilly and the ISAC.

Until the final database lock, no unblinded reports will be accessible to study personnel who are to remain blinded until the end of the trial.

Personnel unblinded from the time of the first unblinded analysis:

- IDMC members
- ISAC
- Lilly IVRS and clinical trial material representatives

Depending on the recommendation of the IDMC, a Lilly internal review group (IRG) may be unblinded to study data. The Lilly IRG comprises a limited number of internal Lilly medical and statistical experts, who have no direct involvement in the clinical development of dulaglutide.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. This controlled access will be limited to certain IVRS or clinical trial material personnel. The IVRS representative will not be responsible for any analysis decisions or production work for the IDMC summaries and analyses that are described in the IDMC charter. The ISAC is responsible for creating and reviewing test programs and outputs for IDMC reports based on data blinded at the treatment group level (Treatment A versus Treatment B) prior to each IDMC review. The ISAC statistician is responsible for the production of the unblinded summaries and analyses for the IDMC from programs developed by the ISAC described above.

5.3. Data Handling and Storage

Transfers of data to the ISAC and to Lilly will be the responsibility of the blinded statistician and data management group at the CRO. Further details on data handling will be provided by the CRO.

The Lilly IVRS team will generate and maintain the randomization schedule and treatment group assignments. All treatment code information will be stored electronically on a secure server system directory with access only to the Lilly IVRS team members. This team will provide the treatment codes to the unblinded ISAC statistician through secure router ID at the time of the analyses for the IDMC.

5.4. Unblinded Data

Access to unblinded data by treatment group will be restricted to the IDMC and ISAC until the trial reaches its scheduled termination. If the IDMC recommends early termination, unblinded data will be provided to the sponsor. If the IDMC recommends a major protocol change, the IDMC Chair, the Lilly Research Laboratories Designee, and the Chair of the Steering Committee will discuss whether the Lilly Internal Review group or the Chair of the Steering Committee, or both, should review select unblinded data; the data to be reviewed will depend on the issues raised.

The IDMC understands that Lilly will behave in accordance with its own internal policies regarding review of unblinded data.

The IDMC may request, in a confidential manner, input from additional independent scientists to assist in the IDMC's decision-making. The IDMC may share select blinded data from the trial with these scientists.

5.5. Other Unblinding Issues

5.5.1. *Unblinding of Individual Patients during the Study*

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. This controlled access will be limited to certain IVRS or clinical trial material personnel. 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 IVRS. 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.

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

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 the ISAC, that provides support to the IDMC, can view group unblinded data and conduct additional analyses of the safety data.

The unblinded ISAC statistician will monitor the number of patients unblinded during the study for any trends that need to be raised to the attention of the IDMC Chair. The ISAC statistician will also maintain a list of people who received unblinded information during the trial.

Periodically and at the end of the study, the Lilly IVRS representative will provide the details of the patients and the date that they were unblinded to the unblinded ISAC statistician for review by the IDMC. Following the final review before the trial ends, the unblinded ISAC statistician will place this information into the correct server directory with all the other interim reports to be sent to the Lilly blinded statistician at the end of the trial.

5.5.2. Other Data That May Unblind Patients

It is assumed that there is no other clinical data (for example, laboratory results, ECG findings, vital sign measurements) that might potentially disclose individual patient treatment assignment to investigators, the Steering Committee, or all other Lilly and ICON study personnel during the conduct of the study.

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