CLINICAL STUDY PROTOCOL
PROTOCOL NUMBER DAL-301
DALCETRAPIB

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Confidentiality Statement

SYNOPSIS OF PROTOCOL NUMBER DAL-301

TITLE	A 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
SPONSOR	DalCor Pharma UK Ltd Altrincham, Swiss Branch Zug Baarerstrasse 2, CH-6304 Zug Switzerland Tel: +41 41 727 67 89
INDICATION	Reduction of cardiovascular mortality and morbidity in subjects with a documented recent Acute Coronary Syndrome (ACS) and the AA genotype at variant rs1967309 in the adenylate cyclase type 9 (ADCY9) gene
OBJECTIVES	The primary objective of this trial is to evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality (cardiovascular 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. Key secondary objectives of this trial are as listed below: <u>Time to first occurrence of:</u> • The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization • 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 all cause death, resuscitated cardiac arrest, non-fatal MI, or non-fatal stroke Other secondary objectives of this trial are as listed below: • Assessment of the long-term safety profile of dalcetrapib in this population • Evaluation of the effects of dalcetrapib on lipids and hsCRP in this population • Evaluation of the effects of dalcetrapib on : o The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure o The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization, or hospitalization for new or worsening heart failure o The composite of all-cause death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure o Fatal or non-fatal MI o All-cause death
TRIAL DESIGN	This is a placebo-controlled, randomized, double-blind, parallel group, phase III multicenter study in subjects recently hospitalized for ACS and with the appropriate genetic profile. Subjects will provide informed consent before any study-specific procedures are performed. Subject enrollment may begin in the hospital and will continue following release from the hospital. Screening procedures may be performed at the time of the index ACS event or anytime thereafter, with the condition that randomization must occur within the mandated window (1-3 months after the index event). Subjects will be assessed based on their medical history. Those who are likely to qualify will undergo cobas® ADCY9 Genotype CTA (Clinical Trial Assay) testing to evaluate genetic determination for the presence of 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 will be eligible for randomization. Eligible subjects must be stabilized on statin and/or other medical therapy and have completed all planned revascularization procedures prior to randomization. Subjects must be randomized between 1 and 3 months after the index event. Eligible subjects in stable condition will be randomized to 600 mg of dalcetrapib or placebo

	in a 1:1 ratio. Subjects will receive study medication or placebo on a background of contemporary, evidence-based medical care for ACS. This is an event driven study and approximately 582 primary events are needed to reach 85% statistical power given all other assumptions. Subjects will visit the clinic 1 and 6 months after randomization. Thereafter visits will be approximately every 6 months for efficacy and safety assessments until completion of the trial. Phone assessments will be performed 3 months after randomization and at the end of the study for subjects remaining on IP. Additionally, for any subject prematurely discontinuing study medication, assessments will be conducted every 6 months for the collection of study endpoints and concomitant medication.
NUMBER OF SUBJECTS	Approximately 50,000 screened and 6000 randomized
TARGET POPULATION	In order to be included in the trial, subjects must fulfill all of the inclusion criteria and none of the exclusion criteria listed below. Inclusion Criteria Subjects with the appropriate genetic background and recently hospitalized for ACS (between 1 and 3 months following the index event), will be enrolled in this trial. ACS is defined as the occurrence of at least one of the following events: **Myocardial Infarction (MI)** Spontaneous MI A diagnosis of a qualifying MI event will be defined by a rise and/or fall of cardiac biomarkers (preferably cardiac troponin) with at least one determination greater than the 99th percentile upper reference limit (URL) plus at least one of the following described below: • Symptoms of myocardial ischemia, or • New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block, or • Development of pathological Q waves in the ECG, or • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or • Identification of an intracoronary thrombus by angiography Procedure-Related MI after Percutaneous Coronary Intervention (PCI) A procedure-related MI after PCI is defined as an increase of cardiac troponin values with at least one determination greater than 5 times the 99th percentile URL in patients with normal baseline values (less than or equal to 99th percentile URL) or a rise of cardiac troponin values > 20% if the baseline values are elevated and are stable or falling; plus at least one of the following described below: • Symptoms suggestive of myocardial ischemia • New ischemic ECG changes • Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality • Angiographic findings consistent with a procedural complication **Hospitalization for ACS (ECG Abnormalities without Biomarkers):** A diagnosis of a qualifying ACS event without increases in cardiac biomarkers will require admission to hospital or emergency room (exceeding 23 hrs) with symptoms presumed to be caused by myocardial ischemia with an accelerating tempo in the prior 48 hrs and/or prolonged (at least 20 min) rest chest discomfort and new ECG findings (or presumed new if no prior ECG available) as described below and at least one of the following: • at least 50% stenosis of an epicardial coronary artery

- positive exercise or pharmacologic stress indicating reversible ischemia
- presence of pathologic Q-waves on ECG

Examples of New ECG findings include:

- New or presumed new ST depression of at least 0.5mm in at least 2 contiguous leads or T wave inversion of at least 1mm in leads with predominant R wave or R/S >1 in at least 2 contiguous leads
- New or presumed new ST elevation at the J point in ≥ 2 contiguous leads with the following cut-off points: ≥ 0.2mV in men or ≥ 0.15mV in women in leads V2-V3 and/or ≥0.1 mV in other leads or new or presumed new left bundle branch block (LBBB)
- New tall R wave of at least 40ms in V1 and/or V2 and R/S ≥ 1 in V1 with concordant positive T-wave in the absence of a conduction defect
- New Q waves ≥ 30 ms wide and at least 1mm deep in any 2 leads of a contiguous lead grouping or Q wave >20ms or QS complex in leads V2 and V3 (these criteria also apply to silent MI detected during a routine follow-up visit)

In addition, the following inclusion criteria apply:

1. Both male and female subjects age 45 years and over at screening visit (V1)
2. Signed informed consent (approved by Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) obtained prior to any study specific screening procedures
3. AA genotype at variant rs 1967309 in the ADCY9 gene as determined by cobas® ADCY9 Genotype CTA testing, conducted at a designated investigational testing site (ITS)
4. Clinically stable, ie, free of ischemic symptoms at rest or with minimal exertion for at least 1 week prior to randomization
5. Prior to randomization, subject must have evidence of guidelines-based management of LDL-C, at a minimum to include medical and dietary treatment to a target level of LDL-C <100 mg/dl (<2.6 mmol/L). Subjects with an LDL-C level ≥100 mg/dL (≥ 2.6 mmol/L) may be randomized if they cannot reach the target goal of less than 100 mg/dL despite lipid-lowering regimen, or are unable to tolerate lipid-lowering regimen.

Exclusion Criteria

1. Females who are pregnant (negative pregnancy test required for all women of child-bearing potential at Visit 2, Day 0) or breast-feeding
2. Women of childbearing potential (women who are not surgically sterile or postmenopausal defined as amenorrhea for >12 months) who are not using at least one method of contraception
3. New York Heart Association (NYHA) Class III or IV heart failure
4. Last known hemoglobin <10 g/dL
5. Index ACS event presumed due to uncontrolled hypertension
6. Systolic blood pressure (BP) >180 mmHg and/or diastolic blood pressure >110 mmHg by the time of randomization despite anti-hypertensive therapy
7. Last known serum triglyceride level > 500 mg/dL (> 5.65 mmol/L) as assessed within 6 months prior to randomization
8. Last known hemoglobin A1c (HbA1c) >10% as assessed within 6 months prior to randomization
9. Subjects with clinically apparent liver disease, eg, jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis
10. Last known ALT or AST level > 3 times the upper limit of normal (ULN) or last known alkaline phosphatase level > 2 times the ULN as assessed within 6 months prior to randomization (excluding index event)
11. History of persistent and unexplained creatine phosphokinase (CPK) levels > 3 times the ULN as assessed within 6 months prior to randomization (excluding index event)
12. Last known serum creatinine > 2.2 mg/dL (195 µmol/l) as assessed within 6 months prior to randomization
13. Previous exposure to anacetrapib or evacetrapib or documented allergic reaction to any CETP inhibitor
14. History of malignancy (except for curatively treated basal cell or squamous cell carcinoma of the skin) during the 1 year prior to the screening

	15. Any clinically significant medical condition that according to the investigator could interfere with the conduct of the study 16. Subjects whose life expectancy is shorter than 3 years 17. Presence of any last known laboratory value as evaluated prior to randomization that is considered by the investigator to potentially limit the patient's successful participation in the study 18. Current alcohol or drug abuse or history thereof within 2 years prior to screening that would likely interfere with compliance, based on investigator assessment 19. Subjects who have received any investigational drug within 1 month of randomization, or who expect to participate in any other investigational drug or device study during the conduct of this trial 20. Subjects unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study 21. Subjects who have undergone coronary artery bypass graft (CABG) surgery between the index event and randomization
LENGTH OF STUDY	This study is an event-driven study and will last until approximately 582 primary events have occurred. The estimated total duration is approximately 54 months including enrollment and follow-up.
INVESTIGATIONAL MEDICINAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	Dalcetrapib and matching placebo will be provided as 300 mg film-coated tablets. Subject will take 600 mg of dalcetrapib (2 tablets) once daily, preferably with the largest meal of the day. Dalcetrapib and matching placebo are to be taken on a background of contemporary evidence-based medical care for status post-ACS, as individually prescribed by the treating physician.
STANDARD OF CARE	All co-existing medical conditions should be treated with optimized usual care and any concomitant medication prescribed as per the prescribing information.
ASSESSMENTS OF: EFFICACY	**Primary Study Endpoint** The primary endpoint of this study is the time to first occurrence of any component of the composite endpoint, as adjudicated by the Clinical Endpoint Committee (CEC). Components of the primary endpoint are: • Cardiovascular (CV) death • Resuscitated cardiac arrest • Non-fatal MI • Non-fatal stroke **Secondary Study Endpoints** The key secondary endpoints of this study are listed below. <u>Time to first occurrence of:</u> • The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization • 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 all cause death, resuscitated cardiac arrest, non-fatal MI, or non-fatal stroke Other secondary endpoints are listed below: <u>Time to first occurrence of</u> • The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure • The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization, or hospitalization for new or worsening heart failure • The composite of all-cause death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure • Fatal or non-fatal MI

- All-cause death

Exploratory Study Endpoints are listed below

Healthcare resource utilization information
Change from baseline for:
- Blood levels of TC, TG, LDL-C, and HDL-C
- Blood levels of hsCRP

SAFETY

Safety Endpoints
Safety evaluation will include the following:
- Adverse event assessments
- Vital signs

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

PROCEDURES (summary):

A table of assessment is shown below

STATISTICAL ANALYSES
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 85% power if it continues until approximately 582 primary positively CEC adjudicated events occur in the combined treatment groups.

The total number of subjects to randomize, 6000, is chosen so that the expected number of events is approximately 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.

Primary and Secondary Efficacy Analyses:

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 lost to follow-up (while event free) will be censored at the time that they are last known to be event free. The strata will be defined by the region (Eastern Europe, Western Europe, North America, South America, and other) and the ACS index event (MI or ACS [ECG abnormalities without biomarkers]).

In order to control the Type I error that results from the multiplicity of endpoints, a closed test procedure will be used for testing the significance of the three key secondary endpoints of main interest. This will be done if the primary analysis results in significant treatment effects at $p < 0.048$. In that event, these three endpoints will be tested using the Hochberg's step-up procedure again testing against a $p < 0.048$.

For the secondary endpoints that are expressed as time to event, an analysis similar to that for the primary endpoint will be conducted.

Exploratory Analyses:

The changes from baseline in lipid levels and 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.

In addition to the above, exploratory analyses will be performed to evaluate risk reduction as it relates to changes or actual lipid and hsCRP values while subjects are on randomized treatment and to explore potential treatment effects beyond those attributable to changes in lipid levels. Exploratory analyses will also evaluate the effect of prognostic factors.

In addition, if significant treatment effect is demonstrated in the analysis of the primary endpoint, sensitivity analyses will be performed to establish the robustness of the results with respect to any potential dependence on the analysis assumptions.

Subgroup analyses may be performed in subgroups such as those defined by: geographic location, gender, race, age, body mass index (BMI), and diabetes. Details are provided in the Statistical Analysis Plan.

Interim analyses:

When approximately 70% (408) of the primary study endpoints have occurred and have been positively adjudicated, an interim analysis will be conducted by the independent Data Safety Monitoring Board (DSMB). The DSMB will determine if there is sufficient evidence of efficacy benefit to justify continuation of the trial to its completion. This futility assessment will be based on the conditional power of the trial derived under various relative risk reduction assumptions. Following this assessment, the DSMB may recommend terminating the trial.

Full details will be described in the DSMB charter and Statistical Analysis Plan.

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	Phone 14 days after end of study
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	

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

** Procedures that require physical contact with patients such as obtaining, blood pressure, pulse, weight, and an End of Study physical exam are to be performed whenever possible, but may be considered as optional in situations where direct physical contact with the patient is not locally allowed or determined to be hazardous to the patient and/or staff due to the COVID-19 pandemic.

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

ACS	Acute coronary syndrome
ADCY9	Adenylate cyclase type 9
AE	Adverse event
ALT [SGPT]	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST [SGOT]	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CEC	Clinical Endpoints Committee
CETP	Cholesteryl ester transfer protein
COVID-19	Coronavirus disease of 2019
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK-MB	Creatine kinase – isozyme MB
CPK	Creatine phosphokinase
CRO	Contract Research Organization
CV	Cardiovascular
CVD	Cardiovascular Disease
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EEG	Electroencephalogram
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
hsCRP	High-sensitivity C-reactive protein
IEC	Independent Ethics Committee
IB	Investigator Brochure
ICH	International Conference on Harmonization

IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent to treat
IWRS	Interactive Web Response System
LBBB	Left bundle branch block
LDL-C	Low density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
SAE	Serious adverse event
TC	Total cholesterol
TG	Triglycerides
UA	Unstable angina
ULN	Upper limit of normal
URL	Upper Reference Limit

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background

Coronary heart disease (CHD) is a major contributor to mortality, affecting individuals of all ethnic and sociological backgrounds [1]. CHD is influenced by many potential factors, including gender, age, genetics, smoking, high blood pressure, diabetes, and altered plasma lipids [2,3]. Specifically, disturbances in plasma lipoprotein profiles, including elevations of plasma total and low density lipoprotein cholesterol (LDL-C), elevated plasma triglycerides (TG), and decreased high density lipoprotein cholesterol (HDL-C), have all been linked to an increased risk of developing CHD [3-7].

Many studies have demonstrated that high serum levels of LDL-C are a major risk factor for CHD. For over two decades, large, well-controlled randomized trials have consistently documented the ability of LDL-C reduction with HMG CoA reductase inhibitors (statins) to reduce the risk of major coronary events. Epidemiological studies have also consistently shown that decreased HDL-C levels are associated with an increased risk of developing CHD [8,9] and treatment guidelines published by the National Cholesterol Education Program (NCEP) expert panel suggest that HDL-C values below 40 mg/dL confer a significant risk of CHD [10]. However, most clinical trials with HDL-C elevating drugs have failed to demonstrate clinically meaningful benefit on the risk of future cardiovascular events.

Cholesteryl ester transfer protein (CETP) inhibition has been under evaluation as a potential mechanism to raise HDL-C levels and confer cardio-protection to subjects at risk for CHD. To date, four CETP inhibitors have been or are being evaluated in late-stage clinical trials, including torcetrapib, dalcetrapib, evacetrapib and anacetrapib. The development of torcetrapib was halted following the observation of increased cardiovascular events and total mortality in a large outcome trial. These effects have been associated with an off-target effect on the renin-angiotensin-aldosterone axis, and unrelated to CETP inhibition or HDL-C elevation. Evacetrapib and anacetrapib are currently under evaluation in large Phase III cardiovascular outcomes trials. Dalcetrapib has been extensively studied and is addressed below.

1.2 Rationale

Dalcetrapib is a compound selected for its capacity to modulate plasma CETP activity and increase HDL-C levels. Detailed information on results of preclinical and clinical studies with dalcetrapib is contained in the Investigator Brochure (IB). Dalcetrapib has been evaluated in several large clinical trials, most notably dal-OUTCOMES, a 15,871 subject trial designed to

evaluate its effect in subjects with recent acute coronary syndrome (ACS) [11]. After subjects were followed for a median of 31 months, and at a pre-specified interim analysis that included 1135 primary end points, the independent data safety monitoring board (DSMB) recommended termination of the trial for futility. As compared with placebo, dalcetrapib did not alter the risk of cardiovascular morbidity and mortality or total mortality despite an effect on HDL-C levels (30% increase). However, the trial demonstrated the safety and tolerability of dalcetrapib in this population.

With the hypothesis that the responses to dalcetrapib may vary according to the genetic profile, the Montreal Heart Institute has recently conducted a pharmacogenomic evaluation using a genome-wide approach in the dal-OUTCOMES study (discovery cohort, n=5749)[12]. Results demonstrated that subjects with the AA genotype at variant rs1967309 in the adenylate cyclase type 9 (ADCY9) gene experienced a 39% reduction in the risk for cardiovascular morbidity and mortality with dalcetrapib compared to placebo [HR=0.61; 95%CI 0.41, 0.92]. The results were confirmed through a targeted genotyping panel in the dal-PLAQUE-2 imaging trial that demonstrated a significant reduction of carotid intima-media thickness in subjects with the AA genotype treated with dalcetrapib as compared with placebo. Importantly, evaluation of the AA genetic subset demonstrated the safety and tolerability of dalcetrapib in this population. Thus, treatment with dalcetrapib in subjects with the AA genotype at variant rs 1967309 in the ADCY9 gene appears to confer significant cardiovascular benefit and no augmentation of the adverse profile.

Personalized medicine represents an opportunity to utilize our knowledge of the human genome in order to make better treatment decisions for patients. This trial is designed to prospectively confirm the results demonstrated in a genetically defined sub-set of subjects evaluated in dal-OUTCOMES and dal-PLAQUE-2. As such, it represents the first late-stage personalized medicine initiative directed toward reducing the risk of cardiovascular morbidity and mortality in a population at high risk for future events.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is to evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality (cardiovascular 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.

2.2 Secondary Objectives

Key Secondary objectives of this trial are as listed below:

Time to first occurrence of:

- The composite of cardiovascular (CV) death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for ACS (with electrocardiogram [ECG] abnormalities) requiring coronary revascularization
- 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 all cause death, resuscitated cardiac arrest, non-fatal MI, or non-fatal stroke

Other Secondary objectives of this trial are as listed below:

- Assessment of the long-term safety profile of dalcetrapib in this population
- Evaluation of the effects of dalcetrapib on lipids and high-sensitivity C-reactive protein (hsCRP) in this population
- Evaluation of the effects of dalcetrapib on :
    - The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure
    - The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization, or hospitalization for new or worsening heart failure
    - The composite of all-cause death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure
    - Fatal or non-fatal MI
    - All-cause death

3. STUDY DESIGN

3.1 Overview of Study Design and Dosing Regimen

This is a placebo-controlled, randomized, double-blind, parallel group, multicenter study in subjects recently hospitalized for ACS and with the appropriate genetic profile. Subjects will provide informed consent before any study-specific procedures are performed. Subject enrollment may begin in the hospital and will continue following release from the hospital. Screening procedures may be performed at the time of the index ACS event or anytime thereafter, with the condition that randomization must occur within the mandated window (1-3 months after the index event). Subjects will be assessed based on their medical history. Those who are likely to qualify will undergo centralized genetic testing to evaluate the presence of the AA genotype at variant rs 1967309 in the ADCY9 gene. The investigational cobas® ADCY9 Genotype CTA will be used for centralized testing and will support the

randomization of patients into this trial. Pending the outcome of this trial, this assay may potentially become a companion diagnostic to identify patients likely to benefit from dalcetrapib.

Those subjects meeting the genetic testing criteria and all other inclusion criteria and none of the exclusion criteria will be eligible for randomization. Eligible subjects must be stabilized on contemporary evidence-based medical care for status post-ACS as individually prescribed by the treating physician and have completed all planned revascularization procedures prior to randomization. Subjects must be randomized between 1 and 3 months from the index event. A total of 6,000 eligible subjects in stable condition will be randomized to 600 mg of dalcetrapib or placebo in a 1:1 ratio. Subjects will receive study medication or placebo on a background of contemporary, evidence-based medical care for ACS.

This is an event driven study and approximately 582 primary events are needed to reach 85% statistical power assuming a 22% relative risk reduction in the primary endpoint. Patients will be expected to remain in the trial until the time at which approximately 582 primary events have occurred and have been adjudicated. Participating sites will be informed when the study has reached approximately 582 study primary endpoints and will be asked to schedule the end of study treatment visit for their subjects. There is no minimum or maximum study treatment duration defined for this trial, but the expected overall duration is 54 months including recruitment and follow-up. Subjects will visit the clinic 1 and 6 months after randomization. Thereafter visits will be every 6 months for efficacy and safety assessments until completion of the trial as defined in section 5.4. Phone assessments will be performed 3 months after randomization and at the end of the study for subjects remaining on IP. Additionally, for any subject prematurely discontinuing study medication, assessments will be conducted approximately every 6 months for the collection of study endpoints.

3.1.1 Rationale for Study Design

A double-blind, randomized trial design was selected to allow for an unbiased evaluation of dalcetrapib as a treatment for subjects with a recent event of ACS. A composite endpoint including cardiovascular death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke was selected as the primary measure of efficacy because of its clinical relevance.

3.1.2 Rationale for Dose Selection

Doses of 300, 600, and 900 mg of dalcetrapib were evaluated in phase II studies. Increases in levels of HDL-C (an indicator of CETP inhibition) were observed when increasing the dose from 300 to 600 mg of dalcetrapib, while no substantial further effect on CETP inhibition was observed when comparing 600 with 900 mg of dalcetrapib. No significant difference between the 600 and 900 mg dose of dalcetrapib was observed with respect to safety

assessments in phase II studies. As a result, a dose of 600 mg of dalcetrapib was selected for previous phase III studies, including dal-OUTCOMES, which demonstrated that this dose is safe and well-tolerated in this population. Importantly, since the pharmacogenomic evaluation conducted in the dal-OUTCOMES study demonstrated a significant reduction in the risk for cardiovascular morbidity and mortality with 600 mg dalcetrapib vs. placebo, 600 mg of dalcetrapib was selected for evaluation in this trial.

3.1.3 End of Study

The end of the study is defined as the date of the last visit of the last subject to complete the study, or the date at which the last data point, which is required for statistical analysis (i.e. key safety and efficacy results for decision making), is received, whichever is the later date.

3.2 Number of Subjects/ Assignment to Treatment Groups

Approximately 50,000 subjects will be screened for this study in order to identify 6000 subjects meeting the single genetic criterion and other inclusion/exclusion criteria required for randomization in this trial. Subjects will be assigned to treatment groups in a 1:1 ratio, stratified by region (Eastern Europe, Western Europe, North America, South America, and other) and ACS index event (MI or hospitalization for ACS [ECG changes without biomarkers]), to ensure equal number of subjects receiving active treatment and placebo in these strata.

3.3 Clinical Trial Centers

This is a multi-national, multi-center study.

4. STUDY POPULATION

In order to be included in the trial, subjects must fulfill all of the inclusion criteria and not meet any of the exclusion criteria listed below.

4.1 Inclusion Criteria

Subjects with the appropriate genetic profile and recently hospitalized for ACS (between 1 and 3 months following the index event) will be enrolled in this trial. ACS is defined as the occurrence of at least one of the following events:

Myocardial Infarction

Spontaneous Myocardial Infarction

A diagnosis of a qualifying MI event will be defined by a rise and/or fall of cardiac biomarkers (preferably cardiac troponin) with at least one determination greater than the 99th percentile upper reference limit (URL) plus at least one of the following described below:

- Symptoms of myocardial ischemia, or
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block, or
- Development of pathological Q waves in the ECG, or
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or
- Identification of an intracoronary thrombus by angiography

Procedure-Related Myocardial Infarction after Percutaneous Coronary Intervention (PCI)

A procedure-related MI after PCI is defined as an increase of cardiac troponin values with at least one determination greater than 5 times the 99th percentile URL in patients with normal baseline values (less than or equal to 99th percentile URL) or a rise of cardiac troponin values > 20% if the baseline values are elevated and are stable or falling; plus at least one of the following described below:

- Symptoms suggestive of myocardial ischemia
- New ischemic ECG changes
- Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
- Angiographic findings consistent with a procedural complication

<u>Hospitalization for ACS (ECG Abnormalities without Biomarkers):</u>

A diagnosis of a qualifying ACS event without increases in cardiac biomarkers will require admission to hospital or emergency room (exceeding 23 hrs) with symptoms presumed to be caused by myocardial ischemia with an accelerating tempo in the prior 48 hrs and/or prolonged (at least 20 min) rest chest discomfort and new ECG findings (or presumed new if no prior ECG available) as described below and at least one of the following:

- at least 50% stenosis of an epicardial coronary artery
- positive exercise or pharmacologic stress indicating reversible ischemia
- presence of pathologic Q-waves on ECG

Examples of New ECG Findings Include:

- New or presumed new ST depression of at least 0.5mm in at least 2 contiguous leads or T wave inversion of at least 1mm in leads with predominant R wave or R/S >1 in at least 2 contiguous leads

- New or presumed new ST elevation at the J point in at least 2 contiguous leads with the following cut-off points: ≥ 0.2mV in men or ≥ 0.15mV in women in leads V2-V3 and/or ≥0.1 mV in other leads or new or presumed new left bundle branch block (LBBB)
- New tall R wave of at least 40ms in V1 and R/S ≥ 1 in V1 and/or V2 with concordant positive T- wave in the absence of a conduction defect
- New Q waves ≥30 ms wide and at least 1mm deep in any 2 leads of a contiguous lead grouping or Q wave >20ms or QS complex in leads V2 and V3 (these criteria also apply to silent MI detected during a routine follow-up visit)

In addition, the following inclusion criteria apply:

1. Both male and female subjects age 45 years and over at screening visit (V1)
2. Signed informed consent (approved by Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) obtained prior to any study specific screening procedures
3. AA genotype at variant rs 1967309 in the ADCY9 gene as determined by cobas® ADCY9 Genotype CTA testing, conducted at a designated investigational testing site (ITS)
4. Clinically stable, ie, free of ischemic symptoms at rest or with minimal exertion for at least 1 week prior to randomization
5. Prior to randomization, subject must have evidence of guidelines-based management of LDL-C, at a minimum to include medical and dietary treatment to a target level of LDL-C <100 mg/dl (<2.6 mmol/L). Subjects with an LDL-C level ≥100 mg/dL (≥ 2.6 mmol/L) may be randomized if they cannot reach the target goal of less than 100 mg/dL despite lipid-lowering regimen, or are unable to tolerate lipid-lowering regimen.

4.2 Exclusion Criteria

1. Females who are pregnant (negative pregnancy test required for all women of child-bearing potential at Visit 2, Day 0) or breast-feeding
2. Women of childbearing potential (women who are not surgically sterile or postmenopausal defined as amenorrhea for >12 months) who are not using at least one method of contraception
3. New York Heart Association (NYHA) Class III or IV heart failure
4. Last known hemoglobin < 10 g/dL
5. Index ACS event presumed due to uncontrolled hypertension
6. Systolic blood pressure (BP) >180 mmHg and/or diastolic blood pressure >110 mmHg by the time of randomization despite anti-hypertensive therapy
7. Last known serum triglyceride level > 500 mg/dL (> 5.65 mmol/L) as assessed within 6 months prior to randomization
8. Last known hemoglobin A1c (HbA1c) >10% as assessed within 6 months prior to randomization

9. Subjects with clinically apparent liver disease, eg, jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis
10. Last known ALT or AST level > 3 times the upper limit of normal (ULN)or last known alkaline phosphatase level > 2 times the ULN as assessed within 6 months prior to randomization (excluding index event)
11. History of persistent and unexplained creatine phosphokinase (CPK) levels > 3 times the ULN as assessed within 6 months prior to randomization (excluding index event)
12. Last known serum creatinine > 2.2 mg/dL (195 μmol/l) as assessed within 6 months prior to randomization
13. Previous exposure to anacetrapib or evacetrapib, or documented allergic reaction to any CETP inhibitor
14. History of malignancy (except for curatively treated basal cell or squamous cell carcinoma of the skin) during the 1 year prior to the screening
15. Any clinically significant medical condition that according to the investigator could interfere with the conduct of the study
16. Subjects whose life expectancy is shorter than 3 years
17. Presence of any last known laboratory value as evaluated prior to randomization that is considered by the investigator to potentially limit the patient's successful participation in the study
18. Current alcohol or drug abuse or history thereof within 2 years prior to screening that would likely interfere with compliance, based on investigator assessment
19. Subjects who have received any investigational drug within 1 month of randomization, or who expect to participate in any other investigational drug or device study during the conduct of this trial
20. Subjects unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study
21. Subjects who have undergone coronary artery bypass graft (CABG) between the index event and randomization

4.3 Concomitant Medication and Treatment

Subjects should receive contemporary evidence-based medical care for status post-ACS as individually prescribed by the treating physician.

Subjects should also receive instructions on a heart healthy diet. A recommended diet is provided in Appendix 1. Subjects should also receive counseling on appropriate life style modifications such as weight control, physical activity, smoking cessation etc.

All background medications should be administered as per the local prescribing information and all medications prohibited for concomitant use with any of the standard background therapies are not allowed in subjects receiving these background therapies.

Periodic assessment of LDL-C, hemoglobin A1c, and blood pressure may be performed as clinically indicated. Investigators may adjust the subject's background medication (including statins which may be increased or decreased) at any time after randomization to meet standard of care requirements. Patient HDL-C levels should not be evaluated by the investigator or the patient at any time after randomization, for the duration of the study.

Based on drug-drug interaction studies, there are no medications prohibited to be co-administered with dalcetrapib. In subjects receiving digoxin, plasma concentrations of digoxin should be monitored. For subjects receiving warfarin, the International normalized ratio (INR) should be checked on a regular basis to ensure that the INR is within the appropriate therapeutic target range.

The use or change in dose of any concomitant medication will be recorded on the electronic case report form (eCRF).

4.4 Criteria for Premature Study Withdrawal

Subjects have the right to withdraw consent from the study at any time for any reason. An excessive rate of premature study withdrawals can render the study un-interpretable; therefore, unnecessary study withdrawal of subjects should be avoided. Should a subject decide to withdraw consent from the study, all efforts will be made to complete and report the observations prior to study withdrawal as thoroughly as possible.

The investigator should contact the subject or a responsible relative either by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject's withdrawal from the study must be made with an explanation of why the subject is withdrawing from the study.

4.5 Criteria for Premature Study Medication Discontinuation

Based on extensive experience with dalcetrapib 600 mg/day in previous Phase III trials, dalcetrapib is well tolerated. However, if tolerability leads to considerations of study medication discontinuation, it is preferable to titrate the patient down to 300 mg/day (1 tablet per day instead of 2 tablets per day) at the investigator's discretion rather than discontinuing study medication. Any dose changes will be recorded in the eCRF. Subjects stopping study medication should be followed until the end of the study with the same procedures and not be withdrawn unless the subject refuses to give further information.

Additionally, for any subject prematurely discontinuing study medication, assessments will be conducted every 6 months for the collection of study endpoints and concomitant medications. Every effort must be made to obtain endpoint data through the duration of the trial, even if the patient discontinues study medication.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

A detailed schedule of assessments by visit is shown in Table 1.

5.1 Screening Assessments and Procedures (Visit 1)

All subjects must provide written informed consent before any study specific assessments or procedures are performed.

The screening assessment will consist of: 1) review of subject history to determine likely eligibility based on non-genetic inclusion and exclusion criteria; 2) written informed consent and 3) blood draw for investigational cobas® ADCY9 Genotype CTA testing for genetic assessment, conducted at a designated investigational testing lab for centralized testing. In the unlikely event that the genetic sample is deemed unanalyzable the patient would be asked to provide another genetic sample.

Subjects may undergo a blood draw for local laboratory assessments at this visit if the investigator determines it necessary to evaluate eligibility (e.g. troponin). Subjects who do not meet eligibility criteria at the screening visit based on last known laboratory values may undergo repeat testing prior to randomization.

The screening assessments of V1 may be performed at the time of the index ACS event, or any time thereafter with the condition that randomization must occur within the mandated window (1-3 months) after the ACS event. Investigators may perform the informed consent process and screening procedures in the hospital or after discharge in the ambulatory setting.

Subjects who meet the eligibility criteria based on the results of the investigational cobas® ADCY9 CTA genetic testing, and who meet all other inclusion and no exclusion criteria will be allowed to continue in the study and be scheduled for the randomization visit (V2). All other subjects will be recorded as screen failures.

During the 1-3 month window between the index ACS event and randomization, subjects should receive information on a heart healthy diet (see Appendix 1) and counseling on lifestyle changes as appropriate. Contemporary evidence-based medical care for ACS, including antiplatelet agents (aspirin, P2Y12 blocker), statins, beta-blockers, ACE-inhibitors

(or angiotensin-receptor blockers), and medication for optimal control of hypertension, angina, and diabetes should be initiated as appropriate. Subjects should receive instructions on lipid-lowering medications such as statins and/or ezetimibe (ie, start lipid-lowering medication if subject is not yet receiving lipid-lowering medication, increase the dose or change to a more effective medication if subject is already on a lipid-lowering drug) in order to achieve target levels of LDL-C (at a minimum < 100 mg/dL, or < 2.6 mmol/L).

5.2 Randomization Procedures (Visit 2)

Subjects who meet all eligibility criteria will be scheduled for Visit 2, the randomization visit. Subjects will be randomized between 1 and 3 months following the index ACS event. Women of childbearing potential must have a negative pregnancy test at this visit in order to proceed with randomization. At this visit patients will undergo all study procedures as outlined in Table 1, Schedule of Assessments, including a physical exam, collection of medical history (including smoking history), etc.

Once a subject has fulfilled all eligibility criteria, he/she will be randomized to dalcetrapib or matching placebo using an interactive web response system (IWRS). The importance of compliance with study medication should be emphasized.

An optional blood draw for pharmacogenomics (DNA) and soluble biomarker (non-genetic) investigations may be performed on patients who volunteer to participate in this sub-study, and provide additional informed consent at this visit. These samples will be frozen and kept for future use to evaluate biomarkers related to cardiovascular disease and the response to treatment.

5.3 Assessments and Procedures During the Double-blind Treatment Period

Subjects will visit the study clinic 1 month and 6 months after randomization and every 6 months thereafter. With the exception of the screening visit, subjects should ideally be in a fasting state (minimum of 10 hours) for all visits requiring a blood draw (Visits 2 and 5) to be submitted to the central lab. Serum creatinine, HbA1c, fasting lipids and hsCRP will be evaluated for all subjects at Visits 2 and 5. If the patient forgot to fast or fasted for less than 10 hours, the sample should still be collected and sent to the central lab for analysis and documented accordingly in the CRF. At each site visit (and phone visit) after randomization, subjects will be assessed for the occurrence of adverse events and endpoint events.

Subjects will receive a new drug supply at each visit except at visit 3 (1 month) and visit 4 (3 month phone call). At each visit subjects will be required to bring in old unused drug for

assessment of compliance and the importance of compliance to study medication is to be emphasized.

All study assessments will be performed and lab samples will be collected as outlined in Table 1, Schedule of Assessments.

5.3.1 Assessments and Procedures in Response to COVID-19

During the coronavirus disease of 2019 (COVID-19) pandemic, in-person study visits may be replaced by phone visits or virtual visits if necessary. Communication with patients and visits may also occur by email and text message when necessary. Procedures that require physical contact with patients including the physical exam and vital signs (blood pressure, pulse, and weight) are to be performed whenever possible, but may be considered as optional in situations where direct physical contact with the patient is not locally allowed or determined to be hazardous to the patient and/or staff due to the COVID-19 pandemic. Sponsor approval must be obtained within one month if patients are on study drug for more than one year without blood pressure, pulse, or weight assessments. If clinical sites are closed or have limited access, the physical exam and vital signs (blood pressure, pulse, and weight) may be collected at a location other than the clinical site (i.e. a remote location, the patient's home, etc) where possible and locally allowed.

If study visits at clinical sites are, or are expected to be significantly impacted, study medication may be dispensed within a study visit window or in advance through a secure delivery method. All study medication will be appropriately handled and tracked to ensure compliance with stability parameters.

Patients will be provided directions to save their unused study medication materials (used and unused drug supply containers) to return at their next on-site visit. Study medication may also be returned by the patient to the site through a secure delivery method.

All COVID-19 related contingency measures will be recorded in the eCRF.

5.4 End of Treatment and Safety Follow-Up

As an endpoint driven study, subjects will be on study treatment until approximately 582 study primary endpoints have occurred and have been adjudicated. Participating sites will be informed when the study has reached approximately 582 study primary endpoints and will be asked to schedule the end of study treatment visit for their subjects. The end of study visit must be scheduled within a month of being notified when possible.

Patients still taking study medication at the end of treatment visit will also have a safety follow-up phone call 14 days (+1 week window if needed) after the end of treatment visit. The safety follow-up may be conducted via telephone unless the investigator considers a visit necessary because of ongoing adverse events for which he/she would like to obtain a follow-up measurement.

5.5 Assessments and Procedures for Subjects Who Prematurely Discontinue Study medication

For subjects who prematurely discontinue study medication but wish to remain in the trial, they will continue being followed as per the planned study assessments and procedures.

For subjects who prematurely discontinue study medication and also refuse further study visits and procedures, every effort should be made to retain the subjects in the study to obtain information by phone on the occurrence of endpoint events.

For subjects who refuse further study medication, procedures, or phone contact, an end of treatment visit should be performed if possible. For these patients the investigator should make every effort to obtain information on whether or not the subject is alive or dead at the end of the study. If these patients are unable to be reached, this information may be obtained through publicly available sources and/or as permitted by local regulations. If locally allowed, a third party may be used to locate alternative subject contact information and/or vital status in the public domain. That information will be provided to the investigator.

5.6 Assessments and Procedures at Occurrence of Efficacy Endpoints

Occurrence of study endpoints, from randomization to trial completion, must be reported to the sponsor within 24 hours of the site's notification that the study endpoint has occurred. As endpoints will be adjudicated by an independent Clinical Endpoint Committee (CEC), endpoint classification forms will be provided as part of the eCRF. The investigator will record the event on these electronic forms and forward the supporting documentation (hospital admission and discharge note, autopsy reports, ECGs etc.) in a timely manner. These data will be provided to the CEC for adjudication of the event. The CEC consists of the chairman and additional qualified members. Procedures and processes for the CEC will be detailed in the CEC charter.

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	Phone 14 days after end of study
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	

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

** Procedures that require physical contact with patients such as obtaining, blood pressure, pulse, weight, and an End of Study physical exam are to be performed whenever possible, but may be considered as optional in situations where direct physical contact with the patient is not locally allowed or determined to be hazardous to the patient and/or staff due to the COVID-19 pandemic.

5.7 Efficacy Assessments and Procedures

Efficacy assessments of this study are listed below. A detailed description of the analysis of these parameters is included in Section 8, 'Statistical Considerations and Analytical Plan'. All primary and secondary endpoint events will be adjudicated by the CEC.

5.7.1 Primary Efficacy Assessment

The primary efficacy assessment in this trial is the time to the first occurrence of any component of the composite endpoint of:

- Cardiovascular (CV) death
- Resuscitated cardiac arrest
- Non-fatal MI
- Non-fatal stroke

A detailed description of criteria for classification of endpoints is documented in the CEC charter. The charter will also include information on supporting documents to be provided,

data flow and meeting schedule of the CEC. Study sites will be given a list of the documents that they will need to provide when an endpoint is suspected.

5.7.2 Secondary Efficacy Assessments

The key secondary efficacy assessments in this trial are the time to the first occurrence of:

- The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization
- 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 all cause death, resuscitated cardiac arrest, non-fatal MI, or non-fatal stroke

Other secondary efficacy assessments are listed below.

Time to first occurrence of:

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

5.7.3 Exploratory Assessments

Blood draw for serum creatinine, fasting lipids, hsCRP, and HbA1c will be obtained according to the schedule summarized in Table 1 and analyzed by the central laboratory. Exploratory laboratory assessments are change from baseline in levels of lipids as well as the change in hsCRP. Healthcare resource utilization information will also be collected.

Patients who volunteer for the optional biomarker sub-study will have additional blood samples collected at Visits 2 and 5 for future genetic and non-genetic analyses. Protection

of subject confidentiality will extend to any data generated from the assaying of these samples. These samples will be frozen and kept for future use to evaluate biomarkers related to cardiovascular disease and the response to treatment.

A laboratory manual providing instructions for the collection and handling of blood samples will be provided.

5.8 Safety Assessments and Procedures

5.8.1 Adverse Events

Adverse events will be collected throughout the study after randomization. At each visit starting at V3, 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.

5.8.2 Vital signs

Seated blood pressure and pulse will be recorded after at least a 5-minute rest. Vital sign checks will be performed according to the schedule summarized in Table 1.

5.8.3 Physical examination and medical history

Physical examinations will include examination of the following body systems: general appearance, chest/lungs, and cardiovascular. All clinically significant changes from randomization to trial completion should be reported as an AE in the source data and the eCRF. Medical history will consist of detailed information regarding the index ACS event, and risk factors for cardiovascular disease.

5.8.4 Laboratory Assessments

Blood samples are to be collected at Visit 1 (screening), Visit 2 (Day 0) and Visit 5 (Month 6). Blood samples at Visits 2 and 5 are ideally to be collected in the fasting state (minimum of 10 hours without food; subjects are allowed to drink water, but no coffee or tea).
The procedures for the collection, handling, storage and shipping of laboratory samples are specified in a separate laboratory manual.

5.8.4.1 Serum Creatinine and HbA1c

Blood draw for serum creatinine and HbA1c will be obtained according to the schedule summarized in Table 1 and analyzed by the central laboratory. All clinically significant changes from randomization to trial completion should be reported as an AE in the source data and the eCRF.

5.8.4.2 Pregnancy Test

β-HCG levels test will be obtained and analyzed locally in all women of childbearing potential prior to randomization (Table 1).

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Dose and Schedule of Study medication and Placebo

DalCor (sponsor) will supply dalcetrapib 300mg film-coated tablets and matching placebo tablets to investigators. Subjects will take 600 mg of dalcetrapib or placebo (2 tablets) once daily. Study medication should be taken with food, preferably with the largest meal of the day. Subjects should be encouraged to take the medication at approximately the same time each day.

Subjects who take study medication with breakfast should be instructed not to take study medication at home in the morning of V2 and V5 (fasting blood samples are preferred) but to wait until after collection of blood at the clinic.

6.1.1 Dose Modifications and Delays

In the event of a subject forgetting to take drug with their largest meal that day, they can take the study drug later in the day and return to their regular schedule the next day. In the event of a subject not taking drug on a given day, he or she should not take more than the daily dose on the following day.

Temporary interruptions of study medication are allowed. Interruptions of study medication for longer than 14 days need approval of the sponsor whenever possible. In the event of a subject experiencing intolerable adverse events considered related to study medication by the investigator, the investigator should consider decreasing the dose to one tablet once daily before interrupting or permanently discontinuing study medication.

6.2 Formulation, Packaging and Labeling

Dalcetrapib will be provided as film-coated tablets of 300 mg. Tablets are white and capsule-shaped, identical in appearance to placebo tablets.

The study medication must be stored in a locked, secured, temperature controlled location of up to 25^{o} C. A daily temperature log must be maintained by the site. Any temperatures exceeding 25^{o} C should be reported to the Sponsor/designee immediately along with the following information: the minimum and maximum temperature of the excursion, duration in hours, and the medication kit numbers involved. The drug should be immediately placed at the proper temperature and quarantined (not dispensed to subjects) until notification from the Sponsor is received that the drug is acceptable to use or must be destroyed/returned.

Likewise, subjects should be informed that study medication must be stored at 25^{o} C or below.

Subjects will take their daily dose of dalcetrapib or placebo as shown below.

	No. of Tablets	
Dose Group	300 mg dalcetrapib tablet	Placebo
600 mg of dalcetrapib	2	0
Placebo	0	2

Please note that placebo tablets contain lactose (435 mg/tablet) and may lead to problems in subjects with severe lactose intolerance.

Each site will receive a supply of individually labeled double-blind study medication kits. Each kit will be labeled with a label including dosing instructions, the visit number and the subject number to be added by site personnel.

6.3 Randomization

Subjects will be randomized to dalcetrapib 600 mg or placebo in a 1:1 ratio stratified by region and ACS index event (MI or hospitalization for ACS [ECG Abnormalities without Biomarkers], see sections 4.1.1 and 4.1.2), according to a computer-generated global randomization code. The subject randomization numbers will be allocated sequentially in the order in which the subjects are enrolled. Investigators are to use the IWRS to obtain randomization numbers for subjects they randomize in the study.

The Master Randomization List will be kept in a central repository at the Coordinating Center with access to the unblinded statistician only. No open key to the code will be available at the study center, to the monitors of the Contract Research Organization (CRO), project statisticians, or to the project team.

6.4 Blinding and Unblinding

The blind during the study is maintained by administration of placebo tablets to subjects in the placebo group. The Randomization List will not be available at the study center, to the Project Manager and monitors of the contract research organization(s) CRO(s), project statisticians or to the project team. If the identification of the test medication is necessary for subject management (in the case of serious adverse event) the investigator will be able to break the code by contacting the IWRS provider. A note to file should be written which will be archived with other study documents. Treatment codes should not be broken except in the case of emergency situations. If the investigator wishes to know the identity of the treatment given to study subjects for any other purpose, this request should first be discussed with the DalCor Chief Medical Officer.

Unblinding for ongoing safety monitoring by the DSMB will be performed according to adequate procedures in place to ensure integrity of the data as outlined in a separate DSMB charter.

All other individuals directly involved in this study will remain blinded until the final analysis of the primary parameter.

6.5 Assessment of 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.

A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the subject to whom the study medication was dispensed
- the date[s] and quantity of the study medication dispensed to the subject
- the date[s] and quantity of the study medication returned by the subject

This inventory must be available for inspection by the Monitor. The dispensing logs must be returned to DalCor or DalCor designee at the end of the study.

6.6 Destruction of Study Medication

Each site will be instructed by their monitor on the details of drug return/destruction for their site.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events (AEs) and Laboratory Abnormalities

7.1.1 Clinical AEs

Per the International Conference of Harmonization [ICH], 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 a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product. Pre-existing conditions which worsen during a study are to be reported as AEs.

7.1.1.1 Intensity

All clinical AEs encountered during the clinical study will be reported on the AE page of the eCRF. Intensity of AEs will be graded on a four-point scale [mild, moderate, severe, life-threatening] and reported in detail on the eCRF.

Mild	discomfort noticed but no disruption of normal daily activity.
Moderate	discomfort sufficient to reduce or affect daily activity.
Severe	inability to work or perform normal daily activity
Life-Threatening	represents an immediate threat to life

7.1.1.2 Drug - Adverse Event Relationship

Relationship of the AE to the treatment should always be assessed by the investigator as either Related or Not Related . The following criteria should be considered in order to assess the relationship:

- reasonable temporal association with administration of the study drug
- existence of alternative causes that could on their own have caused the reaction, like the subject's medical condition
- known pattern of response to the suspected drug
- de- and rechallenge information

7.1.1.3 Serious Adverse Events

A Serious Adverse Event (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 which could hypothetically have caused a death had it been more severe].
– required in-patient 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.

***** *NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a serious adverse event (SAE) under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness.*

Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

The study will adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 and comply with local regulatory requirements (see Appendix 2).

7.1.1.4 Project-Specific Definition of SAEs

In this trial, positively adjudicated endpoints by the CEC (irrespective of investigators' causality) as well as those negatively adjudicated by the CEC and reported as unrelated to study medication by the investigators will be exempted from SAE reporting. However, all other events meeting SAE criteria will be reported as SAEs to the Sponsor.

Thus, the following events will not be reported as SAEs unless negatively adjudicated and considered study medication related by the investigator:

Cardiovascular (CV) death
Resuscitated cardiac arrest
Non-fatal MI
Non-fatal stroke
Hospitalization with ACS (with ECG abnormalities)
Hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization
Unanticipated coronary revascularization
Hospitalization for new or worsening heart failure
All-cause death

These events will be reported on the appropriate eCRF pages for the collection of information on endpoint events and forwarded to the CEC.

7.1.2 Treatment and Follow-up of AEs

All AEs, especially those that could be related to study medication, should be followed-up until they have returned to baseline status or stabilized. If after follow-up, return to baseline status or stabilization cannot be established an explanation should be recorded on the eCRF.

7.1.3 Laboratory Test Abnormalities

Any treatment-emergent abnormal laboratory result that is clinically significant, should be recorded as a single diagnosis, if possible, on the AE page in the eCRF.

7.1.4 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range or baseline and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the AE page of the eCRF.

7.2 Handling of Safety Parameters

7.2.1 Reporting of AEs

All new adverse events occurring during the study should be recorded on the AE page of the eCRF. Adverse events that occur intermittently should be recorded as one AE. Adverse events should be collected and reported from randomization to trial completion.

7.2.2 Reporting of Serious Adverse Events

Any clinical AE or abnormal laboratory test value that is serious [as defined in section 7.1.1.3 above] and which occurs during the course of the study must be reported to the sponsor within 24 hours of the investigator becoming aware of the event.

Related Serious Adverse Events MUST be collected and reported regardless of the time elapsed from the last study medication administration, even if the study has been closed.

Like AEs in general, unrelated Serious Adverse Events must be collected and reported during the study and to trial completion.

The definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to. Complete information can be found in Appendix 2.

7.2.3 Pregnancy

A female subject must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy, and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the test medication must also be reported to the investigator.

7.3 Warnings and Precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigators' Brochure.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Endpoints

8.1.1 Primary 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

8.1.2 Secondary and Exploratory Endpoints

The key secondary endpoints of this study are listed below.

Time to first occurrence of:

- The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization
- 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 all cause death, resuscitated cardiac arrest, non-fatal MI, or non-fatal stroke

Other secondary endpoints are listed below:

Time to first occurrence of

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

Exploratory endpoints are listed below

Healthcare resource utilization information
Change from baseline for:

- Blood levels of TC, TG, LDL-C, and HDL-C
- Blood levels of hsCRP

8.1.3 Safety

Safety of the treatment will be evaluated by AEs and vital signs.

8.2 Statistical and Analytical Methods

8.2.1 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 85% power if it continues until at least 582 primary CEC adjudicated events occur in the combined treatment groups.

The total number of subjects to randomize, 6000, is chosen so that the expected number of events is at least approximately 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.

Sample size was calculated using nQuery, version 7.0.

8.2.2 Analysis Populations

8.2.2.1 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.

8.2.2.2 Intent to Treat (ITT) Population

All subjects randomized will be included in the ITT population.

8.2.2.3 Per-Protocol Population

A per-protocol population is defined as patients who meet all inclusion/exclusion criteria, are determined to be at least 80% compliant to study medication, and have completed the study with no premature study or medication discontinuation. This population will be used only in the context of exploratory analysis as described in section 8.2.4.3.

8.2.2.4 Safety Analysis Population

All subjects who received at least one dose of treatment will be included in the safety analysis population. Subjects will be assigned according to the true treatment received for analysis purposes.

8.2.2.5 Co-Diagnostic Analysis: Intent-to-Diagnose (ITD)

Patients who provide written informed consent and have blood drawn for screening will be tested for RS1967309 of ADCY9 by the cobas® ADCY9 Genotype CTA. Patients with AA genotype results will be allowed to proceed in the study and be further evaluated for eligibility into the study treatment phase and patients 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. Patients who have a biologic sample obtained after Informed Consent are part of the Intent-to-Diagnose population.

8.2.3 Efficacy Analysis

8.2.3.1 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 lost to follow-up (while event free) will be censored at the time that they are last known to be event free. The strata will be defined by region (Eastern Europe, Western Europe, North America, South America, and other) and the ACS index event (MI or ACS [ECG abnormalities without biomarkers], see sections 4.1.1 and 4.1.2).

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

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

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 95.2% confidence interval (CI) and a p-value.

The primary analysis will be based on the ITT population and conducted at the 0.048 significance level to account for interim assessments of efficacy as outlined in section 8.2.3.4.

8.2.3.2 Secondary and Exploratory Analysis

For the secondary endpoints that are expressed as time to event, an analysis similar to that for the primary endpoint will be conducted.

The changes from baseline in TC, TG, LDL-C, HDL-C and hsCRP levels 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.

Secondary and exploratory analyses will be conducted on the ITT population. In order to control the Type I error that results from the multiplicity of endpoints, the key secondary endpoints will be formally tested using the Hochberg's step-up procedure only if the primary analysis results in significant treatment effect at $p < 0.048$. Otherwise, statistical tests for the secondary endpoints will be presented solely for illustrative purposes.

8.2.3.3 Sub-population Analyses

For illustrative purposes, the following factors:

- Geographic location
- Age
- Gender
- Race
- BMI
- Diabetes

may be used to define subgroups of subjects within which the primary and selected secondary efficacy endpoints will be evaluated using Cox proportional hazards models similar to the ones described in section 8.2.3.1, adding to the models 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. The sub-population analyses would be conducted on the ITT population.

8.2.3.4 Interim Analysis

When approximately 70% (408) of the primary study endpoints have occurred and been positively adjudicated, an interim analysis will be conducted by the independent Data Safety Monitoring Board (DSMB). The DSMB will determine if there is sufficient evidence of efficacy benefit to justify continuation of the trial to its completion. This futility assessment will be based on the conditional power of the trial derived under various relative risk reduction assumptions. Following this assessment, the DSMB may recommend terminating the trial.

Full details will be described in the DSMB charter and Statistical Analysis Plan.

8.2.4 Exploratory Analyses

8.2.4.1 Effect of Prognostic Factors

In order to characterize any 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, the following potentially prognostic factors:

- Baseline HDL-C
- Baseline LDL-C
- Baseline TG
- Baseline TC
- Gender
- Age

A factor will be identified as prognostic if the corresponding model term is associated with a p-value of less than 0.2 in a multivariate stratified Cox proportional hazards model that includes all factors. Factors that are determined to be prognostic by this criterion will be included in the final model to provide an estimate of treatment effect that adjusts for factors that are likely to influence the primary endpoint. This will be done on the ITT population.

8.2.4.2 Effect of Lipid Changes and Changes in hsCRP while on Treatment

In order to evaluate risk reduction as it relates to changes or actual values in lipids and hsCRP while subjects are on randomized treatment, additional exploratory analyses will be

conducted on the primary endpoint. These will include, but will not necessarily be limited to, analyses that:

- include changes or actual values in lipids and hsCRP as time-dependent covariates in proportional hazard regression models

- take a subset of subjects who are event free at 6 months and use the change from baseline in lipids and hsCRP (or actual values) at that time as fixed covariates in a regression analysis of subsequent events.

In all analyses, randomized treatment will be both included and excluded as a factor in the regression models in order to evaluate if there are additional effects of treatment beyond those that are attributable to changes in lipid levels. These analyses would be conducted on the ITT population.

8.2.4.3 Sensitivity Analyses

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.

In particular, the effect of censoring subjects who are lost to follow-up (while event free) will be evaluated by imputing event outcomes for such subjects in the analysis. Various imputation rules will be applied and will be established prior to database closure and the breaking of the blind. The sensitivity of the primary analysis to treatments or procedures that would be expected to affect the primary endpoint will be assessed by additionally censoring such subjects at the time of the treatment or procedure.

The consistency of treatment effect across the ACS index event strata and across regions will be tested using a term of treatment by strata interactions in the Cox regression model. Interaction will be considered significant if $p < 0.1$ and in the event that significant interactions are observed, estimates of treatment effect will only be reported by strata.

8.2.5 Safety Analyses

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

8.2.5.1 Adverse Events

Treatments will be examined with respect to the incidence of adverse events, serious adverse events (SAEs) and adverse events leading to premature study withdrawal or dose modifications.

Summary statistics will be presented for all treatment-emergent events and, in addition, by intensity and relationship to study medication as judged by the investigator. In the latter instances, 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 body system as defined by the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), following classification of investigator assessments into MedDRA preferred terms.

8.2.5.2 Laboratory Data

Any clinically significant changes in laboratory data will be reported as an adverse event and will be included in the adverse event safety analyses.

8.2.5.3 Vital Signs

Any clinically significant changes in vital signs will be reported as an adverse event and will be included in the adverse event safety analyses.

9. DATA QUALITY ASSURANCE

Data for this study will be recorded via an Electronic Data Capture (EDC) system using electronic Case Report Forms. The eCRF can be used as the source document if the eCRF is the original place of data entry, per the FDA Guidance. Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the Investigator. A comprehensive validation check program will be defined and outlined in the Edit Checks Specifications as a part of the Data Management Plan. Throughout the study the Study Management Team will review data according to the Data Management Plan.

9.1 Assignment of Preferred Terms to Original Terminology

For classification purposes, preferred terms will be assigned by the lead Data Coordinator, reviewed by the Medical Monitor/DalCor Chief Medical Officer based on the original terms entered on the eCRF, using the latest version of the MedDRA for adverse events and diseases, and WhoDRUG for medications.

10. STUDY COMMITTEES

10.1 Executive Committee and Steering Committee

The Study Executive Committee is composed of medical and scientific experts and includes the Principal Investigator. The Executive Committee, together with the sponsor, developed the protocol. The Executive Committee is also responsible for evaluating any changes in the medical environment during the course of the trial that affect the assumptions underlying the original protocol design and amending the protocol accordingly.

The Steering Committee is composed of the Executive Committee and the national coordinators of each participating country/region. A separate charter describing roles and responsibilities of the members of the two committees will be maintained by the sponsor.

10.2 Data Safety Monitoring Board (DSMB)

The primary role of the DSMB, which consists of physicians and statisticians, is to ensure the safety of the subjects. A detailed description of the procedures, data flow and meeting schedule of the DSMB will be maintained in a separate DSMB charter by the sponsor.

10.3 Clinical Endpoints Committee (CEC)

The Clinical Endpoints Committee (CEC) consists of independent members and will be responsible for the adjudication and classification of deaths and non-fatal cardiovascular events.

Criteria for adjudication, procedures, data flow and meeting schedule are described in a separate CEC charter maintained by the sponsor.

11. REFERENCES

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the subject. For studies conducted in the European Union (EU)/ European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the investigator will additionally ensure that the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards", are adhered to.

In other countries where "Guidelines for Good Clinical Practice" exist DalCor and the investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator [if acceptable by local regulations], to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The electronic Case Report Forms [eCRFs] for this study contain a section for documenting informed subject consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects [including those already being treated] should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.
An optional informed consent will be provided at randomization for additional future genetic and non-genetic testing to explore the relationship between treatment response and genetic/non-genetic determinants.

12.3 Independent Ethics Committees/Institutional Review Board

Independent Ethics Committees [non-US]: This protocol and any accompanying material provided to the subject [such as subject information sheets or descriptions of the study

used to obtain informed consent] as well as any advertising or compensation given to the subject, will be submitted by the investigator to an Independent Ethics Committee.

Approval from the committee must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the Independent Ethics Committee approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee.

Institutional Review Board [US]: It is the understanding of the sponsor that this protocol [and any modifications] as well as appropriate consent procedures, will be reviewed and approved by an Institutional Review Board. This board must operate in accordance with the current Federal Regulations. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the sponsor and the investigator [investigator representative[s] in the case of a multicenter trial]. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Chief Medical Officer.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change[s] involves only logistical or administrative aspects of the trial [e.g. change in monitor[s], change of telephone number[s].

14. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, DalCor and the investigator will assure that adequate consideration is given to the protection of the subject's interests.

15. STUDY DOCUMENTATION, ECRFS AND RECORD KEEPING

15.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories [1] Investigator's Study File, and [2] subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

Subject clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs] would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram (EEG), X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrollment logs. The Investigator must keep these two categories of documents on file for at least 15 years after completion or discontinuation of the study or longer if required by local regulation. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, DalCor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and DalCor to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

15.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the DalCor Quality Assurance Unit or its designee, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.4 Electronic Case Report Forms

For each subject randomized, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome. Data from subjects enrolled and screened, but who do not get randomized (screen failures) will not be collected in the eCRF. However, some information such as demographic data, ACS event type, ACS event date, will be collected in the IWRS system for all screened patients.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

16. MONITORING THE STUDY

It is understood that the responsible DalCor monitor [or designee] will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial [eCRFs and other pertinent data] provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports, study medication and other subject records needed to verify the entries on the eCRF. The investigator [or his/her deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

When site access is not possible due to COVID-19, virtual monitoring may occur where locally permitted.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission to DalCor, e.g., subjects' written consent forms, in strict confidence.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to DalCor prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accord with standard editorial and ethical practice, DalCor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of DalCor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate DalCor personnel. Authorship will be determined by mutual agreement.

Appendix 1 Study Recommended Diet and Principles

TLC Diet – A diet for high cholesterol heart disease recommended by AHA

The TLC diet was introduced in May 2001 when the National Cholesterol Education Program (NCEP) released new diet guidelines for people with high cholesterol and risks of hear disease. The American Heart Association (AHA) accepted and endorsed this report and began incorporating these recommendations into its materials on dietary and lifestyle change for people with high blood cholesterol. For people at high risk or who hav known cardiovascular disease, NCEP and AHA now recommend the new Therapeutic Lifestyle Changes (TLC) diet to replace the "old" Step 1 and Step 2 diets.

Summary of the TLC Diet for High Cholesterol

- Saturated fat: Less than 7% of total calories
- Polyunsaturated fat: Up to 10% of total calories
- Monounsaturated fat: Up to 20% of total calories
- Carbohydrate: 50% to 60% of total calories
- Soluble fiber: At least 5 to 10 grams a day
- Protein: Approximately 15% of total calories
- Cholesterol: Less than 200 mg a day
- Total calories: Balance calories taken in and calories burned to reach and stay at a healthy weight.

For a detailed customized TLC diet plan, please consult with your Registered Dietitian.

Appendix 2 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event 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 patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].

– required in-patient 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

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event are indicated by selecting one or more options. (Check all that apply)

– Pre-existing/Underlying disease – specify

– Study treatment – specify the drug(s) related to the event

- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) – specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the investigator within 14 days during the protocol-defined follow-up period after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, should also be reported if considered related to test “drug”.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.