AstraZeneca

Statistical Analysis Plan

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EXSCEL

A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

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PPD

24 MAR 2017

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Date

A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

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A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
BMI	Body mass index
CV	Cardiovascular
DPP-IV	Dipeptidyl peptidase-IV
eCRF	Electronic case report form
EQ-5D	EuroQol-5D (health status questionnaire)
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HR	Hazard ratio
ITT	Intent-to-treat
LDL	Low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
SAE	Serious adverse event
SAP	Statistical analysis plan

AMENDMENT HISTORY

Date	Brief description of change
13 Oct. 2010	Initial Approved SAP'
19 Feb. 2015 The protocol was amended on 25 Oct 2013 on the following, so was the SAP accordingly.	▪ During second half of 2013, blinded review of the primary endpoint event rate, it was discovered that the observed event rate is lower than expected. That led to change in study assumptions. The sample size was increased from 9,500 to 14,000. The number of primary events were reduced to 1360 to detect 15% RRR with 85% power. ▪ Intention to treat analysis, the definition of primary end point is further clarified in that it will not include events after Executive committee cutoff date to close the study nor it will include events observed during the 10 week post study period. ▪ At the request of DSMB, on treatment analysis has been added.
09 March 2016 Due to stand-alone protocol amendment	▪ The primary analysis will include adjudicated events through the Trial Termination Visit (rather than just the Cut-Off Date) ▪ Clinical Events will continue to be collected and managed as they have been throughout the entire study (refer to Protocol Section 10.3.1 and Protocol Appendix 1). ▪ Clarify that if the study terminates early for superiority, the key secondary endpoints will be tested at the same significance level as the primary endpoint in the interim analysis using the hierarchical test strategy. ▪ Clarify sensitivity analysis #3 in section 4.5.1.4. ▪ Clarify censoring schemes in Section 4.1.2.1. ▪ Update to region and race definitions (including the addition of Section 5.6) ▪ Remove analysis of hypoglycaemia from efficacy, and clarify hypoglycaemia assessments fall under safety endpoints ▪ Updated section 4.6.3 to add information about additional analysis of calcitonin elevations. ▪ Minor administrative/wording changes to Sections 2.2, 4.4.3, 4.5.3, and 5.5. ▪ Removal of the table of potentially clinical significant vital signs, as vital signs are not collected in a rigorous manner and because this study is focused on outcomes making "potentially clinically significant" changes less relevant.

Date	Brief description of change
23 Feb 2017	▪ Section 1.1.2. Added detail on the components of the primary endpoint. ▪ Section 4.5.1. Inclusion of hazard ratio and confidence intervals for treatment effect on each of the components (non-fatal MI, non-fatal Stroke, CV death) of the primary composite endpoint. ▪ Section 2.1.3. Clarified definition of 'as treated'. ▪ Section 2.2. Defined early discontinuation of study drug. ▪ Section 3.1. Positively adjudicated strokes classified as subdural hematomas are excluded from the definition of stroke in the analysis. ▪ Section 3.1.1. Definition of fatal/non-fatal events was updated to include a 30 day window between the date of the event and the date of the death due to the event. ▪ Section 4.1.2. Clarification of censoring dates. ▪ Section 4.1.2.2. Added detail to description of tipping point analysis. ▪ Section 4.3.2. Updated race definition. ▪ Section 4.4.3. Updated definitions of baseline and new concomitant medications. ▪ Section 4.5.2.3. Added exploratory analysis of recurrent MACE events. ▪ Section 4.5.4. Removed language that quality of life data would be summarized descriptively for the CSR (instead, will be independently analysed and reported). ▪ Section 6. Added changes of analysis from protocol. ▪ Section 4.5.2.1. Added analysis on the homogeneity of the effect of treatment on fatal vs nonfatal MI's and on fatal vs nonfatal strokes.

1. STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective will be to evaluate the effect of EQW, used in addition to the current usual care for glycemic control, on major CV outcomes as measured by the primary CV composite endpoint of CV-related death, nonfatal myocardial infarction (MI), or nonfatal stroke when administered to patients with type 2 diabetes.

Safety hypothesis: EQW, when used in addition to usual care, is non-inferior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

If the objective for safety is met, the following efficacy objective will be considered

Efficacy hypothesis: EQW, when used in addition to usual care, is superior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

1.1.2 Secondary Objectives

The secondary objectives are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1. All cause mortality
2. Each of the components of the primary composite CV endpoint combining fatal and nonfatal events:
   a) CV death
   b) Fatal or nonfatal MI
   c) Fatal or nonfatal stroke
3. Hospitalization for acute coronary syndrome (ACS)
4. Hospitalization for congestive heart failure (CHF)

1.1.3 Additional Objectives

Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1. Revascularization procedures. This will include percutaneous coronary intervention (PCI) with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting
2. Time to initiation of first co-interventional agent (i.e., next antihyperglycemic agent [AHA] or chronic insulin therapy)
3. Number of episodes of severe hypoglycemia

4. Absolute values of and changes in markers of cardiovascular risk including: HbA1c, body weight, blood pressure, lipid profile
5. Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire
6. Medical resource use and total direct medical costs
7. Incremental cost-effectiveness analysis of EQW as part of usual care compared with usual care without EQW

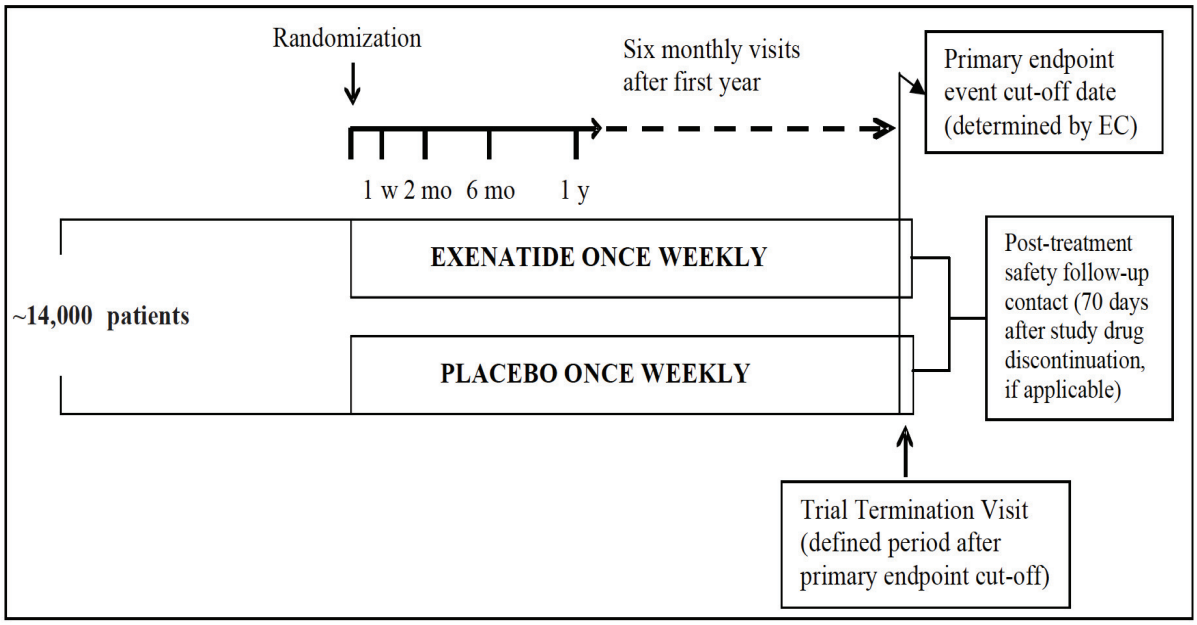
1.2 Study Design

EXSCEL is a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA1c ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral antihyperglycemic agents (AHAs) or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 70% having had a prior CV event.

Approximately 14,000 patients meeting enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either exenatide once weekly (EQW) 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until a minimum of 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. The EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cutoff date (i.e., the date at which the anticipated number of events is expected to have accrued); Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established; all patients will be expected to have follow-up until the Trial Termination Visit.

Patients will be enrolled in the Americas (North/South America), Europe, South Africa and Asia/Australasia. Trial follow-up will consist of a blend of trial visits, laboratory review and phone calls during the double-blind placebo-controlled treatment period. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. There is no requirement to achieve glycemic equipoise between randomized groups but all patients during the double-blind treatment period will have their AHA regimens adjusted as deemed necessary by their usual care provider with the addition or substitution of other AHAs, including insulin, but excluding GLP-1 receptor agonists, to achieve appropriate individualized glycemic goals in line with national guidelines.

Figure 1.1 Illustrates the flow of participants in the EXSCEL trial



1.3 Number of Patients

Sample size calculations

The primary safety/efficacy endpoint is the time from randomization to the first confirmed CV event defined as a CV-related death, nonfatal MI or nonfatal stroke.

The primary safety hypothesis of non-inferiority of EQW to placebo is:

H_0: HR [EQW:placebo] ≥1.3 versus H_1: HR [EQW:placebo] <1.3

In order to test the above hypothesis with 90% power and 1-sided α=0.025, a total number of 611 patients with composite CV events are required assuming a risk reduction of 0% on EQW compared with placebo.

The primary efficacy hypothesis of superiority of EQW to placebo is:

H_0: HR [EQW:placebo] ≥1 versus H_1: HR [EQW:placebo] <1In order to test the above hypothesis with 85% power and 2-sided α=0.05, a total number of 1360 patients with composite CV events are required assuming a risk reduction of 15% on EQW compared with placebo. With 1360 events, the power will be much larger than 90% to assess the primary safety objective of non-inferiority of EQW compared with placebo.

In addition, with the following assumptions made for this study,

- An annual composite cardiovascular primary endpoint event rate estimated to be around 2.2% per year for the population to be enrolled
- A planned accrual period of about 5 years
- An estimated annual lost-to-follow up rate of 1%
- An anticipated treatment discontinuation rate of 5% per year.

It is expected that a total of 14,000 patients need to be randomized in a 1:1 ratio into EQW and placebo to achieve the targeted 1360 patients with confirmed composite CV events.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

2.1.1 Intent-To-Treat (ITT) Population

The Intent-To-Treat (ITT) Population will consist of all patients consented and randomized in the study without a major GCP violation. For all analyses using the ITT population, patients will be analyzed **As Randomized**.

2.1.2 Per-Protocol Population

Per-Protocol Population is a subset of the ITT Population excluding data from patients with major protocol deviations (Section 2.2) expected to affect the primary efficacy endpoint. For any analysis utilizing the per-protocol population, patients will be analyzed **As Randomized**.

2.1.3 Safety Population

The Safety Population will consist of all patients in the ITT Population who took at least one dose of study medication. When summarizing data using this population, patients will be analyzed **As Treated**. If a patient receives any exenatide study drug, then the patient will be counted in the exenatide arm, regardless of the amount of medication received; otherwise the patient will be counted in the placebo arm.

2.2 Protocol Deviations

All important protocol deviations will be summarized by treatment group. At the end of the study, any major protocol deviations that are thought to potentially affect the analysis will be reviewed and finalized by the team in a blinded manner, prior to data base lock. Major protocol deviations include, but are not limited to the following:

1. Patient randomized but not dosed will be excluded from the per protocol population.
2. If percent of injection missed > 50% (as assessed by calculation of patients who report temporary discontinuation of study drug; see Section 4.4.2) the patient will be excluded from the per protocol population.
3. Violations of selected inclusion/exclusion criteria at enrolment that would exclude a patient from the per protocol population:

a. Patient has a diagnosis of type 1 diabetes mellitus.
b. Patient does not have diagnosis of type 2 diabetes mellitus.

4. Received incorrect treatment for >6 months; the data collected up to the start of incorrect treatment will be included in the per-protocol population (i.e. data collected after incorrect treatment will be excluded)
5. Early discontinuation from study medication; the data collected up to 70 days after the last dose of study medication or the trial termination visit date (whichever occurs first) will be included in the per-protocol population. Early discontinuation from study medication is defined as a last dose date of study medication that is more than 21 days prior to the end of study date.
6. Initiation of a prohibited medication (an open-label approved or investigational GLP-1 receptor agonist, or another investigational drug or device); the data collected up to the initiation of the prohibited medication will be included in the per-protocol population.

3. STUDY ENDPOINTS

3.1 Primary Safety and All Efficacy Endpoints

Relevant suspected safety events and efficacy endpoints will be adjudicated by the Clinical Events Committee (CEC). The definition of confirmed ssafety events and efficacy endpoints including CV-related death, stroke and myocardial infarction (MI) can be found in the CEC charter.

Confirmed, positively adjudicated hemorrhagic strokes, classified as subdural hematomas will be excluded from any analyses of adjudicated stroke events.

Clinical endpoints occurring through the Trial Termination Visit will be adjudicated and will be included in the primary analysis. Site-reported clinical events occurring after the Trial Termination Visit will not be adjudicated and will not be part of the primary analysis.

3.1.1 Primary Safety/Efficacy Endpoint

The primary safety/efficacy endpoint is time from randomization to the onset of the first occurrence of any confirmed event in the primary composite CV endpoint (CV-related death, nonfatal MI, nonfatal stroke).

Where fatal/non-fatal events are defined as follows:

If there is an event of MI and there is a death due to MI and the date of the MI is within 30 days of the death, then the MI is fatal; if the MI is greater than 30 days prior to the death then the MI is non-fatal; if the cause of death is not MI then the MI is non-fatal

If there are multiple MI's and there is a death due to MI, then the MI closest and within 30 days prior to the death is a fatal MI; all others are non-fatal;

Similar logic is used for stroke events.

3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the time from randomization to first occurrence of confirmed:

- all-cause mortality (defined as death due to any cause)
- CV-related death
- fatal or nonfatal MI (MI)
- fatal or nonfatal stroke (stroke)
- hospitalization for acute coronary syndrome
- hospitalization for heart failure

Hospitalization for acute coronary syndrome is defined as a confirmed myocardial infarction or hospital admission for unstable angina. Myocardial infarction includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction or ST-elevation unknown.

Hospitalization for congestive heart failure is defined as a confirmed hospital admission for congestive heart failure requiring treatment with increased oral or intravenous diuretics, inotropes, or vasodilator therapy.

3.1.3 Additional Efficacy Endpoints

- Time to composite of CV-related death or hospitalization for congestive heart failure, defined as time from randomization to time of first CV-related death or hospitalization for congestive heart failure, in overall and in patients with prior history of CHF at baseline.
- Time to revascularization procedure, defined as time from randomization to time of first cardiovascular or peripheral revascularization procedure. This will include percutaneous coronary intervention with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting.
- Time to initiation of first co-interventional agent, defined as the time from randomization to the start date of one or both of the below agents
  - Additional AHA
  - Chronic insulin therapy (only applies to patients not on chronic insulin therapy at randomization)

  Chronic insulin therapy is defined as a continuous period of insulin use of more than 6 months.

- Absolute values and change from baseline in HbA1c, body weight, blood pressure, heart rate and lipid profile (HDL, LDL, triglycerides, total cholesterol) at the protocol defined measurement time points (see Appendix).
- Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire. Mobility, self-care, usual activities, pain and discomfort, and anxiety and depression dimensions will be converted into health state utilities using the United Kingdom tariff for all patients. This analysis will described in a separate analysis plan document.
- Medical resource use and total direct medical costs. This analysis will described in a separate analysis plan document.
- Incremental cost-effectiveness analysis of EQW as part of usual care compared with usual care without EQW. This analysis will described in a separate analysis plan document.

3.2 Other Safety Endpoints

Other safety endpoints include selected adverse events (AEs), serious adverse events (SAEs), and certain laboratory parameters (serum creatinine and calcitonin; see Section 4.6.3) and vital signs (see Section 4.6.4). Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70 day post treatment follow-up period. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event. An adverse event that does not meet the definition of a serious event will be considered non-serious and will not be collected, with the exception of potential clinical events (non-serious AEs) and expected events of diabetic complication (for details see protocol Section 10.3).

4. ANALYSIS METHODS

4.1 General Principles

In addition to specific analyses and presentations that are detailed in the following sections, results will be summarized for continuous measures using descriptive statistics, including the number of patients, mean, standard deviation, median and range as appropriate. For natural logarithm transformed data, geometric mean, standard error of the geometric mean will also be provided. For categorical variables counts and percentage per treatment group will be presented.

For all time-to event analyses, the treatment groups will be analyzed using a Cox proportional hazards model that includes treatment as an explanatory factor unless specified otherwise. Prior CV event group at randomization from the IVRS randomization strata (prior CV event or no prior CV event, refer to "Prior CV event at randomization based on IVRS" in short) will be included as a stratification factor. The Efron method[1] will be used for handling ties. P-value

and confidence intervals for the HR will be based on the Wald statistic. In addition, the summary tables of these analyses will include the number of patients with the event and Kaplan-Meier estimates of the event rate per treatment group presented annually through the last time point where the 90th percentile of events are collected. Kaplan-Meier failure rates along with respective 95% CI will also be calculated and plotted by treatment group and prior CV risk at randomization based on IVRS, with number of patients at risk indicated below the plot at specific times. The median and total person-years of follow-up for the entire study will also be reported.

An on-treatment analysis using the ITT population will be performed for the primary and some secondary endpoints as sensitivity analyses. This analysis will include those events that occurred from randomization through the last dose of study medication or the Trial Termination Visit, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized. An on-treatment censoring scheme, as described later in the text, will also be applied for analysis for on-treatment + n days, where n=7, 30, and 70.

For all time to event analysis of composite endpoints including mortality, if the death occurred after 6 months from the last visit where all components of the endpoint could be assessed, the death will not be counted towards any composite endpoint where death is a component. Instead, such patients will be censored in accordance with the relevant censoring scheme. For analysis of mortality as an endpoint, such deaths will be counted as events. Unless otherwise specified all hypothesis testing will be performed using two-sided tests at the 0.05 level of significance. Statistical analyses will be performed using Version 9.2 (or newer) of SAS® on Unix operating system.

Selected analyses described here will be summarized separately for the US and the China population respectively.

4.1.1 Control of Type I Error

Type I error will be controlled at a one-sided 0.025 level for multiplicity across primary and secondary objectives and in consideration of planned interim analyses. The alpha of 0.02495 represents the final one-sided significance level to be used when the study has been completed in entirety. At an interim analysis, testing for superiority of primary efficacy endpoint will occur, and the significance level for superiority will be replaced by one-sided 0.00005 at the first and one-sided 0.0005 at the second interim (see Section 4.7). Statistical testing will proceed sequentially and statistical significance will be assessed in the following hierarchical order. When a test is found to be statistically significant, testing will proceed to the next test. If a test is not statistically significant, the subsequent one will not be assessed for statistical significance although nominal p-values will be provided.

Hierarchical Testing Order:

1. Non-inferiority test for the primary composite CV endpoint (alpha= 0.02495 1-sided)
2. Superiority test for the primary composite CV endpoint (alpha= 0.02495 1-sided)
3. Superiority test for secondary efficacy endpoint of all-cause death (alpha= 0.02495 1-sided)
4. Superiority test for secondary efficacy endpoints: CV-related death, MI, and stroke (alpha= 0.02495 1-side): The hypothesis for these three secondary efficacy endpoints (null hypothesis is denoted as $H_{0[41]}$, $H_{0[42]}$, $H_{0[43]}$,) will be tested at one-sided 0.02495 level by using the Hochberg procedure[2], which proceeds as follows:
   - *Ordering the raw p-values (one-sided) such that* $p_{(1)} \leq p_{(2)} \leq p_{(3)}$
   - *Step 1. If* $p_{(3)} < 0.02495$, *reject* $H_{0[4i]}$, $i = 1,2,3$ *and stop; otherwise go to Step 2.*
   - *Step 2. If* $p_{(2)} < 0.02495/2$, *reject* $H_{0[4i]}$, $i = 1,2$ *and stop; otherwise go to Step 3.*
   - *Step 3. If* $p_{(1)} < 0.02495/3$ *reject* $H_{0[4i]}$, $i = 1$.
5. If superiority tests for all three secondary efficacy endpoints in number 4 are met, proceed with superiority test for secondary endpoints: hospitalization for acute coronary syndrome and hospitalization for heart failure. The hypothesis for these two secondary efficacy endpoints (null hypothesis is denoted as $H_{0[51]}$, $H_{0[52]}$,) will be tested at one-sided 0.02495 level by using the same Hochberg procedure as described above.

Non-inferiority will be tested only at the completion of the study. Secondary endpoints will only be tested once, at the completion of the trial or if the decision is made to terminate the trial early. If the study terminates early for superiority, the key secondary endpoints of CV death, MI, stroke and all-cause mortality will be tested at the same significance level as the primary endpoint in the interim analysis using the hierarchical test strategy. Additional efficacy endpoints will be tested at the 2-sided 0.05 level.

4.1.2 Censoring

4.1.2.1 Censoring Scheme

Primary Censoring Scheme: in time-to-event analyses in the ITT population, patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be assessed, and 2) the right censoring date. The conclusions regarding non-inferiority or superiority will be based on the analyses using this censoring scheme. Patients without any assessment of the endpoint will be censored at randomization.

On-treatment Censoring Scheme: in the on-treatment time-to-event analyses, patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be

assessed, and 2) the date of last dose of study medication, and 3) the right censoring date. Patients who never start the study drug will be censored at randomization.

On-treatment + n days Censoring Scheme (where n=7, 30, and 70): patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be assessed, 2) the date of last dose of study medication + n days, and 3) the right censoring date. Patients who never start the study drug will be censored at randomization.

Cut-off Date Censoring Scheme: patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be assessed, and 2) the primary endpoint cut off date. The primary endpoint cut off date will be determined by the Executive Committee as the date when the sites will start bringing patients back for the Trial Termination visit. Patients without any assessment of the endpoint will be censored at randomization.

Right censoring date is defined as the last known alive date as collected at the trial termination visit (TTV form) except for deceased patients where it is the adjudicated date of the death.

4.1.2.2 Assumption on Non-informative Censoring

The time to event analysis (Cox regression) relies on the assumption of non-informative censoring. To examine this assumption, variables that may be related to censoring, for example, the most frequent major protocol deviation, certain SAEs, will be explored. Rates per 100 patient-years will be calculated per treatment group and compared between patients censored early without complete follow-up, and those with complete follow-up.

To assess possible effects of informative censoring on the primary efficacy endpoint, sensitivity analyses will be done as follows. First, the tipping point analysis will be performed where in patients who prematurely discontinued the study without having a primary endpoint event prior to discontinuation, events will be imputed during their missing follow up time (i.e. time from censoring to trial termination visit) under various scenarios for the hazard rates for non-completers in each arm. For each scenario, 2000 imputations will be performed and the results will be combined across 2000 combined datasets (actual events in completers + imputed events in non-completers) using SAS PROC MIANALYZE. Specifically, log-hazard ratio estimate of treatment effect will be calculated as an average and its associated variance will be obtained using Rubin's[8] (1987) formula, which combines within-imputation and between-imputation variances. Hazard ratios, Wald's 95% CIs and Wald's test p-values will also be calculated. The goal of this analysis is to find scenarios where the primary analysis results will be “tipped”, i.e. the conclusion will change.

4.2 Study Conduct

Major protocol deviations will be identified for all patients who are randomized (see Section 2.2).

4.3 Study Population

4.3.1 Patient Disposition

The number of patients included in each study population (i.e., Intent-to-Treat, Per-Protocol and Safety) will be summarized by treatment group. The number and percentage of patients who completed and patients who discontinued from treatment and who withdrew from study will be presented for each treatment group and overall for the ITT Population. Reasons for discontinuation from treatment and discontinuation from the study will be summarized (number and percentage) overall and by treatment group for the ITT Population.

4.3.2 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for the ITT Population, Per Protocol Population and Safety Population.

The following demographics and baseline characteristics will be summarized:

- Prior CV event at randomization based on IVRS (yes, no)
- Prior CV event at randomization based on CRF (yes, no)
- Geographic region: North America, Latin America, Europe and Asia Pacific
- Country
- Age: calculated as ((date of randomization- date of birth) +1)/365.25
- Age group (<65, >=65 years, >=75 years)
- Gender
- Race:
    - Indian (American) or Alaska Native
    - Asian: Asian (Oriental), Asian (Other)
    - Black
    - Native Hawaiian or Other Pacific Islander, includes Maori (New Zealand) and Aboriginal (Australian)
    - White: Caucasian or White
    - Hispanic
- Ethnicity: Latino, non-Latino
- Weight
- Height
- BMI
- BMI group: <30, >=30 kg/m^2
- Baseline antihyperglycemic agents therapy
    - None

  - Oral agent use (oral defined as all but insulin or pramlinitide; including "other")
    - Oral agent monotherapy
    - Oral agent dual combo therapy
    - >/= 3 oral agents
  - Insulin use
    - Insulin alone
    - Insulin + 1 oral agent
    - Insulin + >1 oral agent
  - DPP-4i use
- Baseline laboratory results HbA1c
- HbA1c group: <8.0%, >=8.0%
- Duration of diabetes: calculated as (year of randomization – year of diagnosis) +1
- Duration of diabetes group: <5, 5-14, >=15 years
- eGFR: according to the Modification of Diet in Renal Disease (MDRD) formula3
- eGFR groups (ml/min/1.73m2):
  - <60, >=60
  - Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15

Differences in the countries that have historically comprised Eastern vs. Western Europe will also be explored. Medical complications at baseline (amputation, foot ulcer, retinopathy, blindness, albuminuria and diabetic neuropathy) and other medical history (coronary artery stenosis >=50% by coronary catheterization, MI etc.) will also be summarized by treatment group.

4.4 Extent of Exposure

4.4.1 Study Medication

Exposure to study medication for the ITT and Safety Population during the study period will be summarized in terms of treatment duration, which is calculated as the number of days from the date of first medication taken to the date of last dose taken, inclusively ((date of last dose taken – date of first medication taken)+7). This duration will not be adjusted for any period the patient may have been off of study drug temporarily. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group.

4.4.2 Measurement of Treatment Compliance

Number of patients who had more than 4 consecutive missing doses and percent of injections missed will be summarized by treatment group (Data for patients with less than 4 missing dose is not collected in CRF given the long half-life of the study drug).

Percent of injections missed are not directly recorded, as compliance is not recorded in the study database, but will be calculated for those patients who have recorded temporary discontinuation periods by:

(1- (total number of known missed injections for temporary discontinuation periods / number of planned injections based on first and last dose date))*100%

Kaplan Meier estimates of time to permanent study drug discontinuation will be summarized by treatment.

Treatment compliance will also be summarized in terms of percent of time on study drug, which is calculated as actual time on study drug (not adjusting for temporary discontinuations) divided by the study duration, defined as time to last known alive date if patient is alive or at withdrawn consent status, study cut-off date if patient is lost to follow up, and death date if status is deceased.

4.4.3 Concomitant Medication

A baseline concomitant medication is defined as a medication which was reported to have been taken on the concomitant medication eCRF form at the Screening/Randomization visit. A baseline diabetes medication is a diabetes medication that is reported to have been taken on the medical history eCRF form. A new diabetes/concomitant medication is defined as no indication of usage at baseline as well as indication of usage during at least one post-randomization visit.

Patients taking baseline diabetes/concomitant medications will be summarized by treatment group in the ITT and Safety populations. Similar summaries will be presented for patients taking new diabetes/concomitant medications and for patients taking a diabetes/concomitant medication at any visit (i.e. at baseline or at any time during a post-randomization visit).

4.5 Primary Safety and All Efficacy

All confirmed efficacy events will be listed, indicating the patient id, randomized treatment group, age, gender, race and day of event relative to start of dosing. The time of death and cause of death will also be included in the listing of deaths.

4.5.1 Analysis of the Primary Safety/Efficacy Endpoint

The primary safety/efficacy endpoint is defined as the time from randomization to the onset of any event in the primary composite CV endpoint (CV-related death, nonfatal MI, nonfatal stroke).

In the unlikely event that two or more confirmed endpoints occur on the same day, the following hierarchy will be used to ascribe the primary component of the composite:

- Nonfatal Myocardial infarction
- Nonfatal Stroke
- CV-related Death

The contribution of each component of the primary composite safety/efficacy endpoint to the overall treatment effect will be examined.

Event rates of the primary composite CV endpoint will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of the primary composite CV endpoint, by treatment group and prior CV risk at randomization based on IVRS.

Homogeneity of the effect of treatment on the components of the primary safety/efficacy CV composite endpoint will be assessed using the method proposed by Lunn and McNeil[9] (1995). Briefly, this method requires augmenting the analysis dataset by including one observation per component of the CV composite per subject, with an additional variable indicating the type of the potential event (CV-related death, nonfatal MI, nonfatal stroke). If a patient experienced an event which counted as the first instance of the CV composite endpoint, the event status for that event will be one and it will be zero for the other two types of events, which will be censored at the time the first event occurred. If a patient did not have CV composite endpoint, event status will be zero for all three component types of events. For example, if a patient had nonfatal MI on day 270 which counted as his first occurrence of the CV composite, he would have three observations in the analysis dataset: 1) type=nonfatal MI, status=1, time=270; 2) type=nonfatal stroke, status=0, time=270; 3) type=CV death, status=0, time=270. The augmented dataset will be analyzed using Cox regression with (time, status) as response variables and event type, treatment and treatment by event type interaction as covariates. To account for the use of multiple observations per subject in the analysis, Lin-Wei robust sandwich variance[3] will be used. The test of treatment by event type interaction will be the test of homogeneity of treatment effect on the components of the CV composite endpoint. Hazard ratios and 95% CIs for treatment effect on each component of the primary endpoint will be produced.

4.5.1.1 Primary Safety Analysis: Non-inferiority of EQW versus Placebo

To determine whether EQW is non-inferior to placebo, a non-inferiority margin of 1.30 in terms of hazard ratio with respect to developing the primary composite CV endpoint will be used.

The primary safety hypothesis (H_1) is defined as:

H_0: HR $\geq$ 1.3 *vs.* H_1: HR < 1.3

The hypothesis of non-inferiority will be tested at a one-sided significance level of 0.02495 in the ITT population using a Cox Proportional Hazards model which includes treatment as explanatory factor with prior CV event at randomization based on IVRS as a stratification factor. The two-sided 95% confidence interval for the hazard ratio of EQW to placebo will be estimated. If the upper limit of the two-sided confidence interval for the estimated HR for the stratified Cox model is below the non-inferiority margin of 1.30 then non-inferiority of the

primary composite CV endpoint in patients treated with EQW in addition to usual care compared to that of patients treated with usual care alone will be declared.

4.5.1.2 Primary Efficacy Analysis: Superiority of EQW versus Placebo

If the non-inferiority hypothesis is met, the hypothesis of superiority of EQW, when used in addition to usual care versus usual care without EQW with regard to the risk of developing the primary composite CV endpoint will be tested at a one-sided significance level of 0.02495 (i.e. two-sided 0.0499).

The efficacy hypothesis (H_1) is defined as:

$$H_0: HR \geq 1 \textit{ vs. } H_1: HR < 1$$

The Intention to Treat (ITT) population will be used to evaluate the primary efficacy hypothesis. The p-value will be estimated using the same Cox Proportional Hazards model as in the non-inferiority analysis . The estimated HR and two-sided 95% confidence interval for the hazard ratio of EQW to placebo will also be presented.

The above primary safety and efficacy analyses will use the Primary Censoring Scheme (see Section 4.1.2.1).

4.5.1.3 Assessment of Model Assumption

The assumption of proportional hazards for the factor for treatment group will be assessed visually using log-cumulative hazard plots for each stratum, and with models which assess the treatment effect in categorized time intervals (< 1 year, 1- <2 years, 2-<3 years, >=3 years), or time-dependent covariates in the model. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses. If there is evidence of non-proportionality appropriate further analyses using Lin-Wei information sandwich[3] may be conducted.

4.5.1.4 Sensitivity Analyses of the Primary Efficacy Endpoint

It is expected that complete information on the components of the primary composite endpoint (and as much as possible of the eCRF data for patients contacted by telephone) will be obtained for all patients including those who prematurely discontinue investigational product, unless they refuse any form of follow-up and withdraw consent or where final status could not be determined.

For the primary efficacy endpoint, the following sensitivity analyses will also be performed:

1. Analyze the data in ITT population using Primary Censoring Scheme (see Section 4.1.2.1) and using a Cox proportional hazards model that includes treatment as an explanatory factor and prior CV risk group at randomization based on CRF data as stratification variable.

2. On-treatment analysis in the ITT population using On-treatment and On-treatment + n days Censoring Schemes (see Section 4.1.2.1) and using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis.
3. Analyze the data in Per-Protocol population using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis. Patients with protocol violations will be analyzed as indicated in the Per-Protocol section while others will be analyzed using Primary Censoring Scheme (see Section 4.1.2.1).
4. Analyze the data in ITT population using Cut-off Date Censoring Scheme (see Section 4.1.2.1) and using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis.

In case of a difference in inference between the primary analysis and the sensitivity analyses, further exploratory analyses will be conducted to understand the reasons for a possible difference. Models with additional variables will be considered as appropriate. The site-reported primary efficacy endpoint, regardless of the status of adjudication, will be summarized descriptively.

4.5.1.5 Planned Subgroup Analyses

Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups.

Subgroup analyses to evaluate variation in treatment effect will be performed on the basis of tests for interaction using the Cox proportional hazards model stratified by prior CV event at randomization based on IVRS (not applicable for the first subgroup listed) with terms for treatment group, the subgroup variable and treatment by subgroup variable interaction. P-values for the interaction with treatment for each of these subgroup variables will be provided and p-value of <0.1 will be considered as significant interaction. However, it is recognized that testing many subgroups can yield spurious false positive outcomes so that any significant interaction will be further examined to better understand its nature. If some subgroups have very few patients with events, they may be excluded from the interaction test.

Additionally, treatment effects within each subgroup will be examined separately using Cox proportional hazards models stratified by prior CV event at randomization based on IVRS (not applicable for the first subgroup listed) with terms for treatment group. Event rates by treatment and HRs with 95% confidence intervals will be reported for each subgroup. Forest plots will be generated displaying the estimated hazard ratios and 95% confidence intervals for each subgroup will be presented.

The following subgroups determined at baseline will be examined:

- Prior CV event at randomization based on IVRS: yes, no
- History of congestive heart failure: yes, no

- Geographic region:North America, Latin America, Europe and Asia Pacific
- Age groups: <65, >=65 years; <75, >=75 years
- Gender
- Race: Indian (American) or Alaska Native, Asian: Asian (Oriental), Asian (Other), Black, Native Hawaiian or Other Pacific Islander, includes Maori (New Zealand) and Aboriginal (Australian), White: Caucasian or White, Hispanic
- BMI group: <30, >=30 kg/m^2
- Baseline antihyperglycemic oral agent therapy (oral defined as all except insulin or pramlinitide; including "other"): oral agent vs. no oral agent
- Baseline Insulin use: Insulin use vs. no insulin use
- Baseline DPP-4i use: DPP-4i use vs. no DPP-4i use
- HbA1c group: <8.0%, >=8.0%
- Duration of diabetes group: <5, 5-14, >=15 years
- eGFR groups (ml/min/1.73m2):
    - <60, >=60
    - Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15

(see Section 4.3.2for subgroup definitions)

4.5.2 Analyses of the Secondary Endpoints

4.5.2.1 Main Analyses

The secondary efficacy endpoints will be analyzed similarly to the primary efficacy analysis. For each of the secondary efficacy endpoints listed in Section 3.1.2 the p-value and two-sided 95% confidence interval for the hazard ratio of EQW to placebo will be estimated using a Cox Proportional Hazards model which includes treatment as explanatory factor and prior CV event at randomization based on IVRS as a stratification factor.

Homogeneity of the effect of treatment on fatal vs nonfatal MI and on fatal vs nonfatal stroke will be assessed using the method proposed by Lunn and McNeil[9] (1995).

Following the sequential testing strategy outlined in Section 4.1.1, if superiority for the primary efficacy endpoint is demonstrated at the one-sided 0.02495 (i.e. two-sided 0.0499) significance level then superiority of EQW relative to placebo for all-cause death will be tested at the one-sided 0.02495 significance level and so on.

Event rates will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of each secondary efficacy endpoint, by treatment group and prior CV risk at randomization based on IVRS.

4.5.2.2 Sensitivity Analyses

An on-treatment analysis using the ITT population using On-treatment and On-treatment + n days Censoring Schemes will be performed for all cause death as a sensitivity analysis. The site-reported all cause death, regardless of the status of adjudication, will be summarized descriptively.

4.5.2.3 Exploratory Analyses

As a patient can have recurrent events, there will be three additional separate analysis; 1) time to all MI events (fatal and nonfatal), 2) time to all stroke events (fatal and nonfatal), and 3) time to all MI, stroke and CV death combined. These analysis will be performed using the Andersen-Gill[5], modified Cox regression approach, for EQW versus Placebo.

4.5.3 Analysis of Additional Efficacy Endpoints

All time to event additional efficacy endpoints (congestive heart failure, revascularization procedure, and initiation of first co-interventional agent) will be analyzed using the same approach as in the primary efficacy analysis based on the ITT population.

Change from baseline in HbA1c, body weight, blood pressure and lipid profile on ITT population will be analyzed by mixed models for repeated measures (MMRM). The model will include change from baseline of the measure of interest as the dependent variable, baseline value of the measure of interest, time, prior CV event at randomization based on IVRS, treatment group, time by treatment interaction and baseline value by time interaction as fixed factors, and patient random effect. We will evaluate the linearity assumption for time and time by treatment interaction effects. In case the linearity assumptions are violated, piecewise-linear or higher order polynomial terms for time may be included in the model. To model the covariance structure, the within patients unstructured covariance structure will be used. The MIXED model is computationally intensive, if the algorithm does not converge, the Toeplitz, first-order autoregressive or compound symmetric covariance structure will be used. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided nominal p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the time points at 1, 2 and 3 years although descriptive summaries at all visits will also be presented.

Triglycerides data will be analyzed after the natural logarithmic transformation. The LS mean and the corresponding 95% CI will be calculated at the log scale, and the geometric mean ratio and the corresponding 95% CI will be calculated by taking the anti-log of the corresponding values within each treatment group and for treatment comparisons.

Note that a baseline assessment and at least one post-randomization measurement is required for inclusion in this analysis.

4.5.4 Analysis of quality of life (QoL), Costs and Cost Effectiveness

Analyses evaluating quality of life, medical resource use, total direct medical costs and the cost-effectiveness of EQW in addition to usual care compared with usual care without EQW, will be described in a separate SAP. These analyses will meet objectives 5, 6 and 7 as described in Section 1.1.3, and will be reported independently from the Clinical Study Report.

4.5.5 Genetic and Biomarker Samples

As part of this study, pharmacogenomic, proteomic, and metabolomic analyses may be performed on samples from patients who have given appropriate consent. These analyses, if performed, will be described separately.

4.6 Other Safety

Primary safety analyses are described in Section 4.5.1.1. This section describes analyses for the other safety endpoints. Other safety endpoints include selected AEs (see Section 3.2), SAEs, selected laboratory parameters and vital signs.

Adverse events will be coded using MedDRA, Version 17.0 or newer.

All safety observations will be listed regardless of when it occurred and whether the patient was taking blinded study drug.

All adverse events will be summarized for the Safety Population during the treatment period (from start of study drug to study drug end), after treatment (after study drug discontinuation to end of study) as well as overall (throughout the study period). Other safety endpoints (e.g. labs, vitals) will also be summarized as indicated in the specific sections below.

4.6.1 Serious Adverse Events

The number and percentage of patients reporting SAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term (PT); and by SOC, PT, and severity. If more than one event occurs with the same PT for the same patient, the patient will be counted only once for that PT using the most severe occurrence for the summarization by severity.

The incidence of most frequent SAEs and SAEs leading to temporary or permanent discontinuation of study medication will be summarized by PT and treatment group, sorted in decreasing frequency for the EQW treatment group. In addition, the incidence of fatal SAEs (i.e. events that caused death) will be summarized separately by PT and treatment group. Also, the incidence of “related” AEs will be summarized in a similar manner.

SAEs will also be presented by SOC, PT and treatment group in subgroups of patients defined by baseline DPP-IV therapy (DPP-IV inhibitors vs non- DPP-IV inhibitors), baseline renal function, age and prior CV event (yes vs no).

Selected SAEs will be listed, such as those leading to treatment discontinuation or those associated with an overdose, indicating the patient ID, treatment group, age, gender, race, day of onset relative to first dose date, resolution date, relationship, severity, action taken and outcome.

In addition, adjudicated all-cause death will be summarized descriptively for the Safety population.

4.6.2 Other Adverse Events

Diabetic complications and expected events collected in the study will be summarized by treatment. Summaries ofneoplasia, pancreatitis, and severe hypoglycemia will be presented separately as well.

All reported severe hypoglycemic events, adjudicated ventricular fibrillation/tachycardia, adjudicated acute pancreatitis and adjudicated charter-defined malignancies will be summarized by treatment. The number and incidence rate per 100 patient-years of these events by treatment groups will be reported. The numerator is the number of events; the denominator is the overall total exposure (person-years) within the period specified calculated from start of event counting period up to the end of event counting period regardless if the patient had events or not. The resulting incidence rate is multiplied by 100 to express the rate per 100 person-years. For severe hypoglycemia events, the incidence rate will be presented per person-years by treatment group for the entire study and additionally within the following sub-groups: patients who were on insulin and/or a sulfonylureas during the study vs. those that were not. Additionally, the number of severe hypoglycemia events will be compared between treatment groups using a negative binomial regression if there are sufficient events in both treatment groups. Kaplan Meier estimates of time to first incidence of: severe hypoglycemic events, confirmed acute pancreatitis and charter-defined malignancies will be summarized by treatment.

Analysis of severe hypoglycemic events will also be generated in the ITT population.

4.6.3 Clinical Safety Laboratory endpoints

Calcitonin concentrations and serum creatinine were measured periodically in this trial. Descriptive statistics for above laboratory values and eGFR and changes from baseline at each assessment time point, and the maximum and minimum values will be presented by treatment group.

In addition, for patients with a screening calcitonin >40ng/L or a follow-up calcitonin ≥ 50ng/L, data was collected to elicit the degree of safety workup undertaken following the

notification of an abnormal calcitonin value. This data will be summarized descriptively and also listed.

Potentially clinically significant (PCS) values of the lab parameters of interest are listed in Table 4.6.3.1. The number and percentage of patients with post-baseline PCS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of patients with baseline and at least one post-baseline assessment. The numerator is the total number of patients with at least one post-baseline PCS value. A listing of patients with post-baseline PCS values will also be provided.

Table 4.6.3.1 Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	Flag	Observed Value
Calcitonin	High	>= 50 ng/L
eGFR	Low	< 30 mL/Min/1.73m^2

In addition to calcitonin and creatinine, additional labs were collected periodically when available (eg, HbA1c, lipids [HDL, LDL, TC, and TG], hemoglobin, Hs-CRP, RDW (red cell distribution width), BNP, Urine albumin/creatinine ratio). Descriptive statistics for these additional laboratory values and changes from baseline at each assessment time point will be presented by treatment group.

4.6.4 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, heart rate and body weight) and their changes from baseline at each visit, to the maximum and minimum values will be presented by treatment group.

4.7 Interim Analysis

Two formal interim analyses were planned after approximately 453 and 906 primary composite CV events are adjudicated, corresponding to one-third and two-thirds, respectively, of the target 1360 primary composite events.

To adjust the multiplicity for the interim analysis, the Haybittle-Peto[i] spending function will be used. The study termination guideline for overwhelming superiority will be two-sided p-value < 0.0001 (i.e. <0.00005 one-sided) for the first interim analysis and two-sided p-value <0.001 (i.e. <0.0005 one-sided) for the second interim analysis. To control the Type 1 error rate at 0.05, a significance level of 0.0499 (two-sided) will be used for the final analysis.

At an interim analysis, only superiority test of primary efficacy endpoint will occur. The hypothesis will be tested at one-sided 0.00005 at the first interim (and at one-sided 0.0005 at

the second interim) in the ITT population using a Cox Proportional Hazards model which includes treatment as explanatory factor with prior CV risk at randomization based on IVRS as a stratification factor.

If the stopping boundary for efficacy is met at either of the interim analyses, the DSMB may recommend terminating the study earlier than planned. The DSMB may, however, also advise terminating the study early for safety or ethical reasons.

The interim analyses will be performed by an independent statistical group. Further details regarding interim analyses, including details on interim assessments of safety can be found in the DSMB Charter.

5. CONVENTIONS

5.1 Baseline Measurements

Unless specified otherwise, a baseline value is the last assessment taken prior to or at randomization. When there is a missing baseline assessment it will not be imputed, thus, patients are excluded from any changes from baseline analysis for which they have a missing baseline value.

5.2 Multiple Measurements

For tabulations of changes from baseline or shift analyses, if multiple measurements are obtained within the same nominal visit, then the measurement obtained on the day closest to the target day for that nominal visit will be used; in the case of a tie, the measurement obtained on the earlier day will be used in the analyses; in the case of multi measurement at same day and time, the worst value will be used.

5.3 Counting Rules for Adverse Events

5.3.1 At Patient Level

Where a patient has the same AEs (SAEs), based on PT, reported multiple times in a single analysis period, the patient will only be counted once at the PT level in adverse event frequency tables.

Where a patient has multiple AEs (SAEs) within the same SOC in a single analysis period, the patient will only be counted once at the SOC level in adverse event frequency tables.

When a patient has the same AEs (SAEs), based on PT, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event

- Onset date and time

1. When assessing relationship to study medication, relationship will be categorized into two categories - related and unrelated ("definitely related to study drug", "probably related to study drug", and "possibly related to study drug" will be categorized into "related" while "probably not related to study drug" and "definitely not related to study drug" will be categorized into "unrelated") . Related events will take precedence over unrelated events in determining the event to include in summary tables.
2. More intense events will take precedence over less intense events in determining the event to include in summary tables.
3. Earlier onset date-time events will take precedence over late onset date-time events in determining the onset to include in summary tables.

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

5.3.2 At Event Level

At event level, each unique AE record will be counted. Unique AE record can be obtained by collapsing all AE records following a standard algorithm described below. This algorithm is not applicable to hypoglycemic events. In addition to frequency summary, exposure adjusted summary will also be provided where the overall exposure of a patient is calculated from first dose day to the last day of treatment regardless of whether a patient has had an event or not.

To ensure that multiple events for the same patient are counted accurately in the summaries, for each patient and PT, AE records will be collapsed into a single record (unique AE) when:

1. Multiple AE records have the same onset date,
2. The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events),
3. The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

The unique AE record will contain the earliest onset date, latest resolution date (if available), highest intensity, highest relationship in the following order (highest to lowest: definitely related to study drug, probably related, possibly related, probably not related, definitely not related), and highest action taken in the following order (highest to lowest: drug discontinued,

drug interrupted, none). In addition, the unique AE record will be classified as a SAE if at least 1 AE record was classified as a SAE and also the unique AE record will be classified as requiring treatment if at least 1 AE record required treatment.

5.4 Missing Date of Study Medication

Imputations associated with missing date of study medication will be described in a separate document.

5.5 Missing Dates

Imputations associated with missing dates, such as dates of birth and death will be described in a separate document.

5.6 Allocation of Countries to Regions

North America: Canada, US

Latin America: Argentina, Brazil, Chile, Columbia, Mexico

Asia Pacific: Australia, China, Hong Kong, Malaysia, New Zealand, Philippines, South Korea, Taiwan, Thailand

Europe:

Western: Austria, Belgium, Germany, United Kingdom, Spain, Italy, Netherlands, South Africa, Israel

Eastern: Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovakia, Ukraine

6. CHANGES OF ANALYSIS FROM PROTOCOL

1. When summarizing data using the Safety population, patients will be analyzed As Treated. If a patient receives any exenatide study drug, then the patient will be counted in the Exenatide arm, regardless of the amount of medication received; otherwise the patient will be counted in the placebo arm. Protocol indicated: ‘if a patient is found to have taken a study therapy for the entire duration of the study, different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received‘.
2. Protocol deviation of ’Received incorrect treatment for >3 months’ in the protocol was changed to ’Received incorrect treatment for >6 months’ in this SAP, because visits occurred every 6 months and is when an error in treatment would most likely be identified.

3. Patients are censored as described in Section 4.1.2.1. Protocol indicates 'patients who do not have any events during the study will be censored at the Trial Termination Visit date', and Section 4.1.2.1 provided more specific details and explanation.
4. Section 9.11 of the protocol had the following sentence added as a minor clarification in Amendment 6: *For the main clinical study report (CSR), the quality of life data will be summarized descriptively for baseline and changes from baseline by treatment*. In fact that will not be done, as the data is complex and not suited for simple descriptive analyses. This data will be prepared independently from the main CSR, as stated in previous sections of the SAP and protocol.

7. CONTENT OF REPORTS

The results of this study will be presented in a standard Clinical Study Report (CSR).

8. REFERENCES

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9. APPENDIX

APPENDIX 1: Trial Plan (Protocol BCB109)

		Treatment Initiation		Follow-up [4]		Drug or Study Termination		
Evaluation	Screening Day -1	Randomization Day 0 Visit 1 [1]	Week 1 and Month 2 Visit 2 and 3	Semi-Annual	Annual	Drug Termination [5]	Trial Termination [8]	Post-Treatment Follow-up Contact [9]
Informed Consent/HIPAA [2] and Stored Blood Sample Authorization	X							
Medical History	X							
Physical Examination	X							
Height	X							
Blood Pressure, Heart Rate and Body Weight	X	X		X	X	X	X	
Calcitonin Blood Sample		X			X		X	
Collect and review available information including most recent HbA_{1c}, serum creatinine and lipid profile	X [6]			X	X	X	X	
Randomization		X						
If consent obtained, collect blood sample for genetic and genomic analysis		X [7]						
If consent obtained, blood sample (serum and plasma) and urine sample for archive		X			Year 1 only		X	
Drug Dispensation		X		X	X			
Used/Unused Vial Assessment				X	X	X	X	
Clinical and SAE Event Assessment		X	X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X	X	
Confirm competency			X					

		Treatment Initiation		Follow-up [4]		Drug or Study Termination		
Evaluation	Screening Day -1	Randomization Day 0 Visit 1 [1]	Week 1 and Month 2 Visit 2 and 3	Semi-Annual	Annual	Drug Termination [5]	Trial Termination [8]	Post-Treatment Follow-up Contact [9]
with injections [3]								
EQ-5D Completion		X		Month 6 only	X	X	X	

[1] Wherever possible the screening and randomization visit should be combined.
[2] Informed Consent Form and if applicable, authorization to use and disclose protected health information.
[3] Patients will return approximately 1 week (±3 days) as well as 2 months (± 2 weeks) after Day 0 to perform a self-injection under the observation of the clinical site to confirm competency with injection. An additional visit can be considered at ~1 month if the patient is not able to adequately inject themselves.

[4] Semi-annual (±1 month) and Annual Follow-up (±1 month) Visits will occur in reference to Visit 1 Day 0 for the duration of participation in the trial.

[5] Patients who terminate study medication are required to have a Drug Termination Visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.

[6] It is recommended that serum creatinine value draw dates be within 3 months of randomization but up to 12 months is acceptable (however, if > 6 months old and value is between 30-40mL/min/1.73m^2 it is recommended that a new serum creatinine value is obtained as part of usual care).

[7] Blood sample for genetic and genomic analysis may be collected at any time during the trial after consent is obtained.

[8] For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up.

[9] Patients will be contacted by telephone to check for any clinical events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. (see Section 10.3.1).