STATISTICAL ANALYSIS PLAN

Protocol number: DAL-301

PHASE III, DOUBLE-BLIND, RANDOMIZED PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFECTS OF DALCETRAPIB ON CARDIOVASCULAR (CV) RISK IN A GENETICALLY DEFINED POPULATION WITH A RECENT ACUTE CORONARY SYNDROME (ACS): THE dal-GenE TRIAL

DAL-GENE

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Version	Date (DD-MMM-YYYY)	Author	Summary of Changes
Amendment 1	15-MAR-2021	Sylvie Levesque	Section 6.4.5.2 (Sensitivity Analysis and Robustness Checks) 4) Add sensitivity analysis taking into account the adjudicated primary efficacy endpoints collected between the end of study visit and the 14-day safety follow-up. Section 6.4.5.3 (Analysis Following the Initiation of the COVID-19 Pandemic): Add new section for sensitivity analyses to the COVID-19 pandemic. Section 6.4.5.4 (Analysis Based on Exposure to Study Treatment): Add new section for sensitivity analyses to evaluate the effect of exposure to study treatment. Section 6.5.2.3 (Adverse Events Leading to Premature Drug or to Premature Study Withdrawal): Replace “Adverse events leading to premature study withdrawal or dose modification” by “Adverse events leading to premature drug withdrawal” and “Adverse events leading to premature study withdrawal”. Section 6.5.6 (COVID-19 Outbreak Impact): Add new section on impact of COVID-19. Correction of typos throughout the text.
Amendment 2	10-JUN-2021	Sylvie Levesque	Section 3.2 (Intent-To-Treat (ITT) Population): Add subject numbers who will be excluded from the ITT.
Amendment 3	07-JUL-2021	Sylvie Levesque	Section 6.4.1 (Primary Analysis): Correct the discrepancy between the level of the confidence interval for the hazard ratio and the significance level of the test. The correct level is 95% to match the 0.05 significance level of the primary analysis.

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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
CEC	Clinical Endpoint Committee
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
CTA	Clinical Trial Assay
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End Of Study
HbA1c	Hemoglobin A1c
hsCRP	High-Sensitivity C-Reactive Protein
ITT	Intent-to-Treat
HDL-C	High density lipoprotein cholesterol
LDL-C	Low-Density Lipoprotein Cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MHICC	Montreal Health Innovations Coordinating Center
NOD	New Onset Diabetes
Q1	25^{th} percentile
Q3	75^{th} percentile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TEAEs	Treatment-Emergent Adverse Events
TG	Triglycerides

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the final analysis of DalCor protocol number DAL-301. This plan also provides a description of the analyses used to produce the tables, figures, and listings that will be included in the final statistical report. This SAP is based on the protocol Version 5 dated 11FEB2021 and on the annotated case report form (CRF) version 3.1. In case of differences between the SAP and the protocol, the SAP will supersede the protocol. Any deviation to this SAP would be reported in the statistical report.

2. STUDY DESCRIPTION

2.1 Study Design

This is a placebo-controlled, randomized, double-blind, parallel group, phase III multicenter study in subjects recently hospitalized for acute coronary syndrome (ACS) and with the appropriate genetic profile. Subjects provided informed consent before any study-specific procedures were performed. Subject enrollment was allowed to begin in the hospital and to continue following release from the hospital. Screening procedures were performed at the time of the index ACS event or anytime thereafter, with the condition that randomization had to occur within the mandated window (1-3 months after the index event). Subjects were assessed based on their medical history. Those who were likely to qualify underwent Cobas® ADCY9 Genotype CTA (Clinical Trial Assay) testing to evaluate genetic determination for the presence of the AA genotype at variant rs 1967309 in the ADCY9 gene. Those meeting the genetic testing criteria, all other inclusion criteria and none of the exclusion criteria were eligible for randomization. Eligible subjects had to be stabilized on statin and/or other medical therapy and had to complete all planned revascularization procedures prior to randomization. Subjects were randomized between 1 and 3 months from the index event. A total of 6149 eligible subjects in stable condition were randomized to 600 mg of dalcetrapib or placebo in a 1:1 ratio, stratified by region (Eastern Europe, Western Europe, North America, South America and other) and ACS index event (myocardial infarction [MI] or hospitalization for ACS [electrocardiogram changes without biomarkers]), to ensure equal number of subjects receiving active treatment and placebo in these strata. Subjects received study medication or placebo on a background of contemporary, evidence-based medical care for ACS. Subjects visit the clinic 1 and 6 months after randomization. Thereafter, visits are every 6 months for efficacy and safety assessments until completion of the trial. Phone assessments are performed 3 months after randomization and at the end of the study. Any subject prematurely discontinuing study medication and unable or unwilling to continue study visits, have phone assessments conducted every 6 months for the collection of study endpoints, with the exception of subjects who only agree to a final phone assessment. Due to the coronavirus pandemic of 2019 (COVID-19), to protect subject and study staff safety, it may not be possible for subjects to visit their clinic for study visits for some time and several alternatives for in-person study visits, and dispensing and returning study medication, are allowed as described in the study protocol.

This is an event driven study and approximately 582 subjects with a primary event are needed to reach 85% statistical power assuming a 22% relative risk reduction in the primary endpoint. Subjects will be expected to remain in the trial until the time at which approximately 582 subjects have experienced a positively adjudicated primary event. We will model the accumulation of 582 first primary endpoints (a combination of adjudicated and completed probable packages), and inform the sites when we expect to have the start of the end of study visit window. All subjects who remain in the study (on or off study drug)

will be asked to return for an end of study (EOS) visit. Subjects still taking study medication at the EOS visit will also have a safety follow-up phone call 14 days after the EOS visit for the collection of adverse events, including components of the primary and secondary endpoints. All efficacy and safety events will be collected through the end of the trial.

The end of trial is defined as the date the last data point required for statistical analysis (i.e. key safety and efficacy results) is received, which corresponds to the end of study visit or the 14-day safety follow-up phone call, whichever is the latest. For the primary and secondary efficacy analyses (described in sections 6.4.1 and 6.4.2), follow-up of efficacy endpoints will stop at the end of study visit. In other words, any efficacy endpoints collected between the end of study visit and the 14-day safety follow-up phone call will still be adjudicated but not be included in primary and secondary efficacy analyses.

An independent Data Safety Monitoring Board (DSMB) will monitor the unblinded safety data during the study.

The schedule of assessments is presented in Table 1 below.

Table 1: Schedule of Assessments
Subjects who will be in the study for more than 3 years will continue to visit the clinic every 6 months and have the same assessments performed as during the second and third year.

	V1 Screening	V2 Day 0 (randomization)	V3 1M	V4 3M phone	V5 6M	V6 12M	V7 18M	V8 24M	V9 30M	V10 36M	End of Study VISIT	Phone 14 days after end of study visit
Visit windows (weeks)			± 1	± 3	± 3	± 3	± 4	± 4	± 4	± 4		+ 1
Informed Consent for Study Protocol	X											
ACDY9 genetic determinant (blood draw)	X											
Assessment of eligibility	X	X										
Demographic Information	X											
Query subjects for new/changes in contact information		X				X		X		X		
Pregnancy Test (local)		X										
Physical Exam and Medical History		X									X	
Blood Pressure, Pulse, Weight		X	X		X	X	X	X	X	X	X	
Height		X										
Blood draw for serum creatinine, HbA1c, fasting lipids and hsCRP (central lab)		X			X							
Informed consent for **optiona**l genetic and biomarker evaluations		X										
Blood draw for **optional** genetic and biomarker evaluations		X			X							
Prev/Conc Med		X	X	X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X	X
Dispense Study medication		X			X	X	X	X	X	X		
Return unused Study medication					X	X	X	X	X	X	X	

Note: Optional phone calls by the site to the patient may be conducted between 6 month visit intervals

2.2 Study Objectives

The primary objective of this trial is to evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality (cardiovascular [CV] death, resuscitated cardiac arrest, non-fatal myocardial infarction [MI] and non-fatal stroke) in subjects with a documented recent ACS and the AA genotype at variant rs1967309 in the ADCY9 gene.

The secondary objective of this trial is to evaluate the potential of dalcetrapib to reduce other clinically important events, such as hospitalization for ACS (with ECG abnormalities) or unanticipated coronary revascularization as well as hospitalization for new or worsening heart failure, in combination with the primary endpoint.

Additional objectives of this trial are as listed below:

- Evaluation of the effects of dalcetrapib on lipids and high-sensitivity C-reactive protein (hsCRP) in this population
- Assessment of the long-term safety profile of dalcetrapib, including on diabetes, in this population

3. DATASETS ANALYZED

3.1 Exclusion of Data from Analysis

Subjects will be completely excluded from analyses if they do not satisfy the criteria for inclusion in the specified analysis population, as defined below. If a subject satisfies the criteria for inclusion in an analysis population then no data from that subject will be excluded from use.

3.2 Intent-To-Treat (ITT) Population

All subjects randomized (subjects having a randomization number reported in the electronic case report form [eCRF]) will be included in the ITT population. Subjects will be assigned to treatment groups as randomized for analysis purposes. The ITT population will be used for the assessment of efficacy and safety. Two subjects will be excluded from the ITT population: subject DAL301-18104007 and subject DAL301-36107011 who were randomized in error and never intended to be dosed. None of them took study medication. These two subjects to be removed from the ITT were confirmed by the sponsor prior to database lock and unblinding.

3.3 Co-Diagnostic Analysis: Intent-to-Diagnose (ITD) Population

Subjects who provide written informed consent and have blood drawn for screening will be tested for rs1967309 of ADCY9 by the cobas® ADCY9 Genotype CTA. Subjects with AA genotype results will be allowed to proceed in the study and be further evaluated for eligibility into the study treatment phase and subjects with non-AA genotype will be excluded from the study; however, demographic data for both the AA and non-AA groups will be recorded for evaluation of the cobas® ADCY9 Genotype CTA as a companion diagnostic for dalcetrapib. Subjects who have a biologic sample obtained after Informed Consent will be included in the ITD population.

4. EFFICACY ENDPOINT

Study endpoints will be adjudicated by an independent Clinical Endpoint Committee (CEC) and endpoint classification forms will be provided as part of the eCRF. Procedures and processes for the CEC will be detailed in the CEC charter.

4.1 Primary Efficacy Endpoint

The primary endpoint of this study is the time from randomization to first occurrence of any component of the composite endpoint as adjudicated by the CEC. Components of the primary endpoint are:

- Cardiovascular death
- Resuscitated cardiac arrest
- Non-fatal MI
- Non-fatal stroke

Subjects who discontinued the study without experiencing one of these events will be censored at the time they were last known to be event-free. Time to event (or censoring) will be calculated as the difference (in days) between the adjudicated event date (or date of censoring) and the date of randomization + 1 day.

If a subject reports more than one of the above events, the earliest will be considered for the primary endpoint. If more than one event is reported with the same onset date, the subject will be assigned to the first event in the order of appearance above.

4.2 Secondary Efficacy Endpoints

The secondary endpoints of this study are time from randomization to first occurrence of each of the following composite endpoints, obtained from data adjudicated by the CEC:

- The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, hospitalization for ACS (with ECG abnormalities), or unanticipated coronary revascularization
- The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure

Note: Composite refers to the occurrence of any of the listed endpoints.

The rules described in 4.1 for censoring, for calculation of time to event (or censoring) and in case of multiple events per subject will similarly apply for the secondary endpoints.

4.3 Exploratory Efficacy Endpoints

Exploratory endpoints will include change from baseline to 6 months in:

- Blood levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein (HDL-C)

- Blood levels of hsCRP

5. SAFETY PARAMETERS

Safety will be assessed through the following: adverse events (AEs) and serious adverse events (SAEs), vital signs, physical examination, laboratory parameters and incidence of new onset diabetes.

5.1 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which 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 an investigational product, whether or not considered related to the investigational product. Pre-existing conditions that worsen during a study are to be reported as AEs.

AEs will be collected throughout the study after randomization. At each visit starting at Visit 3 (Month 1), the investigator will ask the subject if any untoward medical event occurred since the last visit. For each event, the date of onset and end, intensity, relationship to study medication, and outcome will be recorded on the eCRF.

5.2 Serious Adverse Events

A SAE is any AE that at any dose fulfills at least one of the following criteria:

- is fatal [results in death; NOTE: death is an outcome, not an event]
- is life-threatening [NOTE: the term "Life-Threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused a death had it been more severe].
- required in-subject hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

It should be noted that implantable cardioverter-defibrillators (ICD) firings are not considered study endpoints but any ICD firing considered by the investigator as clinically relevant and meeting the criteria of an SAE will be reported as such.

5.3 Vital Signs

Seated blood pressure and pulse will be recorded after at least a 5-minute rest. Systolic/diastolic blood pressure and pulse will be recorded at Visit 2 (Day 0), Visit 3 (Month 1), Visit 5 (Month 6), Visit 6 (Month 12), Visit 7 (Month 18), Visit 8 (Month 24), Visit 9 (Month 30), Visit 10 (Month 36) and every 6 months thereafter until the end of the study (if possible).

5.4 Physical Examination

Physical examinations will include examination of the following body systems: general appearance, chest/lungs and cardiovascular, and will be performed at Visit 2 (Day 0) and at the end of the study. All adverse clinically significant changes from randomization to trial completion should be reported as an AE in the source data and the eCRF if an end-of-study Physical Exam is performed.

5.5 Laboratory Parameters

Blood samples are to be collected at Visit 2 (Day 0) and Visit 5 (Month 6) for the analysis of serum creatinine and hemoglobin A1c (HbA1c) (central lab). All adverse clinically significant changes from randomization to trial completion should be reported as an AE in the source data and the eCRF.

5.6 New Onset Diabetes

New onset diabetes (NOD) is defined as a subject:

- without a history of diabetes as reported on the eCRF
- with HbA1c less than 6.5%, and
- without hypoglycemic medications

at the time of randomization, who meet one of the following criteria post-randomization:

- HbA1c value ≥ 6.5%
- new diagnosis of type 2 diabetes mellitus (T2DM) defined as the occurrence of a diabetes-related adverse event
- use of a hypoglycemic medication

6. STATISTICAL METHODOLOGY

6.1 Sample Size

The sample size calculation is based on the primary endpoint. Under the following assumptions:

- an expected relative risk reduction of 22% and
- a statistical significance defined as a two-sided alpha of 0.05

the trial would have more than 85% power if it continues until at least 582 subjects experience a primary CEC adjudicated event in the combined treatment groups.

The total number of subjects to randomize, 6000, was chosen so that the expected number of subjects with an event is at least 582. It is based on the following assumptions, which were reviewed according to actual and planned recruitment rate:

- a 2.8-year recruitment period;
- a 1% yearly lost to follow-up rate; and

- a 7% event rate at 2 years following randomization in the placebo group.

A total of 6149 are actually randomized in the study.

6.2 Statistical Considerations

Statistical analyses will be performed using SAS, Version 9.4 or higher, or other validated software. Unless otherwise specified, all statistical tests will be two-sided.

Study variables are to be presented with descriptive statistics. For continuous variables, the following will be reported: number of observations, mean, standard deviation, median, 25th and 75th percentiles (Q1 and Q3), minimum and maximum. For categorical variables, frequency and percentage will be reported.

Change from baseline is defined as: Post-baseline minus Baseline. Baseline is defined as randomization visit (V2).

6.2.1 Interim Assessment of Futility

On January 23, 2020, after the occurrence of approximately 70% (408) positively adjudicated primary study endpoints, an interim assessment of futility was conducted by the independent DSMB, based on the separate DSMB futility assessment SAP. Following this assessment, the DSMB recommended to continue the trial as planned.

Full details are described in the DSMB charter statistical analysis plan.

6.3 Study Subjects

6.3.1 Subject Disposition

The number of randomized subjects, number of randomized subjects who took study medication, number of randomized subjects completing the study and reasons for study discontinuation will be summarized by treatment group. The number of subjects with survival status assessed at the end of the study will also be presented.

A flow chart following the recommendations of the Consolidated Standards of Reporting (CONSORT) statement will also be provided.

A subject data listing of subject disposition will be provided.

6.3.2 Protocol Deviations

Major protocol deviations are defined as:

- A subject that did not meet entry criteria
- A subject that received the wrong treatment
- A subject that took an over-dose (more than 2 tablets per day)

- A subject that did not complete a planned revascularization procedure prior to randomization

Major protocol deviations will be captured in the clinical database within the standard eCRFs and included in a subject data listing.

6.3.3 Datasets Analyzed

The number of subjects in the ITT population will be summarized.

6.3.4 Demographic and Baseline Characteristics

Demographic data (age, sex [including reproductive status], race, ethnicity) and baseline characteristics which includes history of or current cardiovascular and non-cardiovascular diseases (diabetes), subject region, height, weight, body mass index, vital signs and smoking history will be presented using descriptive statistics by treatment group and overall for the ITT population. For age calculation, missing birth day will be replaced by 15 and missing birth day/month will be replaced by 01/JULY.

The following categories for the ACS index will be summarized:

- Diagnosis of spontaneous myocardial infarction
- Diagnosis of procedure-related myocardial infarction after percutaneous coronary intervention
- Hospitalization for ACS index event

Demographic data that was collected on subjects who provided informed consent and had a blood drawn for screening for rs1967309 of ADCY9 by the cobas® ADCY9 Genotype CTA, including subjects with AA genotype who were allowed to proceed in the study and subjects with non-AA genotype who were excluded from the study, will be reported by the *Roche Molecular Systems* team in a separate report.

6.3.5 Concomitant Medications

The use or change in dose of any medication ongoing or started from the randomization and up to the end of study is recorded on the eCRF. Concomitant medications are coded with respect to indication and generic name using the WHO drug dictionary (September 2016 or higher). Concomitant medications will be presented at randomization.

Frequency of use of medications at randomization will be presented by the level 2 Anatomical Therapeutic Chemical (ATC) classification and preferred term, for each treatment arm. Data will be summarized and presented as proportion of subjects overall and by treatment group receiving any drug in a treatment medication classification at the randomization visit.

A subject data listing of concomitant medications will also be provided.

6.3.6 Treatment Compliance

Accountability and subject compliance will be assessed by maintaining adequate drug dispensing and return records. Subjects will be asked to return all used and unused drug supply containers at each visit as a measure of compliance.

An overall compliance calculation will be performed using the study administration intake recorded. Compliance for the whole study is derived as follows:

$$\text{Compliance} = \frac{\text{\# days subject took study medication}}{\text{\# days in the study}} \times 100$$

days in the study = Date subject completed the study - date of randomization + 1.

Total time on study medication = Date of treatment last dose - date of treatment first dose + 1.

days subject took study medication (duration of treatment exposure) = Total time on study medication - the sum of all interruption durations for each record on the *Treatment Inter/ Disc* Form of the eCRF. It should be noted that only interruptions over 7 days are captured.

Subjects who died with no report of study drug discontinuation will be considered as discontinuing drug on date of death and date of treatment last dose will be imputed as date of death.

Compliance will be summarized by treatment arm using descriptive statistics.

Compliance will also be categorized as follow: < 80% or [80%-100%] and summarized accordingly using frequencies and percentages, by treatment arm, for the subjects of the ITT population.

Compliance results will be listed.

6.4 Efficacy Analysis

All efficacy analyses will be conducted on the ITT population.

6.4.1 Primary Analysis

A stratified Cox proportional hazards model will be used to analyze the primary endpoint. Time to event will start at randomization and subjects who are event-free will be censored at the time that they are last known to be event free. The strata, i.e., as those for randomization, will be defined by region (Eastern Europe, Western Europe, North America, South America and other) and the ACS index event (MI[1] or hospitalization for ACS [ECG abnormalities without biomarkers]). In case of a mismatch between the stratum assigned at time of randomization and the stratum confirmed in the eCRF, the stratum confirmed in the eCRF will be used.

More precisely, the Cox proportional hazards model will include treatment as a main effect, and region and ACS index event type as stratification factors.

The null and alternative hypotheses to be tested with the above Cox model are:

[1]MI corresponds to the following two categories of ACS index event as collected in the eCRF: "Spontaneous myocardial infarction" and "Procedure-related myocardial infarction after percutaneous coronary intervention (PCI)".

$$H_0: \lambda = 1 \text{ vs. } H_A: \lambda \neq 1$$

Where λ is the, assumed constant, hazard ratio for the time to occurrence of the composite events of the primary endpoint for the dalcetrapib and placebo treated groups. The hazard ratio, within strata, will be assumed to depend on treatment alone. The estimated hazard ratio will be presented with a 95% confidence interval (CI) and a p-value.

The primary analysis will be conducted at the 0.05 significance level.

For descriptive purposes, the number and percentage of subjects with each component of the composite primary endpoint will be presented. Time to event will also be graphically displayed using Kaplan-Meier curves.

A subject data listing of primary composite endpoint will also be provided.

6.4.1.1 Evaluation of Primary Endpoint Adjudication

In order to evaluate the consistency of subject outcomes as assessed by the investigator and as adjudicated by the CEC, the concordance between both assessments for the components of the primary endpoint will be summarized using descriptive statistics.

In addition, to go into more depth for death, types of death (CV, non-CV, undetermined), as reported by the investigator and as adjudicated by the CEC, will be summarized using descriptive statistics. No formal statistical testing will be done.

6.4.2 Secondary Analysis

Secondary endpoints are expressed as time to event and an analysis similar to that for the primary endpoint will be conducted.

In order to control the family-wise Type I error that results from the multiplicity of endpoints, the secondary endpoints described in section 4.2 will be formally tested using the Hochberg's step-up procedure only if the primary analysis results in significant treatment effect at $p < 0.05$. Otherwise, statistical tests for the secondary endpoints will be presented solely for illustrative purposes. See section 6.4.6.

Subject data listings will also be provided.

6.4.3 Exploratory Analysis

The changes from baseline to 6 months in TC, TG, LDL-C and HDL-C levels as well as in hsCRP will be compared between treatment groups using an analysis of covariance (ANCOVA) adjusting for baseline value and for the two stratification factors ACS index event type and region. Specifically, the null and alternative hypotheses to be tested are:

$$H_0: \Delta_{placebo} = \Delta_{dalcetrapib} \text{ vs.}$$
$$H_A: \Delta_{placebo} \neq \Delta_{dalcetrapib}$$

where $\Delta_{placebo}$ is the change in the placebo group and $\Delta_{dalcetrapib}$ is the change in the dalcetrapib group. Estimates of treatment effect will be presented with 95% CI and p-values.

Because it is expected that the distribution of hsCRP will be skewed, a log-transformation will be applied to hsCRP data prior to analysis. Geometric mean and geometric mean percent change will be added to the descriptive statistics that will be presented.

Since these analyses are exploratory, a conservative baseline observation carried forward approach will be used in subjects with missing 6-month value. Subjects with no baseline value will be excluded from the analysis.

6.4.4 Sub-population Analyses

For illustrative purposes, the following factors

- Region (Eastern Europe, Western Europe, North America, South America and other)
- Age (< 65, ≥ 65 to < 75, ≥ 75 years)
- Sex (Male, Female)
- Diabetes reported at baseline (Yes, No)

will be used to define subgroups of subjects within which the primary efficacy endpoints will be evaluated using non-stratified Cox proportional hazards models with a term for the treatment group, a term for the factor defining the subgroup and a term for the interaction between the factor and the treatment group. This interaction term will be tested at the 0.1 significance level and will determine whether the treatment effect is affected by the presence of the factor. In addition, under the proposed models, the treatment effect will be estimated and presented with 95% confidence intervals within subgroups.

6.4.5 Additional Analysis

6.4.5.1 Effect of HDL-C at baseline

In order to characterize the potential treatment effect more precisely, an analysis of the primary endpoint will be conducted with the hazard ratio assumed to depend on, in addition to treatment, baseline HDL-C.

Baseline HDL-C will be included in the stratified Cox proportional hazards model used for the primary analysis to provide an estimate of treatment effect that adjusts for HDL-C at baseline.

6.4.5.2 Sensitivity Analysis and Robustness Checks

If a statistically significant treatment effect is demonstrated in the analysis of the primary endpoint, the robustness of the results will be evaluated with respect to their potential dependence on the assumptions made.

1) The effect of censoring subjects who are lost to follow-up (while event-free), i.e. event-free subjects who do not have an end of study visit assessing efficacy endpoints after the start of the EOS visit window (common cut-off date), will be evaluated by imputing event outcomes for such subjects in the analysis. The following imputations rules will be considered.

    a. It will be assumed that an event has occurred shortly after censoring so an event will be imputed at the date of censoring in all event-free subjects who will not have an end of study visit assessing efficacy endpoints after the start of the EOS visit window.

    b. Imputed events will be based on a Weibull regression model that will be fitted to the subjects of the placebo group. This model will then be used to simulate a time to event in all event-free subjects (of both groups) who will not have an end of study visit assessing efficacy endpoints after the start of the EOS visit window (placebo-based imputation) [1]. If the simulated time to event is prior to the study cut-off date, it will be used as an imputed event. Otherwise, the subject will be censored at the study cut-off date. The entire process will be repeated by simulation and will generate multiple imputed datasets. On each imputed dataset, the Cox proportional hazards model used for the primary analysis will be applied and the resulting hazard ratios will be combined using Rubin's rule [2].

    c. The third approach will be similar to b) above. The imputed events will be based on the same Weibull regression model fitted to the subjects of the placebo group. However, instead of using the survival distribution of that model to simulate time to events in subjects of both groups, the hazard of event will be increased by a factor δ ($\delta > 1$) when simulating time to events in dalcetrapib subjects (δ-adjusted hazard imputation) [1]. No such increase will be considered when simulating time to events in placebo subjects. The factor δ will be taken as the inverse of the expected hazard ratio (HR=0.78) and will be set to 1.3 [3]. As in b), the entire simulation process will be repeated and the resulting hazard ratios will be combined using Rubin's rule.

2) The primary analysis is based on a Cox proportional hazards model that assumes proportional hazards. The assessment of proportional hazard will be done by a visual inspection of the log-negative-log plot and through a formal test of the interaction between time and group at the 0.05 significance level.

3) The consistency of treatment effect across ACS index event types will be tested using the interaction term in a non-stratified Cox regression model that will include treatment, ACS index event type and treatment by ACS index event type interaction as main effects. The interaction test will be considered as indicative of a potential interaction in this exploratory analysis if $p < 0.1$. Estimates of treatment effect will be reported separately by strata, along with confidence intervals. The same approach will be used to examine the consistency of treatment effect across regions.

4) In the primary analysis, follow-up of primary efficacy endpoints will stop at the end of study visit. In other words, any primary efficacy endpoints collected between the end of study visit and the 14-day safety follow-up phone call will still be adjudicated but not be included in primary analysis.

However, as a sensitivity analysis, the primary analysis will be repeated, using the same model as described in section 6.4.1, but will include all adjudicated events, including those occurring between the end of study visit and the 14-day safety follow-up phone call.

6.4.5.3 Analysis Following the Initiation of the COVID-19 Pandemic

In order to assess the impact of the COVID-19 pandemic on the primary endpoint, two additional analyses will be performed.

1) Exclusion of primary events after the start of the COVID-19 pandemic

   The CEC reviewed all events occurring after the first reported case of COVID-19 in each participating country (generally the beginning of March, 2020). They assigned terms to each event, based on their clinical judgment, as to whether the event was (a) confirmed/related to COVID-19, (b) possibly related to COVID-19 or (c) not related to COVID-19. An exploratory analysis of the primary endpoint will be performed, excluding all events (a), and also excluding all events (a) or (b) from the definition of the primary endpoint as described below:

   a. The time from randomization to first occurrence of any component of the composite endpoint of CV death, resuscitated cardiac arrest, non-fatal MI or non-fatal stroke (primary endpoint), excluding adjudicated events confirmed/related to COVID-19, will be analysed using the same model as described in section 6.4.1.

   b. The time from randomization to first occurrence of any component of the composite endpoint of CV death, resuscitated cardiac arrest, non-fatal MI or non-fatal stroke (primary endpoint), excluding adjudicated events confirmed/related or possibly related to COVID-19, will be analysed using the same model as described in section 6.4.1.

2) Censoring after SAE diagnosed by investigators as due to COVID-19

   Site Investigators were asked to report all serious adverse events related to COVID-19. Subjects in whom COVID-19-related SAEs occur will be censored at the time of the COVID-19-related SAE in an exploratory analysis of the primary endpoints as described below:

   The time from randomization to first occurrence of any component of the composite endpoint of CV death, resuscitated cardiac arrest, non-fatal MI or non-fatal stroke (primary endpoint), censoring event-free subjects who experienced a COVID-19-related SAE (“COVID” included in the SAE term) at the date of first occurrence of COVID-19-related SAE, will be analysed using the same model as described in section 6.4.1.

6.4.5.4 Analysis Based on Exposure to Study Treatment

Subjects who were off study treatment for an extended period of time may have a different risk profile as compared to the ITT population and two additional analyses will be performed to investigate the effect of exposure to study treatment.

1) Excluding events occurring 14 days after last dose of study treatment in subjects who discontinued study treatment prematurely

   The time from randomization to first occurrence of any component of the composite endpoint of CV death, resuscitated cardiac arrest, non-fatal MI or non-fatal stroke (primary endpoint) will be calculated as number of days between randomization and event in subjects with an event and event-free subjects will be censored at the date they were last known to be event free (as for the primary analysis). However, in subjects who discontinued treatment prematurely (i.e. who reported a study treatment discontinuation on the *Treatment Inter/ Disc* Form of the eCRF), any event occurring 14 days or more after date of last dose will not count as an event. The analysis will be conducted on all randomized subjects (no subject excluded) using the same model as described in section 6.4.1.

2) Excluding subjects who discontinued study treatment prematurely and who had their first event at least 14 days after last dose of study treatment

   The time from randomization to first occurrence of any component of the composite endpoint of CV death, resuscitated cardiac arrest, non-fatal MI or non-fatal stroke (primary endpoint) will be calculated as number of days between randomization and event in subjects with an event and event-free subjects will be censored at the date they were last known to be event free (as for the primary analysis). However, subjects who discontinued treatment prematurely (i.e. who reported a study treatment discontinuation on the Treatment Inter/ Disc Form of the eCRF) and who had a first event occurring 14 days or more after last dose will be excluded. The analysis will not be conducted on all randomized subjects since some would be excluded but it will use the same model as described in section 6.4.1.

6.4.6 Adjustment for multiplicity

Statistical testing of the primary and secondary endpoints will be done hierarchically to control the type 1 error rate at level 0.05. This will be done by testing the primary endpoint first and to test the secondary endpoints using the Hochberg procedure only if the primary analysis results in a significant treatment effect. Other analyses will be interpreted descriptively. The process is described below.

Primary Hypotheses:

The statistical hypotheses to be tested for the primary analysis are:

$$H_0: \lambda = 1 \text{ vs. } H_A: \lambda \neq 1$$

where λ is the HR for the time to occurrence of the primary endpoint for the dalcetrapib and placebo groups.

Secondary Hypotheses:

The statistical hypotheses to be tested for the secondary analyses are:

$$H_{0:S1}: \lambda_{S1} = 1 \text{ vs. } H_{A:S1}: \lambda_{S1} \neq 1$$

$$H_{0:S2}: \lambda_{S2} = 1 \text{ vs. } H_{A:S2}: \lambda_{S2} \neq 1$$

where

λ_{S1} is the HR for time to occurrence of the first secondary endpoint (CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, hospitalization for ACS [with ECG abnormalities], or unanticipated coronary revascularization)
λ_{S2} is the HR for time to occurrence of the second secondary endpoint (CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure)

Primary Analysis

Reject H_0 if p-value from the stratified Cox proportional hazards model is ≤ 0.05.

Secondary Analyses

If H_0 is not rejected, the hypotheses for the secondary endpoints will not be formally tested. If H_0 is rejected, the following rules will be applied:

1. Order the p-values from the stratified Cox proportional hazards models of the secondary null hypotheses, $H_{0:S1}$ and $H_{0:S2}$, from largest to smallest.

2. If the largest p-value is ≤ 0.05, reject both secondary null hypotheses.

3. If the largest p-value is > 0.05 and the smallest p-value is ≤ 0.05/2 = 0.025, reject the secondary null hypotheses corresponding to the smallest p-value.

4. Otherwise, reject none of the secondary null hypotheses $H_{0:S1}$ and $H_{0:S2}$.

6.5 Safety Analysis

All safety parameters will be summarized and presented in tables based on the ITT population.

For the evaluations of adverse events and general laboratory data described below, neither tests of hypotheses nor estimates of treatment effects will be reported, unless otherwise specified. It is, however, anticipated that in some instances there will be numerical treatment differences in the reported summary statistics that are either of interest or concern; in these instances, more extensive exploratory statistical analyses may be performed. The scope of the analyses cannot be determined a priori, but would be expected to include standard regression methods for estimating relative risks such as odds and hazard ratios.

6.5.1 Treatment Exposure

Duration of treatment exposure will be defined as number of days on treatment (computed as described in 6.3.6). Duration of treatment exposure will be summarized by treatment group using descriptive statistics. Duration of treatment exposure will also be categorized according to the following intervals (No exposure, 1-30, 31-182, 183-365, 366-730, 731-1095, and > 1095 days) and summarized accordingly using frequencies and percentages, by treatment group.

In addition, as a separate table, the number of subjects who had a permanent study treatment discontinuation will be summarized using frequencies and percentages, by treatment group.

Information on treatment exposure, study treatment interruption and study treatment discontinuation will also be listed.

6.5.2 Adverse Events and Serious Adverse Events

In general, treatment groups will be compared with respect to the incidence of AEs and SAEs overall and by body system.

6.5.2.1 Adverse Events

Summary statistics will be presented by treatment arm for all treatment-emergent adverse events (TEAEs) and, in addition, by intensity [Mild, Moderate, Severe, Life-Threatening] and relationship to study medication as judged by the investigator [Not Related, Related]. A treatment-emergent AE will be defined as an AE with onset date on or after the date of randomization. For subjects experiencing repeated episodes, only the most severe episode and the episode with the strongest relationship will be reported. Summary statistics will include number and incidence of events where incidence of an event within a treatment group will be determined as the simple proportion of subjects in the group experiencing the event.

Adverse events will be grouped and summarized by system organ class and preferred term as defined by the latest version of the Medical Dictionary for Regulatory Activities (MedDRA, version 19.1 or higher).

All AEs will be included in subject data listings but only treatment-emergent AEs will be summarized.

6.5.2.2 Serious Adverse Events

SAEs will be summarized similarly to all TEAEs and presented in a subject data listing.

6.5.2.3 Adverse Events Leading to Premature Drug or to Premature Study Withdrawal

Adverse events leading to premature drug withdrawal and adverse events leading to premature study withdrawal will be summarized similarly to all TEAEs and presented in a subject data listing.

6.5.2.4 Death

A subject data listing for deaths will be provided.

6.5.3 Laboratory Parameters

For serum creatinine, treatments will be examined with respect to mean and median values over time using both actual values and changes from baseline. Descriptive statistics will be presented. Although it is a safety endpoint, change from baseline to 6 months in HbA1c will be analyzed using an analysis of covariance model as the ones described in section 6.4.3.

Values entered as less than a specified value will be considered as the specified value divided by 2 (e.g. entered value <0.2 will be analyzed as 0.1). Values entered as BLQ (Below Limit of Quantification) will be considered as the limit of quantification divided by 2.

Any adverse clinically significant changes in laboratory data, from randomization to trial completion, will be reported as an adverse event and will be included in the adverse event summary tables described in 6.5.2.

All laboratory results will be listed.

6.5.4 Vital Signs

For sitting diastolic and systolic blood pressure, as well as for pulse rate, treatments will be examined with respect to mean and median values over time using both actual values and changes from randomization. Descriptive statistics will be presented.

Post-randomization vital signs assessments will be assigned to time points based on days from randomization and not on the scheduled visit at which the assessment was made.

Any clinically significant changes in vital signs, from randomization to trial completion, will be reported as an adverse event and will be included in the adverse event summary tables described in 6.5.2.

6.5.5 New Onset Diabetes

Proportion of subjects with NOD will be compared between treatment groups using a Cochran-Mantel-Haenszel test, accounting for the two stratification factors. This analysis will be done for the ITT population, among the subjects with no diabetes at baseline.

6.5.6 COVID-19 Outbreak Impact

Information on visits and study medication allocation impacted by COVID-19 outbreak is to be collected for each subject impacted. Collected data for impact on the visits includes: identification of the visit impacted, how that visit was conducted (on site or by phone) and visit timing with regard to planned visit time windows. Collected data for impact on study medication allocation includes: whether visit to allocate study medication was scheduled or not, how the study medication was dispensed to subject, date of assignment of study medication (as per IWRS) and number of kits dispensed.

COVID-19 outbreak impact information will be presented in a subject data listing.

7. SUMMARY TABLES, FIGURES AND LISTINGS

See the Table Shells document for the list of summary tables, figures and listings.

8 REFERENCES

1. Lipkovich I, Ratitch B, O'Kelly M. *Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints*. Pharmaceut. Statist., 2016, 15, 216-229.
2. Rubin DB. *Multiple imputation for nonresponse in surveys*. John Wiley and Sons, Inc.: New York, 1987.
3. Zhao Y, Herring AH, Zhou H, Ali MW, Koch GG. *A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring.* J Biopharm Stat., 2014, 24 229-253