1. Protocol I1V-MC-EIAN
Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes – the ACCELERATE Study

Confidential Information

Evacetrapib (LY2484595)

Study I1V-MC-EIAN (ACCELERATE) is a Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled, event-driven study in approximately 11,000 patients with high-risk vascular disease (HRVD).

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 24-May-2012 GMT

2. Synopsis

Study Rationale

Evacetrapib (LY2484595) is a potent, selective inhibitor of cholesterol ester transfer protein (CETP) that has demonstrated ability to inhibit CETP activity, increase high-density lipoprotein cholesterol (HDL-C) and decrease low-density lipoprotein cholesterol (LDL-C).

Lipid modification, primarily through reduction in LDL-C by 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), has been shown to reduce major adverse cardiovascular events (MACE) in a wide range of patients, including those with known coronary artery disease (CAD), as well as in patients with a history of acute coronary syndrome (ACS). Further lipid modification through adjunctive treatment with a CETP inhibitor may therefore similarly benefit a wide range of patients.

Epidemiologic data shows that higher levels of HDL-C and lower levels of LDL-C are associated with less atherosclerotic burden and lower risk for MACE. The pharmacodynamic (PD) effect of evacetrapib is expected to lead to a reduction in MACE in patients with vascular disease at high risk of subsequent cardiovascular events.

The PD effect of CETP inhibition has been tested in clinical trials with several CETP inhibitors, including torcetrapib (CP-529,414), anacetrapib (MK-0859), and dalcetrapib (JTT-705). Clinical trials clearly demonstrate CETP inhibition elevates HDL-C, and with more potent agents, lowers LDL-C; however, the hypothesis that lipid modulation by CETP inhibition will reduce the risk of cardiovascular events has yet to be confirmed in a clinical-outcome trial.

Patients for this Phase 3 study (Study I1V-MC-EIAN [ACCELERATE]) are those with known atherosclerotic vascular disease at high risk for subsequent cardiovascular events. The characteristics of these patients, termed high-risk vascular disease (HRVD), are patients with at least 1 of the following: 1) history of ACS (≥30 days through 365 days after discharge for ACS); 2) cerebrovascular atherosclerotic disease; 3) peripheral arterial disease (PAD); or 4) diabetes mellitus (DM) with CAD.

Study EIAN (ACCELERATE) will evaluate the potential of evacetrapib to reduce MACE in patients with HRVD and will evaluate the efficacy and safety profile of evacetrapib.

Clinical Protocol Synopsis: Study I1V-MC-EIAN (ACCELERATE)

Name of Investigational Product:
Evacetrapib (LY2484595)

Title of Study: Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes – the ACCELERATE Study

Number of Planned Patients:	**Phase of Development:** 3
Randomized: Approximately 11,000	

Length of Study: Approximately 24 months competitive enrollment; the study will continue until at least 1136 patients reach the primary composite endpoint; with at least 500 patients experiencing 1 or more of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke; and at least 1.5 years after the last patient entered treatment. The anticipated median duration of treatment is approximately 3 years, with >80% of patients expected to complete at least 2.5 years of follow-up. The anticipated maximum duration of treatment is expected to be up to 4 years.

Approximate first patient visit: Oct 2012 Approximate last patient visit: Sept 2016

Objectives: The primary objective of this study is to test the hypothesis that evacetrapib 130 mg daily, in comparison to placebo, reduces the incidence of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, coronary revascularization, or hospitalization for unstable angina (UA) in high-risk vascular disease (HRVD) patients.

The secondary objectives of the study are to test the hypotheses that evacetrapib 130 mg daily, in HRVD patients compared to placebo:

- Increases high-density lipoprotein-cholesterol (HDL-C) at 3 months after randomization
- Decreases low-density lipoprotein-cholesterol (LDL-C) at 3 months after randomization

Reduces the incidence of the following:

- A composite endpoint of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for UA
- Composite endpoint of CV death, MI, or coronary revascularization
- Composite endpoint of CV death, MI, stroke, or hospitalization for UA
- Composite endpoint of CV death, MI, or stroke
- Recurrence of any component of the primary composite endpoint among those who had already reached the primary endpoint
- Coronary revascularization
- MI
- CV death
- All-cause mortality
- Hospitalization for UA
- Stroke

The tertiary objectives of the study are to test the hypotheses that evacetrapib 130 mg daily in HRVD patients compared to placebo improves lipid profile at 3 months after randomization as measured by:

- Blood lipids (triglycerides [TG]), lipoproteins (non-HDL-C, very-low-density lipoproteins [VLDL-C]), apolipoproteins (Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo B)
- Lipoprotein(a)

Reduces the incidence of the following:

- Non-elective revascularization
- Elective revascularization

Exploratory objectives include:

- To explore the relationship between levels of lipids and the incidence of the primary endpoint
- To evaluate the effects of evacetrapib on exploratory biomarkers associated with the risk of

atherosclerosis, or glucose metabolism
- To characterize the pharmacokinetics (PK) of evacetrapib, explore potential factors that may influence the PK, and explore the association of PK with efficacy, biomarkers, and safety parameters

Other objectives will be outlined in the statistical analysis plan (SAP).
Health Economics objectives include:
- To compare evacetrapib to placebo with respect to major health care resource use, cumulative medical costs, and incremental cost effectiveness

Study Design: Study I1V-MC-EIAN (ACCELERATE) is a Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled, event-driven study with an estimated enrollment of 11,000 patients with HRVD. Patients with HRVD are defined as patients with at least 1 of the following: 1) history of ACS (≥30 days through 365 days after discharge for ACS); 2) cerebrovascular atherosclerotic disease; 3) peripheral arterial disease (PAD); or 4) diabetes mellitus (DM) with coronary artery disease (CAD).
Eligible patients in stable condition (as judged by the responsible physician) and who meet all entry criteria will be randomized to receive either evacetrapib 130 mg daily or placebo daily. Patients will receive, at the discretion of their treating physician, standard therapy for HRVD (for example, aspirin, antihypertensives, and antiplatelets, as dictated by local guidelines and standard of care). Standard therapy is expected to include appropriate diet and exercise and other nonpharmacologic measures. Patients will receive evidence-based management of LDL-C (and TG) to appropriate guideline-driven target levels throughout the study, and are to be on statin therapy throughout the study unless statin intolerant or contraindicated for statins. The anticipated median duration of treatment is approximately 3 years, with >80% of patients expected to complete at least 2.5 years of follow-up. All endpoints will be independently adjudicated by a Clinical Endpoints Committee (CEC). An independent Data Monitoring Committee (DMC) will review unblinded data to ensure patient safety during the conduct of the study.

Diagnosis and Main Criteria for Inclusion and Exclusions:
Patients with HRVD are defined by at least 1 of the following 4 groups. Note that an eligible patient may meet inclusion criteria for more than 1 group.

1) History of ACS (that is, ≥30 days through 365 days after discharge for ACS)

For the purposes of this study, ACS will include 1) unstable angina and non-ST-segment elevation myocardial infarction [UA/NSTEMI] and 2) ST-segment elevation myocardial infarction [STEMI] as follows:
- UA is defined as a history of chest discomfort or ischemic symptoms of ≥10 minutes duration at rest with persistent or transient ST-segment deviation ≥1 mm in 1 or more electrocardiogram (ECG) leads without elevation of creatine kinase-myocardial bands (CK-MB) or troponin T or I.
- NSTEMI is defined as a history of chest discomfort or ischemic symptoms of ≥10 minutes duration at rest with no evidence of persistent ST-segment elevation. Patients must also have CK-MB or troponin T or I greater than the 99th percentile upper reference limit or the upper limit of normal (ULN). If CK-MB or troponin is not available, total CK greater than 99th percentile upper reference limit (or ULN) is acceptable.
- STEMI is defined as a history of chest discomfort or ischemic symptoms of >20 minutes duration at rest with 1 of the following present on at least 1 electrocardiogram (ECG) prior to randomization:
  a) ST-segment elevation ≥1 mm in 2 or more contiguous ECG leads
  b) New or presumably new left bundle branch block (LBBB)
  c) ST-segment depression ≥1 mm in 2 anterior precordial leads with clinical history and evidence suggestive of true posterior infarction

Patients will have either undergone successful coronary revascularization associated with the ACS event prior to date of anticipated randomization or are not anticipated to undergo coronary revascularization.
Patients will NOT qualify for the trial on the basis of MI related to revascularization intervention (either percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery) performed outside the setting of an acute ACS.

2) Cerebrovascular Atherosclerotic Disease

- History of transient ischemic attack (TIA) or ischemic stroke (≥30 days) with carotid stenosis ≥50% in the distribution of the clinical event, **or**
- Asymptomatic carotid artery stenosis ≥70%, **or**
- A history of carotid artery revascularization

3) Peripheral Arterial Disease

Peripheral arterial disease (PAD) for this study will be defined as current intermittent claudication or resting limb ischemia and either an ankle-brachial index (ABI) ≤0.90, or a history of atherosclerotic limb ischemia leading to previous noncoronary revascularization or amputation.

Patients will NOT qualify for the trial on the basis of isolated renal artery stenosis in the absence of other inclusion criteria.

4) Diabetes Mellitus with Documented Coronary Artery Disease

Diabetes mellitus (DM) patients are defined as either receiving concomitant treatment with an oral or parenteral hypoglycemic agent and/or insulin, or being managed by diet alone, as a result of a preexisting diagnosis of DM. A new diagnosis is based on plasma glucose measurements or glycated hemoglobin (HbA1c) levels (with anticipated treatment with an oral or parenteral hypoglycemic agent and/or insulin, or to be managed by diet alone). Patients with DM must have CAD documented by a previous MI, PCI, CABG, or >50% angiographic stenosis of ≥1 major coronary artery.

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

[1] Males or females ≥18 years of age with a diagnosis of HRVD (that is, meet at least 1 of the disease diagnostic criteria described above), and are clinically stable (as judged by the responsible physician)

[2] Must be treated with a statin for at least 30 days prior to screening. If not treated with a statin, patients must have documented statin intolerance, or contraindication to statin (as defined in the protocol)

[3] Have a screening HDL-C ≤80 mg/dL (≤2.1 mmol/L)

[4] Have screening TG ≤400 mg/dL (≤4.5 mmol/L)

[5] Meet 1 of the following criteria:

a) screening LDL-C no more than 10 mg/dL (0.3 mmol/L) above the target chosen by the investigator (either LDL-C <100 mg/dL [<2.6 mmol/L] or LDL-C <70 mg/dL [<1.8 mmol/L])

OR

b) if LDL-C is greater than target, the patient must be on maximum tolerated statin dose (for at least 30 days), have documented statin intolerance, or contraindication to statin

[6] At the time of screening, are able and willing to give written informed consent

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

General Exclusion Criteria

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

[8] Are Lilly employees or are employees of the Academic Research Organization (ARO) or Clinical Research Organization (CRO) (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies but are not permitted to participate at a Lilly facility. Immediate family is defined above

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

[10] Have previously completed or withdrawn from this study, or withdrawn from any other study investigating evacetrapib

Medical Conditions Exclusion Criteria

[11] Females who are known to be pregnant

[12] Females who are breastfeeding

[13] Women of child-bearing potential only (that is, women who are not surgically or chemically sterilized and who are between menarche and 1 year postmenopause), who test positive for pregnancy between screening and randomization (based on the required urine or serum pregnancy test) or who do not agree to use a reliable method of birth control (specified in the Manual of Operations [MOO]) during the study

[14] History of TIA or ischemic stroke <30 days and ACS <30 days

[15] Any reading of systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at screening or randomization

[16] History of hemorrhagic stroke or intracranial hemorrhage

[17] New York Heart Association class III or IV congestive heart failure

[18] Serum creatinine >2.2 mg/dL (>194.5 μmol/L) at screening

[19] Clinically active liver disease (for example, esophageal varices, jaundice, ascites, cholestasis, acute or chronic hepatitis). Patients are not excluded due to Gilbert's Syndrome or a history of cholelythiasis/cholecystectomy

[20] History of malignancy (except for nonmelanoma skin cancer/basal cell or squamous cell carcinoma of the skin) within the preceding 3 years prior to screening

[21] Known malabsorption syndrome with the exception of lactose intolerance

[22] Patients with a known history of primary or secondary hyperaldosteronism

[23] Patients with a history of intolerance/hypersensitivity to CETP inhibitors

[24] Any clinically significant medical condition that according to the investigator could interfere with participation in the study

[25] Patients whose life expectancy is anticipated to be less than 4 years

[26] Unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study

[27] Have a history of drug, alcohol, or substance abuse within the past 6 months, as assessed by the investigator

Prior/Concomitant Therapy Exclusion Criteria

[28] Concurrent or anticipated need for treatment with niacin >250 mg/day

[29] Concurrent or anticipated need for chronic administration of drugs on the exclusion list in the MOO

[30] Previous exposure to (or participation in a trial of) the CETP inhibitors dalcetrapib or evacetrapib within the last 3 months or anacetrapib within the last 12 months.

Investigational Product, Dosage, and Mode of Administration: Evacetrapib 130 mg/day, given once daily orally

Planned Duration of Treatment:

The anticipated minimum duration of treatment is 1.5 years. The anticipated maximum duration of treatment is expected to be up to 4 years.

Reference Therapy, Dose, and Mode of Administration: Placebo, given daily orally

Criteria for Evaluation:

Efficacy:

Primary: Time to first occurrence of any component of the composite cardiovascular (CV) events of death, myocardial infarction (MI), stroke, coronary revascularization, or hospitalization for unstable angina (UA).

Secondary:

- Compared to placebo:
  - Percent change from baseline of mean HDL-C levels at 3 months after randomization
  - Percent change from baseline of mean LDL-C levels at 3 months after randomization
- Time to first occurrence of:
  - A composite endpoint of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for UA
  - Composite endpoint of CV death, MI, or coronary revascularization
  - Composite endpoint of CV death, MI, stroke, or hospitalization for UA
  - Composite endpoint of CV death, MI, or stroke
- Time to first recurrence of:
  - Any component of the primary composite endpoint among those who had already reached the primary endpoint
- Time to first occurrence of:
  - Coronary revascularization
  - MI
- Time to:
  - CV death
  - All-cause mortality
- Time to first occurrence of:
  - Hospitalization for UA
  - Stroke

Tertiary:

- Comparison to placebo for:
  - Percent change from baseline 3 months after randomization of blood lipids (TG), lipoproteins (non-HDL-C, VLDL-C), apolipoproteins (Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo B)
  - Lipoprotein(a)
- Time to first occurrence of:
  - Non-elective revascularization
  - Elective revascularization

Exploratory:

- The incidence of the primary endpoints by the quartile of lipid levels at 3 months following randomization will be measured to explore the relationship between levels of lipids and the incidence of the primary endpoint
- The effects of evacetrapib on exploratory biomarkers associated with the risk of atherosclerosis (for example, high-sensitivity C-reactive protein [hsCRP]) or glucose metabolism (for example, insulin) will be evaluated
- Measures to characterize the PK of evacetrapib, explore potential factors that may influence the PK, and explore the association of PK with efficacy, biomarkers, and safety parameters will be outlined in the PK/PD analysis plan

Safety:

Safety evaluations will be performed by recording treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and by monitoring laboratory parameters, physical examinations, ECGs and vital signs including systolic and diastolic blood pressure and pulse rate.

Population Pharmacokinetics (Pop PK): Venous blood samples will be obtained to measure the plasma concentrations of evacetrapib in approximately 2400 patients in the study, at select sites.
Health Economics: The long-term cost effectiveness of evacetrapib will be examined.

Statistical Methods:
Statistical:
This is an event-driven study. The study will be continued until all of the following criteria are satisfied: 1) at least 1136 patients experience 1 or more components of the primary composite endpoint of CV death, MI, stroke, coronary revascularization, or hospitalization for UA; 2) at least 500 patients experience 1 or more components of the composite endpoint of CV death, MI, or stroke; 3) at least 1.5 years have elapsed from the date of last patient randomized. The study design provides 90% power to detect a 17.5% relative risk reduction for the primary composite endpoint at an alpha of 0.05. The log-rank test will be used for comparing the distribution of time to first occurrence of the primary endpoint between evacetrapib and placebo. Based on evidence from previous trials, the incidence of the primary composite endpoint is anticipated to be 5% per year in the placebo arm. Accounting for lost exposure due to patient withdrawal of consent to further follow up, it is expected that the average follow up of 2.5 years per patient and the study will enroll an estimated 11,000 patients to ensure 1136 patients reaching the primary endpoint at study end.
The actual number of patients enrolled is to be guided by the predictions-based observed-aggregate event accrual during the trial.
Two key analysis datasets are of interest: the intent-to-treat (ITT) set consisting of all randomized subjects and the treated set consisting of subjects receiving at least 1 dose of study drug. All endpoints that occur between randomization and end of follow up will be included, whether or not they occur while the patient is taking study drug.
Time to event is defined as the time from randomization to the onset of the endpoint for efficacy endpoints. Estimating cumulative hazard will be via the Kaplan-Meier method, unless otherwise specified, and comparison of cumulative hazard functions will be based on the log-rank test. The estimates of hazard ratio, under the assumption of proportional hazards, and corresponding confidence intervals will be based on Cox proportional hazards regression analysis. The potential influence of baseline risk factors, additively or interactively, will be assessed using the Cox proportional hazards regression.
All confidence intervals will be 2-sided with a 95% confidence level, and all hypothesis tests will be evaluated at 2-sided significance level of 0.05.
Descriptive summaries for interval scale variables will include number of patients with evaluable information, mean, standard deviation, median, first, and third quartile. Descriptive summaries for categorical scale variables will include number of patients with evaluable information and percentage based on number of patients with evaluable information.
The choice of statistical tests used for comparing evacetrapib and placebo will be guided by the hypothesis and the type of measurement: Fisher's exact for comparing proportions, Pearson's chi-square test for comparing distributions of nominal categorical scale measurements, Cochran-Mantel Haenszel (CMH) row mean-score test comparing medians of ordinal scale measurements, 2-sample t-test for comparing means of interval scale measurements, and the log-rank test for comparing distributions of time to first event.
The DMC is authorized to review results of analyses by therapy prior to database lock. The DMC, with membership external to and independent from the Sponsor, ARO, and CRO, will be charged with ensuring patient safety during the conduct of the trial. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients. The study team will remain blinded until final database is locked, unless the study is prematurely terminated for adverse safety or futility. The first scheduled DMC review will occur approximately 3 months after first patient visit and every 3 months until 1000 patients have been followed for 6 months. Thereafter, DMC reviews will be every 6 months throughout the study. Tabular summaries of clinical endpoint events (reported and adjudicated) including deaths, MIs, strokes, coronary revascularizations, hospitalization for

UA, selected potentially clinically significant laboratory values, AEs, SAEs, discontinuations due to AEs, and other relevant safety information by treatment group will be sent to the DMC by a statistician external to and independent from the Sponsor, the ARO, and the CRO.

Planned interim analyses will be performed to evaluate the need for early termination of the study for adverse safety of evacetrapib or lack of efficacy of evacetrapib. The study will not be terminated for superior efficacy benefit of evacetrapib since the drug is not currently commercially available. Details of membership, operations, and the communication plan will be documented in the DMC Charter.

Population Pharmacokinetics:

All plasma evacetrapib concentration-time data will be pooled and evaluated by a population pharmacokinetic (popPK) approach. A covariate screen of patient and study-specific factors will be included in the analyses based on those factors investigated in previous and ongoing PK analyses and those appropriate for the target population. Exploratory and model-based analyses examining the relationships between evacetrapib exposure and lipid endpoints such as HDL-C and LDL-C will be conducted. Other analyses of efficacy and safety outcome measures may also be assessed as scientifically appropriate and warranted by available data.

Health Economics:

The prospective economic and quality-of-life portion of the study will be conducted to detect differences between treatment groups in medical resource use and cost. The analysis will involve a comparison between treatment groups of medical care resource use and cost for the period of follow-up in the study. Overall resource use patterns in the study will be quantified by attaching United States cost weights to resource use variables for all subjects in the study. If evacetrapib is found to increase both effectiveness and cost, a long-term cost effectiveness analysis that assesses the incremental cost of evacetrapib per quality-adjusted life-year gained will be performed.

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Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes – the ACCELERATE Study

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4. Abbreviations and Definitions

Term	Definition
ABI	ankle-brachial index
ACC	American College of Cardiology
ACS	acute coronary syndrome
ADA	American Diabetes Association
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AHA	American Heart Association
ALT/SGPT	alanine aminotransferase/serum glutamate pyruvate transaminase
Apo A-I, A-II, C-II, C-III, E, B	apolipoproteins
ARO	Academic Research Organization
AST/SGOT	aspartate aminotransferase
ATC classification system	Anatomical Therapeutic Chemical classification system
AUC	area under the plasma concentration-time curve
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAD	coronary artery disease

case report form (CRF) and electronic case report form (eCRF)	Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CE	cholesterol ester
CEC	Clinical Endpoints Committee
CETP	cholesterol ester transfer protein
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CK-MB	creatine kinase-myocardial bands
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
Cmax	the maximum plasma concentration of the drug
CMH	Cochran-Mantel Haenszel
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
Cr	creatinine
CRO	Contract Research Organization
CRP	C-reactive protein
cTnI and T	cardiac troponin I and T
CV	cardiovascular
D/C	discontinuation
DM	diabetes mellitus
DMC	Data Monitoring Committee

ECG	electrocardiogram
eCRF	electronic case report form
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result. Effectiveness is the measure of the produced effect of an intervention when carried out in a clinical environment.
end of study (trial)	End of study (trial) is the date of the last visit or last scheduled follow-up procedure shown in the Study Schedule for the last active subject in the study.
enroll/randomize	The act of assigning a patient to a treatment. Patients who are enrolled/randomized in the trial are those who have been assigned to a treatment.
enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D	EuroQol-5 dimensions
ERB	Ethics Review Board (see IRB/ERB)
FFR	fractional flow reserve
FOIA	Freedom of Information Act
F/U	follow-up
GGT	gamma-glutamyl transferase
GCP	good clinical practices
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HbA1c	hemoglobin A1c
HMG-CoA reductase inhibitors	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors
HRVD	high-risk vascular disease
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug application

institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
intention to treat (ITT)	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IVRS	interactive voice-response system
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
L/V	last visit
MACE	major adverse cardiovascular events
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MOO	Manual of Operations
Non-HDL-C	non-high density lipoprotein cholesterol
NSTEMI	non-ST-segment elevation myocardial infarction
PAD	peripheral arterial disease
patient	A study participant who has the disease or condition for which the investigational product is targeted.

PCI	percutaneous coronary intervention
PK/PD	pharmacokinetics/pharmacodynamics
popPK	population pharmacokinetics
RBC	red blood cell
QCA	quantitative coronary angiography
QD	once daily
Randomize/enroll	The act of assigning a patient to a treatment. Patients who are enrolled/randomized in the trial are those who have been assigned to a treatment.
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SMQ	Standardized MedDRA Query
STEMI	ST-segment elevation myocardial infarction
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
TC	total cholesterol
TIA	transient ischemic attack
TPO	third-party organization
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TG	triglycerides
UA	unstable angina
U/A	urinalysis
US	United States

V	visit
VLDL	very-low-density lipoprotein
VLDL-C	very-low-density lipoprotein cholesterol

Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes – the ACCELERATE Study

5. Introduction

Lowering of low-density lipoprotein cholesterol (LDL-C) by HMG-CoA reductase inhibitors (statins) has demonstrated 20% to 35% relative reductions in cardiovascular (CV) events across a spectrum of clinical presentations. However, atherosclerosis remains a major health burden in developed societies and is an emerging problem in underdeveloped countries, with residual risk for CV events remaining an unmet medical need. The observed residual risk for cardiac events in statin patients (Cannon et al. 2004; PROVE IT-TIMI 22) raises the possibility that additional benefit may be achievable with further modification of lipid levels.

High-density lipoprotein cholesterol (HDL-C) is an emerging target for lipid modification. Based on substantial epidemiological evidence, HDL-C levels are inversely correlated with CV disease risk and have been shown to be a critical determinant of CV risk independent of levels of LDL-C (Castelli et al. 1986; Brown et al. 2001; Robins et al. 2001; Barter et al. 2007; deGoma et al. 2008). This relationship is also observed in studies of medical intervention. Despite the lowering of LDL-C levels by statins, low HDL-C is associated with increased CV risk in patients with coronary artery disease (CAD) (Drexel et al. 2006).

Potential antiatherogenic properties of HDL include promotion of reverse cholesterol transport, antiapoptotic effects, inhibition of platelet activation and coagulation cascade, anti-inflammatory and anti-oxidant effects, and enhancement of endothelial function. Raising HDL-C in patients may provide an additional strategy for addressing residual CV risk.

Inhibition of cholesteryl ester transfer protein (CETP) represents a potent mechanism for increasing HDL-C concentration. CETP is a plasma glycoprotein primarily secreted from the liver that mediates the transfer of cholesteryl ester (CE) from HDL to Apo B-rich lipoproteins, including LDL and very-low-density lipoprotein (VLDL), in exchange for triglycerides (TG), as well as transfer of TG/CE between Apo B-rich lipoproteins (Barter et al. 2003). The mechanism of action of lipid changes with CETP inhibitors differs from the mechanism of action with statins.

The pharmacodynamic (PD) effect of CETP inhibition has been tested in clinical trials with several CETP inhibitors, including torcetrapib (CP-529,414), anacetrapib (MK-0859), and dalcetrapib (JTT-705). Clinical trials clearly demonstrate that CETP inhibition results in increased HDL-C, and with more potent agents decreased LDL-C; however, the hypothesis that increasing HDL-C by inhibiting CETP reduces the risk of CV disease has yet to be confirmed in a clinical outcome trial.

Torcetrapib was the first oral CETP inhibitor to reach an advanced stage of clinical development. The clinical outcome trial, ILLUMINATE, was prematurely stopped due to an excessive rate of mortality (Barter et al. 2007; Rader 2007). This comprised a numerically greater incidence of

death due to both CV and non-CV causes. Three clinical imaging trials also demonstrated that administration of torcetrapib did not slow progression of atherosclerosis within the coronary and carotid arteries (Bots et al. 2007; Kastelein et al. 2007; Nissen et al. 2007). Subsequent analysis revealed evidence of slowing of disease progression with increasing levels of HDL-C, suggesting that an off-target toxicity was more likely to have contributed to the toxicity of torcetrapib, rather than a mechanism-related effect (Nicholls et al. 2008). The experience that torcetrapib elevated blood pressure, in combination with the finding that it promotes adrenal release of aldosterone and cortisol (Hu et al. 2009), points to potential molecule-specific toxicities of torcetrapib. Other CETP inhibitors under investigation or that have been under investigation (anacetrapib and dalcetrapib) did not show an elevated blood pressure or increased mineralocorticoid activity in Phase 2 data (Stein et al. 2009; Cannon et al. 2010 [DEFINE]), adding to the suggestion of an off-target toxicity with torcetrapib.

Evacetrapib (LY2484595) is a potent, selective inhibitor of CETP that has demonstrated an ability to inhibit CETP activity, increase HDL-C, and decrease LDL-C in healthy subjects. Evacetrapib has been evaluated in a number of Phase 1 completed studies to date. The completed studies are I1V-MC-EIAA (EIAA, single-dose dose-escalation study), I1V-MC-EIAB (EIAB, multiple ascending-dose, drug-drug interaction study), I1V-JE-EIAD (EIAD, multiple-dose, ascending-dose study in healthy Japanese subjects), I1V-MC-EIAG (EIAG, relative bioavailability study), I1V-MC-EIAH (EIAH, a disposition [^{14}C] study), and I1V-MC-EIAI (EIAI, new-formulation study).

A Phase 2 study, Study I1V-MC-EIAF (EIAF), conducted by the Sponsor, has been completed and demonstrated significant increases in HDL-C and decreases in LDL-C in patients with hypercholesterolemia or low HDL-C treated with evacetrapib administered as monotherapy and in combination with atorvastatin, simvastatin, or rosuvastatin for 12 weeks. Data demonstrated evacetrapib to be safe and well tolerated. This was the first study of evacetrapib in a patient population. A further Phase 2 study I1V-JE-EIAE (EIAE) in Japanese patients is currently ongoing.

This Phase 3 study, Study EIAN (ACCELERATE), will assess the safety and efficacy of evacetrapib in patients with high-risk vascular disease (HRVD) defined as patients with at least 1 of the following: 1) history of acute coronary syndrome (ACS) (≥30 days through 365 days after discharge for ACS); 2) cerebrovascular atherosclerotic disease; 3) peripheral arterial disease (PAD); or 4) diabetes mellitus (DM) with CAD.

Acute coronary syndrome (ACS) encompasses unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Patients with UA/NSTEMI and STEMI share the underlying pathophysiological mechanism of ruptured atherosclerotic plaque with superimposed thrombosis and distal embolization, and are at heightened risk of recurring CV events (American College of Cardiology/American Heart Association [ACC/AHA] Task Force on Practice Guidelines and the European Society of Cardiology [ESC] Task Force on the Management of Acute Coronary Syndrome) (Braunwald et al. 2002).

Patients with a history of ACS, and with other manifestations of atherosclerotic disease, such as patients with cerebrovascular atherosclerotic disease, PAD, and CAD patients with DM, are at heightened risk of thrombotic events. Ischemic strokes can result from vessel occlusion arising from atherosclerosis in patients with cerebrovascular atherosclerotic disease. Patients with PAD, atherosclerosis of noncoronary arteries, are at high-risk of secondary CV death and events such as MI or stroke. The prognosis is correlated with the severity of the PAD, and PAD carries a greater than 20% risk of a coronary event in 10 years (Shammas et al. 2007). Diabetes mellitus is also a major risk factor for patients with CAD, with DM patients having a higher risk of CV events and death than those without DM (Malmberg et al. 2000).

Patients across the spectrum of vascular disease, including patients with a history of ACS, cerebrovascular atherosclerotic disease, PAD, and DM with CAD, have similar pathophysiology, with atherosclerosis often the underlying cause, and similar long-term residual risk of CV events. Imaging trials of the effects of statins on atherosclerosis have demonstrated a significant correlation between LDL-C lowering and atherosclerosis regression (Yanai et al. 2007). This, combined with a history of lipid-modulating therapy shown to work across the spectrum of disease (for example, Shepherd et al. 1995; Downs et al. 1998; PROVE-IT TIMI 22 study, Cannon et al. 2004) suggests a lipid-modulation target mechanism of action may be similar in all patients. This provides an expectation that evacetrapib could be used to treat HRVD patients with different clinical histories as they have a common atherosclerotic pathogenesis, not affected by existing therapies.

High-risk vascular disease patients were chosen for this study as a largely homogeneous population with underlying pathophysiology, and thus are expected to have similar long-term event rates. The event rates in this study are expected to be similar between patients with a history of ACS (≥30 days through 365 days after discharge for ACS), in patients cerebrovascular atherosclerotic disease, in PAD patients, and in DM patients with CAD, based on evidence from previous trials (Cannon et al. 2004; Bhatt et al. 2006; Barter et al. 2007; Wiviott et al. 2007; Wallentin et al. 2009).

Study EIAN (ACCELERATE) will test the hypothesis that evacetrapib 130 mg daily, in comparison to placebo, will reduce the incidence of the composite endpoint of CV death, MI, stroke, coronary revascularization, or hospitalization for UA in HRVD patients.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the study drug may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure will be assessed by the Sponsor in aggregate periodically during the course of the study and may be found in Section 6 (Effects in Humans) of the IB.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to test the hypothesis that evacetrapib 130 mg daily, in comparison to placebo, reduces the incidence of the composite end point of cardiovascular (CV) death, myocardial infarction (MI), stroke, coronary revascularization, or hospitalization for unstable angina (UA) in high-risk vascular disease (HRVD) patients.

6.2. Secondary Objectives

The secondary objectives of the study are to test the hypotheses that evacetrapib 130 mg daily in HRVD patients compared to placebo:

- Increases HDL-C at 3 months after randomization
- Decreases LDL-C at 3 months after randomization

Reduces the incidence of the following:

- A composite endpoint of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for UA
- Composite endpoint of CV death, MI, or coronary revascularization
- Composite endpoint of CV death, MI, stroke, or hospitalization for UA
- Composite endpoint of CV death, MI, or stroke
- Recurrence of any component of the primary composite endpoint among those who had already reached the primary endpoint
- Coronary revascularization
- MI
- CV death
- All-cause mortality
- Hospitalization for UA
- Stroke

6.3. Tertiary Objectives

The tertiary objectives of the study are to test the hypotheses that evacetrapib 130 mg daily in HRVD patients compared to placebo improves lipid profile at 3 months after randomization as measured by:

- Blood lipids (TG), lipoproteins (non-HDL-C, VLDL-C), apolipoproteins (Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo B)
- Lipoprotein(a)

Reduces the incidence of:

- Non-elective revascularization
- Elective revascularization

6.4. Exploratory Objectives

Exploratory objectives include:

- To explore the relationship between levels of lipids and the incidence of the primary endpoint
- To evaluate the effects of evacetrapib on exploratory biomarkers associated with the risk of atherosclerosis, or glucose metabolism
- To characterize the pharmacokinetics (PK) of evacetrapib, explore potential factors that may influence the PK, and explore the association of PK with efficacy, biomarkers, and safety parameters

Other objectives will be outlined in the statistical analysis plan (SAP).

6.5. Health Economics Objectives

Health economics objectives include:

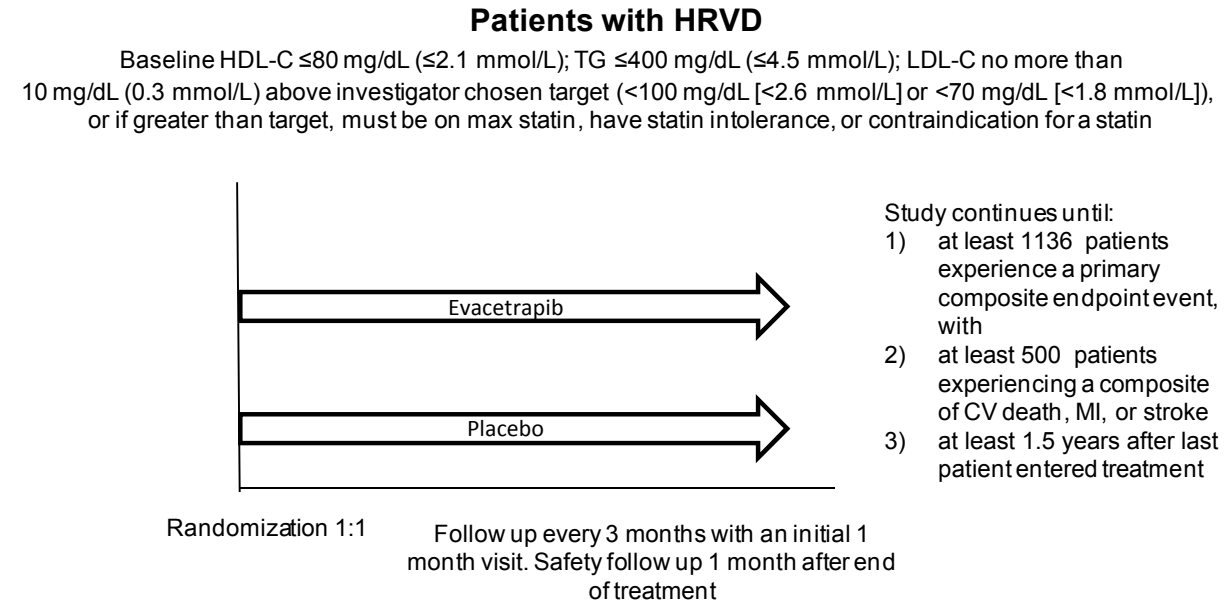
- To compare evacetrapib to placebo with respect to major health care resource use, cumulative medical costs, and incremental cost effectiveness

7. Investigational Plan

7.1. Summary of Study Design

Study I1V-MC-EIAN (ACCELERATE) is a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled event-driven study with an estimated enrollment of approximately 11,000 patients with HRVD.

Patients with HRVD include patients with at least 1 of the following: 1) history of ACS (≥30 days through 365 days after discharge for ACS); 2) cerebrovascular atherosclerotic disease; 3) PAD; or 4) DM with CAD. Figure EIAN.7.1 illustrates the study design.



Abbreviations: CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HRVD = high-risk vascular disease; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TG = triglycerides.

Figure EIAN.7.1. Illustration of study design for clinical protocol I1V-MC-EIAN.

Following signing of an informed consent form (ICF) prior to any study procedures (Visit 1), eligible patients in stable condition (as judged by the responsible physician), and who meet all the entry criteria, will be randomized to receive either evacetrapib 130 mg daily or placebo daily at Visit 2. Baseline assessments will be taken at Visit 2. See Study Schedule (Attachment 1) for visit details. Patients will receive, at the discretion of their treating physician, standard therapy for HRVD (for example, aspirin, antihypertensives, and antiplatelets, as dictated by local guidelines and standard of care). Standard therapy is expected to include appropriate diet and

exercise and other nonpharmacologic measures. Patients must be treated with a statin for at least 30 days prior to screening. If a patient is not treated with a statin they must have documented statin intolerance, or contraindication for statins. Statin intolerance is defined as "unable to tolerate at least two statins at the lowest approved daily dose due to skeletal muscle related symptoms, for example, pain, aches, weakness, or cramping that began or increased during statin therapy and stopped when statin therapy was discontinued". Contraindication for a statin is according to the pertinent prescribing information.

Patients will be randomized at the site level in a 1:1 ratio to receive evacetrapib or placebo. Follow-up visits will occur every 3 months after randomization, with an initial follow-up visit at 30 days. There will be a safety follow-up visit approximately 30 days after end of treatment.

At the time of randomization, LDL-C must be at the target level as chosen by the investigator, of either LDL-C <100 mg/dL (<2.6 mmol/L) or LDL-C <70 mg/dL (<1.8 mmol/L) (allowing for expected variability of +10 mg/dL [+0.3 mmol/L]), or if LDL-C is greater than target, the patient must be on maximum tolerated statin dose (for at least 30 days), have documented statin intolerance, or have a contraindication for statins. Throughout the study, patients will receive evidence-based management of LDL-C (and TG) to appropriate guideline-driven target levels. At the time of protocol approval these targets are as follows: <100 mg/dL [<2.6 mmol/L] or <70 mg/dL [<1.8 mmol/L] based on NCEP ATP III and may be updated as necessary. Patients are to remain on statin therapy throughout the study unless statin intolerant or are contraindicated for statins.

While it is expected that every attempt will be made to manage a patient's LDL-C level, it is recognized that not all patients will be able to achieve the goal LDL-C during the course of the study due to adverse drug effect of concomitant medication. These patients will be expected to receive the maximal tolerated dose of statin or other allowable lipid-modifying therapy as recommended by local guidelines.

A lipid profile will be performed in a central laboratory at randomization, 4 weeks after randomization and at each subsequent on site visit. The members of the study team, including those from the Academic Research Organization (ARO), the Contract Research Organization (CRO), and the Sponsor, will remain blinded to the lipid levels. The investigators will generally not be notified of the results. If the patient's measured LDL-C is > +10 mg/dL (> +0.3 mmol/L) above the accepted target or TG are >500 mg/dL (>5.6 mmol/L), the investigator will be notified of the specific level that exceeds the target. Specific lipid management will be left to the investigator's discretion, including lifestyle changes (low-fat diet and exercise) and adjustment of allowable medication. In view of the magnitude of change in lipid profile anticipated in patients treated with active therapy, the investigator should not obtain lipid levels locally to avoid potential confounding.

The study will continue until at least 1136 patients reach the primary composite endpoint (with at least 500 patients reaching the composite endpoint of CV death, MI, or stroke) and all subjects have had the opportunity to be followed for 1.5 years. Approximately 11,000 patients are expected to be enrolled. The anticipated median duration of treatment is approximately 3 years,

with >80% of patients expected to complete at least 2.5 years of follow-up. The anticipated maximum duration of treatment is expected to be up to 4 years. This study will be conducted under the intent-to-treat (ITT) principle. All endpoints will be independently adjudicated by a Clinical Endpoints Committee (CEC) that will remain blinded to treatment assignment.

7.1.1. Screening

Preliminary assessment of eligibility will include review of medical history, pre-existing AEs, pertinent medical history, including HRVD profile, lipid levels (HDL-C, LDL-C, and TG), and concomitant medications.

Patients who fulfill initial criteria will come in for a screening visit (Visit 1). See Study Schedule (Attachment 1) for visit details. Patients will sign an ICF prior to any study procedure at Visit 1. Central labs will be drawn to determine if a patient qualifies based on screening labs (pregnancy tests will be completed locally, if required), and the site will review the inclusion and exclusion criteria with regards to medical history, vital signs, physical examination, and demographics as described in the protocol to confirm the patient's eligibility for the study. Patients who do not meet entry criteria may undergo one repeat screening visit at the investigators discretion.

7.1.2. Randomization and Active Treatment

If eligibility based on Visit 1 and corresponding laboratory results are confirmed, the patient will be randomized at Visit 2. Blood pressure measurements must be taken before randomization. The study window between Visit 1 and Visit 2 can be up to 45 days. During Visit 2, pertinent medical history, a physical exam, including vitals, and other procedures and assessments will be conducted as per Study Schedule (Attachment 1). If eligibility is confirmed, the appropriate study drug will be dispensed according to the randomization assignment as soon as possible after randomization. The patient is randomized to study drug assignment by calling the interactive voice response system (IVRS) system. Patients will be randomized at the site level in a 1:1 ratio to receive evacetrapib or placebo.

A 1-time collection of samples for DNA storage should be collected at Visit 2 (at time of randomization). If inadvertently not collected at Visit 2, a sample may be collected at a later visit.

Patients will return to the study site for follow-up visits at the end of 1, 3, 6, 9, and 12 months, with follow-up visits occurring every 3 months thereafter with every alternate visit occurring at the site for assessments as indicated by the Study Schedule (Attachment 1). Unscheduled visits may occur as indicated by the Study Schedule (Attachment 1), for example, for an AE. The anticipated minimum duration of a patient on treatment will be 1.5 years, and the anticipated maximum duration of treatment is expected to be up to 4 years.

Patients will complete a follow-up safety assessment approximately 1 month after the end of treatment as indicated in the Study Schedule (Attachment 1).

7.1.3. Study Operations and Medical Oversight

The Sponsor will assign the obligation of study operation management to a CRO – Covance. The Sponsor will assign the obligation of medical and scientific oversight to an ARO – Cleveland Clinic Coordinating Center for Clinical Research (C5Research).

A 24-hour global study Helpline will be established to ensure that medical questions and study operational questions can be answered by the ARO and the CRO. Throughout the study, the ARO and the CRO will maintain a call log where all issues and resolutions will be documented when a site is assisted.

All participating investigators and site staff will be provided the study Helpline contact information and instructed to direct all queries to the Helpline as the primary point of contact.

Additional study oversight will be provided by an Executive Committee and a Steering Committee. The members of the Executive Committee will serve as high-level advisors of the overall conduct of the study, in conjunction with the Sponsor. The Steering Committee will assist in the conduct of the study and, in particular, assist with local issues to support the quality implementation and conduct of the study worldwide.

7.2. Discussion of Design and Control

The study is designed and powered to evaluate the efficacy and safety of evacetrapib in patients with HRVD.

Patients with HRVD will be randomized in this study. Patients with HRVD are at heightened risk of CV thrombotic events. Based on substantial epidemiological evidence, HDL-C levels are inversely correlated with CV disease (Brown et al 2001; Robins et al. 2001; deGoma et al. 2008). As increasing HDL-C and decreasing LDL-C are the primary effects of potent CETP inhibitors, evacetrapib is hypothesized to reduce major adverse cardiovascular events (MACE) in patients who are at high risk for CV outcomes.

Patients with a history of ACS, cerebrovascular atherosclerotic disease, PAD, and DM with CAD are all at high risk of recurrent vascular events by a common underlying pathophysiology of acute or chronic progression of atherosclerotic plaque. Given the epidemiologic and experimental evidence associating favorable lipid profile with fewer MACE, these patients may benefit from the effect of CETP inhibition. Based on evidence from previous trials (Cannon et al. 2004; Bhatt et al. 2006; Barter et al. 2007; Wiviott et al. 2007; Wallentin et al. 2009), the event rates in this study are expected to be similar between the patient groups.

A single dose of evacetrapib will be studied against placebo on a background of standard medications, including statins. This will put into perspective the reduction in incidence of CV endpoints against the current standard of care. This is a placebo-controlled study as no CETP inhibitors are currently on the market to use as an active comparator. Placebo patients will be receiving the current standard of care for HRVD patients.

Patients must have HDL-C ≤80 mg/dL (≤2.1 mmol/L) to be included in the study as HDL-C >80 mg/dL is high enough to avoid enrolling patients with homozygous CETP gene deficiency.

Patients who have HDL-C levels of 60 to 80 mg/dL [1.6 to 2.1 mmol/L] are enrolled in this study as high levels of HDL-C are associated with reduced risk for coronary heart disease, even in the presence of elevated LDL-C (Castelli 1988). Patients must have TG ≤400 mg/dL (≤ 4.5 mmol/L) to be included in the study because patients with high TG levels (TG >400 mg/dL [>4.5 mmol/L]) may require treatment that may have a significant effect on HDL-C, which could potentially confound the study. Patients must have LDL-C at investigator-chosen target level, either LDL-C <100 mg/dL (<2.6 mmol/L) or LDL-C <70 mg/dL (1.8 mmol/L) (allowing for expected variability of +10 mg/dL [+0.3 mmol/L]) to be included in the study unless the patient is on maximum tolerated statin dose (for at least 30 days), has documented statin intolerance, or statins are clearly contraindicated, as requiring patients to be at target level of LDL-C at baseline will reduce the need to add other medications for LDL-C lowering more frequently in the placebo arm postrandomization, and minimize potential bias. For patients who are on maximal tolerated statin dose (for at least 30 days), those who are intolerant of statins, or in whom statin is contraindicated, a LDL-C at baseline of greater than target is acceptable, since those patients have potential to benefit from additional LDL-C reduction with evacetrapib.

Patients are to be treated with evidence-based management of LDL-C by statins, as statins effectively lower LDL-C and attenuate CV risk (Baigent et al. 2010).

Lipid results will be generally blinded to investigators and study team mainly to avoid knowledge of the HDL-C and LDL-C levels during the study. Knowledge of lipids does not unblind, but investigators and the study team may try to guess the treatment assignment, since in general, patients on active therapy will have higher HDL-C, and lower LDL-C than placebo patients. Because there are targets for LDL-C, the investigator will be notified if the target is exceeded so that therapy may be adjusted if appropriate. This will not unblind the investigator, since some patients on active therapy may also exceed the target level. There is no lower target level for LDL-C, so there will be no notification to the investigator of any level of LDL-C other than if the upper level is exceeded. Investigators will not be notified of HDL-C levels as there is no target level for HDL-C. As high levels of TG pose a potential safety risk for pancreatitis, it is reasonable to alert investigators to these levels over 500 mg/dL (>5.6 mmol/L).

As increases in mean systolic and diastolic blood pressure, increases in serum bicarbonate, sodium and aldosterone, and decreases in serum potassium have been observed in Phase 3 studies conducted with another CETP inhibitor (torcetrapib) (Barter et al. 2007; Rader 2007), these parameters will be monitored in this study to ensure patient safety by an independent Data Monitoring Committee (DMC).

The safety follow-up, 1 month after stopping treatment, is included to evaluate any AEs occurring after treatment is stopped.

8. Study Population

Screened patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized at Visit 2.

Study participants should be instructed not to donate blood or blood products during the study or for 4 weeks following the last dose of study drug.

8.1. Inclusion Criteria

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

[1] Males or females ≥18 years of age with a diagnosis of HRVD (that is, meet at least one of the disease diagnostic criteria described in Section 8.1.1 below), and are clinically stable (as judged by the responsible physician)

[2] Must be treated with a statin for at least 30 days prior to screening. If not treated with a statin must have documented statin intolerance, or contraindication to statin (see Section 7.1 for the definitions of statin intolerance and contraindication to statin)

[3] Have a screening HDL-C ≤80 mg/dL (≤2.1 mmol/L)

[4] Have screening TG ≤400 mg/dL (≤4.5 mmol/L)

[5] Meet 1 of the following criteria:

a) screening LDL-C no more than 10 mg/dL (0.3 mmol/L) above the target chosen by the investigator (either LDL-C <100 mg/dL [<2.6 mmol/L] or LDL-C <70 mg/dL [<1.8 mmol/L]),

OR

b) if LDL-C is greater than target, the patient must be on maximum tolerated statin dose (for at least 30 days), have documented statin intolerance, or contraindication to statin

[6] At the time of screening, are able and willing to give written informed consent

8.1.1. Disease Diagnostic Criteria

Patients with HRVD are defined by at least 1 of the following 4 groups. Note that an eligible patient may meet inclusion criteria for more than 1 group:

1) History of ACS (that is, ≥30 days through 365 days after discharge for ACS)

For the purposes of this study, ACS will include: 1) UA/NSTEMI and 2) STEMI as follows:

- Unstable angina (UA) is defined as a history of chest discomfort or ischemic symptoms of ≥10 minutes duration at rest with persistent or transient ST-segment deviation ≥1 mm in 1 or more ECG leads without elevation of creatine kinase-myocardial bands (CK-MB) or troponin T or I.

- Non-ST-segment elevation myocardial infarction (NSTEMI) is defined as a history of chest discomfort or ischemic symptoms of ≥10 minutes duration at rest with no evidence of persistent ST-segment elevation. Patients must also have CK-MB or troponin T or I >99th percentile upper reference limit, or the ULN. If CK-MB or troponin are not available, total CK >99th percentile upper reference limit (or ULN) is acceptable.
- ST-segment elevation myocardial infarction (STEMI) is defined as a history of chest discomfort or ischemic symptoms of >20 minutes duration at rest with 1 of the following present on at least 1 ECG prior to randomization:
  a) ST-segment elevation ≥1 mm in 2 or more contiguous ECG leads
  b) New or presumably new left bundle branch block (LBBB)
  c) ST-segment depression ≥1 mm in 2 anterior precordial leads with clinical history and evidence suggestive of true posterior infarction

Patients will have either undergone successful coronary revascularization associated with the ACS event prior to date of anticipated randomization or are not anticipated to undergo coronary revascularization.

Patients will NOT qualify for the trial on the basis of MI related to revascularization intervention (either percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery) performed outside the setting of an acute ACS.

2) Cerebrovascular Atherosclerotic Disease

- History of transient ischemic attack (TIA) or ischemic stroke (≥30 days) with carotid stenosis ≥50% in the distribution of the clinical event
  Or
- Asymptomatic carotid artery stenosis ≥70%
  Or
- A history of carotid artery revascularization

3) Peripheral Arterial Disease

Peripheral arterial disease (PAD) for this study will be defined as current intermittent claudication or resting limb ischemia and either an ankle-brachial index (ABI) ≤0.90, or history of atherosclerotic limb ischemia leading to previous noncoronary revascularization or amputation. Patients will NOT qualify for the trial on the basis of isolated renal artery stenosis in the absence of other inclusion criteria.

4) Diabetes Mellitus with Documented Coronary Artery Disease

Diabetes mellitus (DM) patients are defined as either receiving concomitant treatment with an oral or parenteral hypoglycemic agent and/or insulin or being managed by diet alone, as a result of a preexisting diagnosis of DM. A new diagnosis is based on plasma glucose measurements or glycated hemoglobin (HbA1c) levels (see Attachment 4 for criteria) (with anticipated treatment

with an oral or parenteral hypoglycemic agent and/or insulin or to be managed by diet alone). Patients with DM must have CAD documented by a previous MI, PCI, CABG, or >50% angiographic stenosis of ≥1 major coronary artery.

8.2. Exclusion Criteria

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

General Exclusion Criteria

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

[8] Are Lilly employees or are employees of the ARO or CRO (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies but are not permitted to participate at a Lilly facility. Immediate family is defined above

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

[10] Have previously completed or withdrawn from this study, or withdrawn from any other study investigating evacetrapib

Medical Conditions Exclusion Criteria

[11] Female patients who are known to be pregnant

[12] Female patients who are breastfeeding

[13] Women of child-bearing potential only (that is, women who are not surgically or chemically sterilized and who are between menarche and 1 year postmenopause), who test positive for pregnancy between screening and randomization (based on the required urine or serum pregnancy test), or who do not agree to use a reliable method of birth control (specified in the Manual of Operations [MOO]) during the study

[14] History of TIA or ischemic stroke <30 days and ACS <30 days

[15] Any reading of systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at screening or randomization

[16] History of hemorrhagic stroke or intracranial hemorrhage

[17] New York Heart Association class III or IV congestive heart failure (Attachment 5)

[18] Serum creatinine >2.2 mg/dL (>194.5 μmol/L) at screening

[19] Clinically active liver disease (for example, esophageal varices, jaundice, ascites, cholestasis, acute or chronic hepatitis). Patients are not excluded due to Gilbert's Syndrome or a history of cholelythiasis/cholecystectomy

[20] History of malignancy (except for nonmelanoma skin cancer/basal cell or squamous cell carcinoma of the skin) within the preceding 3 years prior to screening

[21] Known malabsorption syndrome with the exception of lactose intolerance

[22] Patients with a known history of primary or secondary hyperaldosteronism

[23] Patients with a history of intolerance/hypersensitivity to CETP inhibitors

[24] Any clinically significant medical condition that according to the investigator could interfere with participation in the study

[25] Patients whose life expectancy is anticipated to be less than 4 years

[26] Unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study

[27] Have a history of drug, alcohol, or substance abuse within the past 6 months, as assessed by the investigator

Prior/Concomitant Therapy Exclusion Criteria

[28] Concurrent or anticipated need for treatment with niacin >250 mg/day

[29] Concurrent or anticipated need for chronic administration of drugs on the exclusion list in the MOO

[30] Previous exposure to (or participation in a trial of) the CETP inhibitors dalcetrapib or evacetrapib within the last 3 months or anacetrapib within the last 12 months

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criteria [7] through [10] reduce the potential bias that may be introduced at study site and ensure that patients are able and willing to participate in the study and to follow the protocol schedules and procedures with adequate informed consent. Exclusion criteria [11] to [14], [19], [23], [24], [26], and [27] exclude patients with medical conditions that may increase the risk of this treatment; and exclusion criteria [15] to [18], [20] to [22], and [25] exclude conditions that may bias the interpretation of the endpoints in this study. Exclusion criteria [28] through [30] limit therapies that may confound the analysis of this study.

8.3. Discontinuations

8.3.1. Patients Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. In the rare case where a patient who does not meet enrollment criteria is inadvertently enrolled, the study Helpline should be

contacted within 24 hours of identification. If it is determined after discussion with the study Helpline that, in considering patient safety, it is appropriate to continue study drug (documentation of this is necessary), the patient will continue on study drug and be monitored for all visits and testing (including laboratory measures) for the duration of the study. If after discussion with the study Helpline it is determined that the patient should not continue study drug, study drug will be discontinued, but the patient will remain in the study to be evaluated for efficacy endpoints and AEs until the patients last planned visit, or for 1.5 years following the last dose of study drug (or from the time of randomization if study drug was never initiated), whichever occurs first.

Patients inadvertently enrolled under the following exclusion criteria should be discontinued from study drug (but remain in the study):

- Female patients who are pregnant or are breastfeeding or who do not agree to use a reliable method of birth control during the study
- Clinically active liver disease (for example, esophageal varices, jaundice, ascites, cholestasis, acute or chronic hepatitis). Patients are not excluded due to Gilbert's Syndrome or a history of cholelythiasis/cholecystectomy
- Patients with a history of intolerance/hypersensitivity to other CETP inhibitors
- Any clinically significant medical condition that according to the investigator could interfere with participation in of the study
- Unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study
- Have a history of drug, alcohol, or substance abuse within the past 6 months, as assessed by the investigator

If a patient stops study drug for any of the above exclusion criteria following discussion with the study Helpline, then investigators should notify Lilly or designee. The reason for the patient's inadvertent enrollment should be documented in the electronic case report form (eCRF).

8.3.2. Temporary Discontinuation of Study Drug

There may be situations in which study drug is temporarily discontinued. Study drug should be restarted as soon as possible based on investigator judgment. The dates of study drug discontinuation and restart, and the reason for temporary discontinuation, should be documented in the eCRF. Investigators should contact the study Helpline if study drug is temporarily discontinued. Study Helpline contact should occur prior to study drug discontinuation if possible.

8.3.3. Permanent Discontinuations of Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue study drug. Investigators should contact the study Helpline prior to permanent study drug discontinuation. In keeping with the ITT analysis, the patient will not be permanently discontinued from the study.

If study drug is permanently discontinued, the patient will remain in the study to be evaluated for efficacy endpoints and AEs until the planned termination visit, or for 1.5 years following the last dose of study drug whichever occurs first. If the patient is unwilling or unable to return for follow-up visits in person, the site should attempt to collect as much follow-up information as possible.

The reason for permanent discontinuation of study drug should be documented in the eCRF. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- In the opinion of the investigator, any AE or a significant change in a laboratory value that warrants permanent discontinuation of study drug therapy. Investigators are advised to call the study Helpline (and subsequently discuss with the Helpline) prior to making such a decision
- Female patients who are pregnant or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug
- The patient requests to stop study drug permanently
- The patient study blind is broken

8.3.4. Patient Discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be uncommon, occurring if the patient withdraws consent, or if enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, occurs.

At the time of discontinuing from the study, the study Helpline and IVRS should be contacted, and, if possible, an early discontinuation visit should be conducted, as shown in the Study Schedule (Attachment 1). Refer to the MOO for process details. The patient will be permanently discontinued both from the study drug and from the study at that time. During the study close-out period, survival status will be collected within legal and ethical boundaries for all patients randomized who withdrew participation from the study.

8.3.5. Patients Lost to Follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site (refer to the MOO for process details). Vital

status will be collected within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Vital status will be searched in public sources during the study close-out period. If vital status is determined, the patient will not be considered lost to follow-up.

8.3.6. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

8.3.7. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatments Administered

This study involves a comparison of evacetrapib 130 mg administered orally once daily (QD) versus placebo. Table EIAN.9.1 shows the treatment regimens. Patients will take 1 tablet per day, either active study drug, or an identically appearing placebo tablet.

Table EIAN.9.1 Treatment Regimens

Regimen	Dose Day 1 through Last Day of Treatment	Frequency
Evacetrapib	130 mg (1 × 130-mg tablet)	QD
Placebo	1 placebo tablet	QD

Abbreviation: QD = once daily.

The investigator or his/her designee is responsible for explaining the correct use of the investigational product(s) to the patient, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

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

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

9.2. Materials and Supplies

During active treatment, each patient will take 1 tablet QD. Evacetrapib tablets in a dose strength of 130 mg and placebo tablets in identical appearance will be supplied by Lilly in identical packages (each containing 3 bottles) to maintain the blind.

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

All study drug (used and partially used) will be returned to the Sponsor or destroyed at site level with Sponsor's written approval.

9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an IVRS. The IVRS will be used to assign packages (each package containing 3 bottles of double-blind investigational product) to each patient. Site personnel will confirm that

they have located the correct packages (of 3 bottles) by entering a confirmation number found on the packages into the IVRS.

To achieve between-group comparability for site factor, patients will be randomized at the site level in a 1:1 ratio to receive evacetrapib or placebo.

Patients who fulfill all inclusion and no exclusion criteria are randomly assigned in a 1:1 ratio to double-blind treatment with evacetrapib 130 mg or matching placebo, administered without regard to food, and if possible be taken at the same time every day to aid patient compliance.

After randomization, follow-up visits occur at the end of 1, 3, 6, 9, and 12 months, and every 3 months thereafter, with a safety follow-up 1 month after the end of treatment.

9.4. Rationale for Selection of Doses in the Study

The dose of evacetrapib that will be used in this study is 130 mg. This dose is expected to produce an area under the plasma concentration-time curve (AUC) of 9800 ng*hr/mL (90% confidence interval [CI]: 9000-11,000) and maximum plasma concentration (C_{max}) of 1200 ng/mL (90%CI: 1000-1300) at steady state. This dose was selected based on PK, lipid biomarker, and safety data from the Phase 1 and Phase 2 studies, in combination with PK, safety, and lipid biomarker data from a multiple-dose, dose-escalation study (I1V-MC-EIAL) that used the same tablet formulation as planned for this study. This dose is expected to achieve approximately a 110% elevation in HDL-C and a 30% reduction in LDL-C.

Although raising HDL-C has not been conclusively tied to reducing the risk of adverse CV events, data from the torcetrapib ILLUSTRATE trial showed the highest regression of coronary atherosclerosis occurred in patients who had the highest HDL-C levels (Nicholls et al. 2008), with patients who achieved an HDL-C increase of >79% receiving the greatest benefit. The target HDL-C increase that was chosen for the evacetrapib Phase 3 study was a population mean increase of 110%. Based on the variability observed in the evacetrapib Phase 2 Study EIAF, targeting a population mean increase of 110% is expected to produce an HDL-C increase of >79% in 80% of the patients. The target HDL-C increase of 110% is also similar to the HDL-C increase that was observed and found to be safe in the anacetrapib DEFINE (Cannon et al. 2010) study.

The evacetrapib exposures that will be produced in this study are below the highest exposures that have been evaluated in the Phase 1 and Phase 2 studies. In the 14-day multiple-dose healthy-volunteer Phase 1 Study EIAB, the highest dose produced a steady-state AUC of 13,700 ng*hr/mL, and this exposure level was found to be safe and well tolerated in that study. In the most recent 12-week Phase 2 Study EIAF, the highest dose level produced a steady-state AUC of 19,700 ng*hr/mL, and this exposure was also found to be safe and well tolerated. Therefore, based on data from the completed clinical studies, the planned exposure for the Phase 3 study is expected to be safe.

Population PK and PK/PD evaluations conducted on the Phase 2 Study EIAF have not identified any patient factors that would require dose adjustment.

9.5. Selection and Timing of Doses

The initial dose should be administered as soon as possible after randomization (without regard to food). Subsequent doses should be taken daily without regard to food, and if possible be taken at the same time every day to aid patient compliance.

The use of antacids or bulk-forming laxatives should be avoided within 2 hours before or after study drug administration. Use of H2 receptor blockers or proton pump inhibitors is allowed.

9.5.1. Special Treatment Considerations

Special treatment considerations regarding evidence-based management of lipid levels are described in Section7.1..

9.6. Continued Access to Investigational Product

Study drug will not be made available at the conclusion of the study. Patients will be referred to their local treatment centers for continued therapy as clinically indicated.

9.7. Blinding

This is a double-blind study. It is expected that the need for unblinding of a patient's treatment will be extremely rare. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the patient.

Prior to unblinding the treatment of a patient, the investigator should make every effort to contact the study Helpline prior to unblinding a patient's treatment assignment, to discuss the clinical circumstances. It is important to note that if an AE has occurred, the procedures outlined in Section 10.3.1 of the protocol must be followed in order to document the event. If a patient's treatment assignment is unblinded, the study Helpline must be notified immediately by telephone.

Emergency unblinding for AEs may be performed through the IVRS. This option may be used ONLY if the patient's acute well being requires knowledge of the patient's treatment assignment.

All calls resulting in an unblinding event are recorded and reported by the IVRS. Any patient who is unblinded will be permanently discontinued from study therapy (Section 8.3.3) but should be continued in the study.

9.8. Concomitant Therapy

Patients will be allowed to take any concomitant medications required except those listed in the Exclusion Criteria (Section 8.2). Patients are expected to be on a background of standard of care medication for HRVD. These therapies may include, but are not limited to, aspirin, other antiplatelet agents, H2 receptor blockers, proton pump inhibitors, antihypertensives, and appropriate diet and exercise and other nonpharmacologic measures.

The list of excluded medications and procedures is provided in the MOO. This includes concurrent treatment with niacin >250 mg/day.

9.9. Treatment Compliance

Patient compliance with the study medication will be assessed at all visits and the completion of the study. Compliance for each visit interval is defined as taking 80% to 120% of the study drug dosage prescribed for that interval. If a patient is noncompliant, the patient will be counseled by study staff on the importance of taking the prescribed amount.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

Any potential endpoint event must be reported to the Sponsor or designee by the appropriate form **within 24 hours** after the site staff learns of the clinical event.

All endpoints will be adjudicated by the CEC. Study sites should collect the required documents that include the relevant completed endpoint eCRFs and the requested source documentation to be sent to the CEC in a timely fashion for adjudication of the event as per study-specific instructions contained in the MOO. Additional details are available in the CEC charter.

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

Time to first occurrence of any component of the composite cardiovascular events of cardiovascular (CV) death, myocardial infarction (MI), stroke, coronary revascularization, or hospitalization for unstable angina (UA).

10.1.2. Secondary and Tertiary Efficacy Measures

The secondary efficacy measures are:

Secondary Efficacy Measures

- Compared to Placebo:
  - Percent change from baseline of mean HDL-C levels at 3 months after randomization
  - Percent change from baseline of mean LDL-C levels at 3 months after randomization
- Time to first occurrence of any component of:
  - A composite endpoint of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for UA
  - Composite endpoint of CV death, MI, or coronary revascularization
  - Composite endpoint of CV death, MI, stroke, or hospitalization for UA
  - Composite endpoint of CV death, MI, or stroke
- Time to first recurrence of:
  - Any component of the primary composite endpoint among those who had already reached the primary endpoint
- Time to first occurrence of:
  - Coronary revascularization
  - MI
- Time to:
  - CV death
  - All-cause mortality

- Time to first occurrence of:
  - Hospitalization for UA
  - Stroke

Tertiary Efficacy Measures

- Comparison to placebo for:
  - Percent change from baseline at 3 months after randomization of blood lipids (TG), lipoproteins (non-HDL-C, VLDL-C), apolipoproteins (Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo B)
  - Lipoprotein(a)
- Time to first occurrence of:
  - Non-elective revascularization
  - Elective revascularization

10.1.3. Exploratory Efficacy Measures

- The incidence of the primary endpoints by the quartile of lipid levels at 3 months following randomization will be measured to explore the relationship between levels of lipids and the incidence of the primary endpoint
- The effects of evacetrapib on exploratory biomarkers associated with the risk of atherosclerosis (for example, high-sensitivity C-reactive protein [hsCRP]) or glucose metabolism (for example, insulin) will be evaluated
- Measures to characterize the PK of evacetrapib, explore potential factors that may influence the PK, and explore the association of PK with efficacy, biomarkers, and safety parameters will be outlined in the PK/PD analysis plan

Exploratory measures will be outlined in the SAP.

10.1.4. Definitions of the Components of the Primary Endpoint

10.1.4.1. Cardiovascular Death

Any death with a clear relationship to underlying coronary heart disease (including death secondary to acute MI, sudden death, unobserved and unexpected death, resuscitated out-of-hospital cardiac arrest that does not survive to hospital discharge), stroke, and other death that cannot definitely be attributed to a non-CV cause.

10.1.4.2. Myocardial Infarction

Any suspected MI should be reported as an endpoint by the investigator.

Criteria for Myocardial Infarction

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Supporting information can also be considered from myocardial imaging and coronary imaging.

The diagnosis of MI requires the combination of:

- evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and
- supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred.

An MI may be detected and reported by the investigator based on either clinical presentation or on biomarker elevations following revascularization procedure (for example, PCI, CABG).

10.1.4.3. Stroke

Any suspected stroke or TIA should be reported as an endpoint by the investigator. Transient ischemic attack (TIA) is defined as a transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, *without* acute infarction. Stroke is defined as an acute episode of neurological dysfunction caused by vascular injury lasting ≥24 hours.

Stroke Classification:

A. Ischemic Stroke

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

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

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

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

10.1.4.4. Coronary Revascularization Procedure

Any coronary revascularization procedure should be reported as an endpoint by the investigator.

A coronary revascularization procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow (for example, PCI, CABG). Revascularization should be reported as either elective or nonelective and also as staged or nonstaged clinically driven revascularization in the eCRF.

Elective Procedures:

- An elective procedure is one performed on a patient with stable cardiac function in the days or weeks prior to the procedure. Elective cases are usually scheduled at least 1 day prior to the procedure

Non-Elective Procedures:

- A nonelective procedure is one performed on a patient who has been stabilized following initial treatment of acute coronary ischemia, and there is clinical consensus that the procedure should occur within the next 24 hours

OR

- A procedure that is performed without delay, on a patient with evidence of ongoing refractory ischemia, with or without hemodynamic instability

Staged Revascularization:

Revascularization is considered to be a staged procedure if the need for revascularization of a nonculprit lesion vessel was identified at the time of intervention for the qualifying ACS event, and was subsequently performed as planned, without worsening of symptoms. A procedure whose timing was influenced by worsening symptoms will not be considered a staged revascularization.

Nonstaged Clinically Driven Revascularization:

Revascularization is clinically driven if the patient has a lesion diameter stenosis ≥50% by quantitative coronary angiography (QCA) and clinical or functional ischemia. Clinical or functional ischemia includes any of the following:

- A history of angina pectoris
- Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent)
- Abnormal results of any invasive functional diagnostic test (for example, Doppler flow velocity reserve or fractional flow reserve [FFR])
- A diameter stenosis ≥70% by QCA even in the absence of the above signs or symptoms

Revascularization is nonstaged if it is not planned based on findings (clinical, anatomical, biochemical, or imaging) at the time of randomization.

10.1.4.5. Hospitalization for Unstable Angina

Any hospitalization for UA should be reported as an endpoint by the investigator.

Unstable angina (UA) requiring hospitalization is defined as symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity with no evidence of acute MI, and at least one of the following:

- with ischemic ECG changes
- imaging evidence of myocardial ischemia

- angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs

10.2. Health Economics Measures

Health care resource use will be collected in the eCRF from the time of randomization to end of follow-up for all patients in the study. Measures of resource use will include all-cause hospitalizations and associated lengths of stay (intensive care and routine), emergency room visits, major procedures (such as catheterization, percutaneous intervention, bypass surgery), and admissions to nonacute care facilities. Quality of life will be measured in all patients at baseline and at visits indicated by the Study Schedule (Attachment 1) using the EuroQol-5 dimensions (EQ-5D). If evacetrapib is found to be more effective and more costly than placebo, the long-term cost effectiveness of evacetrapib (incremental cost per quality-adjusted life-year gained) will be examined.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

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

10.3.1. Adverse Events

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

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

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

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

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee via eCRF.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via eCRF.

Any clinically significant findings from ECGs, laboratory tests, vital-sign measurements, or physical examination should be reported to Lilly or its designee as an AE via eCRF.

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

Study site personnel must alert Lilly or its designee within 24 hours of the investigator **unblinding** a patient's treatment group assignment for any reason, via the study Helpline. (See Section 9.7 for further details of unblinding).

If a patient's treatment is discontinued (temporary or permanent) as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to discontinuation of treatment.

10.3.1.1. Serious Adverse Events

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

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

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events (SAEs) occurring after a patient has taken the last dose of investigational product will be collected in the pharmacovigilance system and the eCRF for 30 days after the last dose of investigational product, regardless of the investigator's opinion of causation. Thereafter,

SAEs are not required to be reported unless the investigator feels the events were related to either investigational product, or drug delivery system, or a protocol procedure.

Information on SAEs expected in the study population independent of drug exposure may be found in the IB. In the HRVD population, the occurrence of CAD and resulting ischemic complications (for example, including papillary muscle rupture, ventricular rupture, and subsequent hypotension), noncardiac chest pain, cardiac arrhythmias as related to ischemic cardiac events (not related to congenital anomalies), heart failure, recurrent ischemic events (for example, stent thrombosis, reocclusion, restenosis), procedural complication (for example, vascular pseudoaneursym), cardiac syncope, ischemic/embolic stroke, and TIA are common SAEs, reasonably anticipated due to the disease state and independent of drug exposure. During the course of the study, common SAEs reasonably anticipated due to the disease state and independent of drug exposure will be assessed in aggregate by the Sponsor (blind) periodically (at least quarterly).

Note: Potential study endpoints (that is, death due to any cause, CV death, MI, stroke or TIA, coronary revascularization, or hospitalization for UA), will not be reported as an SAE unless deemed possibly related to study drug.

10.3.1.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.3.2. Specific Safety Measures

10.3.2.1. Blood Pressure and Pulse Rate

Blood pressure will be measured at each visit on site, using a standardized method, such as that recommended by the AHA, and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines (Pickering et al. 2005; Chobanian et al. 2003). The same method (or device) should be used to obtain a patient's blood pressure throughout the study. These will be detailed in the study MOO. Antihypertensive medications may be initiated or adjusted according to standard of care at the discretion of the investigator. Pulse rate will be measured at the same time points of blood pressure measurements.

10.3.2.2. Mineralocorticoid Activity

Mineralocorticoid activity: Aldosterone will be measured at randomization and at visits indicated by the Study Schedule (Attachment 1) for approximately 2000 patients at select sites. Serum electrolytes will be closely monitored in all patients randomized, and any clinically significant changes in electrolytes should be managed according to standard of care at the discretion of the investigator.

10.3.2.3. Collection of Electrocardiograms

Standard 12-lead ECGs are collected at various time points as per Study Schedule (Attachment 1). Electrocardiograms (ECGs) should also be collected in association with potential endpoint events, and stored at the site and evaluated by the investigator. Investigators must document their review of each study-specific ECG by signing or initialing and dating each report. The CEC will review collected ECGs associated with endpoint events.

10.3.2.4. Skin Adverse Events

Skin AEs including rashes will be monitored through routine AE monitoring.

10.3.2.5. Muscle and Liver Injury

Muscle injury: Creatine kinase (CK), hepatic and renal function laboratory data will be integrated with myopathy signs and symptoms. Creatine kinase (CK) elevations >5x ULN will be evaluated and managed according to guidelines provided in the MOO.

Liver injury: Laboratory data will be integrated with hepatic signs and symptoms. Alanine aminotransferase (ALT) increases >2x ULN with symptoms of hepatitis or >3x ULN with or without symptoms of hepatitis will be evaluated and managed according to guidelines provided in the MOO.

10.3.2.6. Very Low LDL-C levels

No specific AEs associated with very low levels of LDL-C have been reported in recent trials with high doses of potent statins. However, potential concerns have been raised about lowering LDL-C to extremely low levels, such as those observed in hypobetalipoproteinemia patients. To address this concern, serum vitamin E levels will be measured in patients (at select sites) with at least 1 value of LDL-C <25 mg/dL (<0.6 mmol/L), in addition to the standard safety monitoring for AEs.

10.3.3. Safety Monitoring

The Lilly clinical research physician or designee will monitor blinded safety data throughout the course of the study. The CRO will be responsible for safety monitoring follow-up at the study site throughout the course of the study. Members of the study team will review blinded, selected aggregate data for trends in safety data, laboratory analytes, and SAEs at periodic intervals.

Unblinded data including, but not limited to, clinical endpoint events (reported and adjudicated) including deaths, MIs, strokes, coronary revascularizations, hospitalization for UA, selected potentially clinically significant laboratory values, AEs, SAEs, discontinuations due to AEs, other relevant safety information, and specific safety measures (Section 10.3.2) will be reviewed regularly by an external independent DMC; see Section 12.2.14).

10.3.4. Complaint Handling

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

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

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

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

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

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

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 3 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Fewer invasive sampling may actually occur, but this will not require a protocol amendment.

10.4.1. Samples for Standard Efficacy, Safety Laboratory Testing

Standard laboratory tests, including chemistry and hematology panels, will be performed. A pregnancy test will be performed at a local laboratory (if applicable). Attachment 2 lists the specific tests that will be performed for this study.

Blood samples will be collected at the times specified in the Study Schedule (Attachment 1). Attachment 3 summarizes the blood volumes for all blood sampling, screening, safety laboratories, and bioanalytical assays during the study.

Blood serum and plasma will be collected by venipuncture/through a central or arterial line.

Screening labs at Visit 1 and clinical laboratory tests after Visit 1 will be analyzed by a central laboratory selected by Lilly. Pregnancy tests will be performed locally.

Laboratory analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results

are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Drug Concentration Measurements

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

At the visits and times specified in the Study Schedule (Attachment 1), venous blood samples will be collected. Blood samples will be used to determine the plasma concentrations of evacetrapib. The actual date and time of each sampling will be recorded.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

10.4.3. Pharmacogenetic Samples

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

Samples will be stored and analysis may be performed on genetic variants thought to play a role in lipid abnormalities and atherosclerosis including, but not limited to, ABCA1, APOA1, APOC3, APOA5, APOE, CETP, LIPC, LIPG, LPL, LCAT, PON1, SCARB1 and WWOX to evaluate their association with observed clinical outcomes to evacetrapib.

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

The sample will be identified by the patient number (coded) and stored for up to a maximum of 15 years (where local regulations or Institutional Review Board [IRB] policy allow) after the last patient visit for the study at a facility selected by the Sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel. The duration allows the Sponsor to respond to regulatory requests related to the study drug.

10.4.4. Nonpharmacogenetic/Biomarker Stored Samples

Collection of samples for potential nonpharmacogenetic biomarker research will be part of this study at select sites unless precluded by local regulations or IRB policy. Serum and plasma samples will be collected at the times specified in the Study Schedule (Attachment 1).

Samples may be used for research to the effects of evacetrapib or CETP inhibition on safety or efficacy biomarkers, including but not limited to the biomarkers of lipid metabolism, atherosclerosis, inflammation, endothelial function, mineralocorticoid activity, rashes, and evacetrapib metabolism, disposition and risk for drug-drug interactions related to lipid abnormalities and atherosclerosis.

Samples will be identified by the patient identifier number (coded) and stored for up to a maximum of 15 years (in accordance with any local regulations regarding duration of storage) after the last patient visit for the study at a facility selected by the Sponsor.

10.5. Appropriateness of Measurements

The primary endpoints in this trial are the incidence of the composite endpoint of CV death, MI, stroke, coronary revascularization, or hospitalization for UA. The endpoint definitions are described in Section 10.1.4, and are based on the Standardized Definitions for End Point Events in Cardiovascular Trials (Hicks et al. 2010).

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

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

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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

11.1. Data Capture System

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

Electronic case report form (eCRF) data collected by the CRO will be encoded by the CRO and stored electronically in the CRO's database system. Validated data will subsequently be transferred to the Sponsor's data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

This is an event-driven study. The study will be continued until all of the following criteria are satisfied:

1) at least 1136 patients experience one or more components of the primary composite endpoint of CV death, MI, stroke, coronary revascularization, or hospitalization for UA
2) at least 500 patients experience 1 or more components of the composite endpoint of CV death, MI, or stroke
3) at least 1.5 years have elapsed from the date of last patient randomized

The study design provides 90% power to detect a 17.5% relative risk reduction for the primary composite endpoint at an alpha of 0.05. The log-rank test will be used for comparing the distribution of time to first occurrence of the primary endpoint between evacetrapib and placebo. Based on evidence from previous trials (Cannon et al. 2004; Bhatt et al. 2006; Barter et al. 2007; Wiviott et al. 2007; Wallentin et al. 2009), an annual incidence of 5% is assumed for the primary endpoint. The number of patients to be enrolled also depends on factors such as the duration of the enrollment, incidence of patients withdrawing consent to further follow up, and the minimum duration of follow up. Assuming an average follow up of 2.5 years per patient, it is expected that the study will enroll an estimated 11,000 patients. The actual number of patients enrolled is to be guided by the predictions-based observed aggregate-event accrual during the trial.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Two key analysis datasets are of interest: the ITT set consisting of all randomized subjects and the treated set consisting of subjects receiving at least 1 dose of study drug. Efficacy analyses will be carried out using the ITT set. Safety analyses will be carried out using the treated set. Patients who discontinue study drug will continue to be followed for 1.5 years after discontinuing study drug or termination of the study, whichever occurs earlier, to ascertain efficacy and AEs. Efficacy endpoints and AEs that occur after permanent discontinuation of study drug will be included in their respective analyses. For those who withdraw consent to further follow-up, all available information from randomization through date of withdrawal of consent will be included in analyses. Available information on patients who are lost to follow-up will be included in the analyses.

Components of the primary and secondary endpoints will be adjudicated by an independent CEC. Unless stated otherwise, endpoint analyses will be based on CEC confirmed events. Specific definitions of efficacy endpoints are outlined in the protocol as well as the CEC Charter. In the composite endpoint analyses, reaching any component of the composite endpoint will be considered as reaching the composite endpoint. In analyzing components of the composite endpoints, reaching that specific endpoint will be considered (whether or not it is the first endpoint to occur).

Unless stated otherwise, all efficacy analyses including the primary endpoint analysis will be conducted in a manner consistent with the ITT principle.

Time to event is defined as the time from randomization to the onset of the endpoint for efficacy endpoints. Estimating cumulative hazard will be via the Kaplan-Meier method, unless otherwise specified; comparison of cumulative hazard functions will be based on log-rank test. The estimates of hazard ratio, under the assumption of proportional hazards, and corresponding CIs will be based on a Cox proportional hazards regression analysis. Subgroup analyses evaluating potential influence of baseline risk factors, additively or interactively, will be assessed using the Cox proportional hazards regression. Pearson's correlation coefficient will be used for evaluating the association between continuous measurements. Cox proportional hazards regression analysis will be used to explore the association between continuous measures and dichotomous outcomes.

All CIs will be 2-sided with a 95% confidence level, and all hypothesis tests, with the exception of interaction effects, will be evaluated at 2-sided significance level of 0.05. For assessing interaction effects, a 2-sided significance level of 0.10 will be used.

Descriptive summaries for interval scale variables will include number of patients with evaluable information, mean, standard deviation, median, and first and third quartile. Descriptive summaries for categorical scale variables will include number of patients with evaluable information and percentage based on number of patients with evaluable information.

The choice of statistical tests used for comparing evacetrapib and placebo will be guided by the hypothesis and the type of measurement: Fisher's exact for comparing proportions, Pearson's chi-square test for comparing distributions of nominal categorical scale measurements, Cochran-Mantel-Haenszel (CMH) row mean-score test comparing medians of ordinal scale measurements, 2-sample t-test for comparing means of interval scale measurements, and the log-rank test for comparing distributions of time to first event.

The Sponsor, ARO, and CRO will have responsibility for the development of the SAP. The CRO will have the responsibility for the execution of the SAP. The SAP will be approved before database lock.

12.2.2. Patient Disposition

The proportion of patients prematurely discontinuing study, overall, and by reasons for discontinuation will be summarized by the 2 treatment groups. The Kaplan-Meier method will be used for illustrating the time profile of the proportion of patients discontinuing from the study by the treatment group. Descriptive statistics of duration of study participation will be summarized by treatment group. Statistical comparisons will be made according to methods described in Section 12.2.1.

12.2.3. Patient Characteristics

Demographics, clinical presentation, medical history including CV risk factors, and other preexisting or ongoing conditions, collected at the time of randomization, will be summarized by

treatment group. Statistical comparisons will be made according to methods described in Section 12.2.1.

12.2.4. Concomitant Therapy

All concomitant medications, by the type of medication per Anatomical Therapeutic Chemical (ATC) classification system will be summarized by treatment group. Concomitant medications of special interest include, but are not limited to, HMG-CoA reductase inhibitors (statins), anti-coagulants, and antihypertensive medications. In addition, HMG-CoA reductase inhibitors will be further summarized by dose and by treatment group. Statistical comparisons will be made according to methods described in Section 12.2.1.

12.2.5. Treatment Compliance

The proportion of patients' prematurely and permanently discontinuing study drug, overall and by reasons for discontinuation, will be summarized by the 2 treatment groups. The Kaplan-Meier method will be used for illustrating the time profile of the proportion of patients discontinuing from the study drug by the treatment group.

The proportion of patients temporarily interrupting study drug, overall and by reasons for interruption, will be summarized by the 2 treatment groups. Descriptive statistics of the duration of exposure to study drug adjusted for interruptions will be summarized by treatment group.

Treatment compliance will be defined by the treatment compliance ratio: the number of doses taken by the subject divided by the number of doses assigned. Compliance is defined as taking between 80% and 120% of the study drug provided.

Statistical comparisons will be made according to methods described in Section 12.2.1.

12.2.6. Primary Outcome and Methodology

The primary endpoint is the time to first occurrence to any component of the composite of CEC confirmed CV death, MI, stroke, coronary revascularization, or hospitalization for UA. The log-rank test with a 2-sided statistical significance level 0.05 will be used to test for the difference between the distribution of time to first occurrence for evacetrapib and placebo. All confirmed endpoints that occur between randomization and end of follow-up will be included, whether or not they occur while the patient is taking study drug.

12.2.7. Efficacy Analyses-Secondary Endpoints

Contingent on successfully establishing that evacetrapib reduces the hazard associated with the primary composite endpoint, the following secondary efficacy endpoints will be evaluated hierarchically, in the order of presentation below, using the log-rank test each at a 2-sided significance level of 0.05.

Comparison to placebo using the 2 sample t-test for:

- Mean of the percent change from baseline HDL-C levels at 3 months after randomization

  - Mean of the percent change from baseline LDL-C levels at 3 months after randomization

Comparison to placebo using the log-rank test for the distribution of:

- Time to first occurrence of:
  - A composite endpoint of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for UA
  - Composite endpoint of CV death, MI, or coronary revascularization
  - Composite endpoint of CV death, MI, stroke, or hospitalization for UA
  - Composite endpoint of CV death, MI, or stroke
- Time to first recurrence of:
  - Any component of the primary composite endpoint among those who had already reached the primary endpoint
- Time to first occurrence of:
  - Coronary revascularization
  - MI
- Time to:
  - CV death
  - All-cause mortality
- Time to first occurrence of:
  - Hospitalization for UA
  - Stroke

12.2.8. Efficacy Analyses-Tertiary Endpoints

Comparison to placebo using the 2 sample t-test for:

- Mean percent change from baseline at 3 months after randomization of blood lipid levels (TG), lipoproteins (non-HDL-C, VLDL-C), apolipoproteins (Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo B)
- Mean percent change from baseline of lipoprotein(a)

Comparison to placebo using the log-rank test for the distribution of:

- Time to first occurrence of:
  - Non-elective revascularization
  - Elective revascularization

12.2.9. Efficacy Analyses-Exploratory Endpoints

Cox proportional regression analysis will be used to explore:

- the relationship between percent change from baseline lipid levels and the incidence of the primary endpoint

Comparison to placebo using the 2 sample t-test for:

- exploratory biomarkers associated with the risk of atherosclerosis or glucose metabolism

12.2.10. Pharmacokinetic/Pharmacodynamic Analyses

All plasma evacetrapib concentration-time data will be pooled and evaluated by a population pharmacokinetic (popPK) approach. A covariate screen of patient and study-specific factors will be included in the analyses based on those factors investigated in previous and ongoing PK analyses and those appropriate for the target population. Exploratory and model-based analyses examining the relationships between evacetrapib exposure and lipid endpoints such as HDL-C and LDL-C will be conducted. Other analyses of efficacy and safety outcome measures may also be assessed as scientifically appropriate and warranted by available data. Further details about the analyses that may be conducted will be presented in the PK/PD analysis plan.

12.2.11. Health Economic Analyses

The prospective economic and quality-of-life portion of the study will be conducted to detect differences between treatment groups in medical resource use and cost. The analysis will involve a comparison between treatment groups of medical care resource use and cost for the period of follow-up in the study. Overall resource use patterns in the study will be quantified by attaching United States cost weights to resource use variables for all subjects in the study. If evacetrapib is found to increase both effectiveness and cost, a long-term cost-effectiveness analysis that assesses the incremental cost of evacetrapib per quality-adjusted life-year gained will be performed.

12.2.12. Safety Analyses

12.2.12.1. Adverse Event, Vital Signs, and Laboratory Analyses

The treatment-emergent adverse events (TEAEs) and SAEs among the treatment groups will be compared using the Pearson's chi-square test. Treatment-emergent adverse events (TEAEs) are defined as events that first occurred or worsened after baseline in patients who have received at least 1 dose of study drug. Vital signs and laboratory values as well as the change from baseline to each follow-up visit and to the end of the study for the patient will be summarized by visit and by treatment group. In particular, the safety parameters identified in Section 10.3.2 will be compared using appropriate statistical methods. Statistical comparisons between treatments at each visit and within treatment changes at each visit will be made according to methods described in Section 12.2.1.

In order to evaluate whether very low LDL-C levels (<25 mg/dL [<0.6 mmol/L]) are associated with an increased risk of AEs, as a first step, comparisons of incidence rates of prespecified TEAEs will be made using Pearson's chi-square test at system organ class as well as preferred-term levels. If statistically significantly higher incidence rates were observed for evacetrapib, incidence rates of specific TEAEs will be compared using Pearson's chi-square test between patients with VLDL-C levels on evacetrapib (at least 1 value of LDL-C <25 mg/dL) and a

complementary cohort of patients with LDL-C levels above 25 mg/dL on evacetrapib to assess whether patients with VLDL-C levels are at a higher risk for specific TEAEs. If patients on evacetrapib with VLDL-C levels will be found to be at higher risk for specific TEAEs, an assessment will be made using logistic-regression analysis to evaluate the possible association between the incidence rate of specific TEAEs and serum vitamin E levels.

12.2.13. Subgroup Analyses

Subgroup analyses, relative to primary efficacy endpoint and all-cause death, will be conducted using a Cox proportional hazards model with subgroup, treatment group, and the interaction between the levels of the subgroup and treatment group as categorical variables. Assessment of heterogeneity of treatment groups will be guided by the interaction testing at a 2-sided significance level of 0.10. Inferential statistics (p-values and 95% CIs) related to comparison between the treatment within subgroups will be per Cox-regression but will be considered exploratory. Planned subgroup analyses will include but are not limited to:

Demographics:
Sex; age, weight, ethnicity, and region of enrollment

Medical History:
Recent ACS (yes, no), diabetics with CAD (yes, no), PAD (yes, no), cerebrovascular atherosclerotic disease (yes, no), single vascular disease: recent ACS only, PAD only, cerebrovascular atherosclerotic disease only, diabetics with CAD only, poly-vascular disease (patients belonging to two or more categories)
Diabetes (yes, no), metabolic syndrome (yes, no), impaired renal function (yes, no), impaired hepatic function (yes, no)

Baseline Lipid Level:
Quartile analysis based on baseline HDL-C level
Quartile analysis based on baseline LDL-C level

On Treatment Lipid Levels:
Quartile analysis based on mean HDL-C level achieved across visits
Quartile analysis based on mean LDL-C level achieved across visits

Statin Use: Dose and Type
Prior to randomization: statin type (none, one type, multiple types)
At randomization: statin dose (none, low dose, medium dose, high dose)
During the trial
Statin intolerant (yes, no)
Statin dose (low dose, medium dose, high dose)
Statin type (atorvastatin only, simvastatin only, rouvastatin only, pravastatin only, fluvastatin only, lovastatin only, pitavastatin only, multiple types)

12.2.14. Interim Analyses

Lilly plans to convene an independent DMC to ensure patient safety during the conduct of the study. The DMC is authorized to review results of analyses by therapy prior to database lock. The DMC, with membership external to and independent from the Sponsor, ARO, and CRO, will be charged with ensuring patient safety during the conduct of the study. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients. The study team will remain blinded until final database is locked, unless the DMC recommends early termination of the study for safety or futility.

The first scheduled DMC review will occur approximately 3 months after first patient visit and every 3 months until 1000 patients have been followed for 6 months. Thereafter, DMC reviews will be every 6 months throughout the study. Tabular summaries of clinical endpoint events (reported and adjudicated) including deaths, MIs, strokes, coronary revascularizations, hospitalization for UA, selected potentially clinically significant laboratory values, AEs, SAEs, discontinuations due to AEs, and other relevant safety information by treatment group will be sent to the DMC by a statistician external to and independent from the Sponsor, ARO, and CRO study operations.

Specific details will be provided in the DMC charter.

Planned interim analyses will be performed to evaluate the need for early termination of the study for adverse safety of evacetrapib or lack of efficacy of evacetrapib. The study will not be terminated for superior efficacy benefit of evacetrapib since the drug is not currently commercially available.

Details of membership, operations, and the communication plan will be documented in the DMC Charter.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.

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

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative site(s). All ICFs must be compliant with the International Conference on Harmonization (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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

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

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

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) the ICH GCP Guideline [E6]
3) applicable laws and regulations

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

All or some of the obligations of the Sponsor will be assigned to a third-party organization (TPO).

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

Evacetrapib is being studied in the United States (US) under a US Investigational New Drug (IND) application. The US IND number is 101,743.

13.3.1. Investigator Information

Licensed physicians including, but not limited to, those specializing in cardiology, endocrinology, or internal medicine will participate as investigators in this clinical study.

13.3.2. Protocol Signatures

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

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

An investigator from the ARO will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol EIAN Study Schedule

Perform procedure as indicated.

Study Schedule, Protocol I1V-MC-EIAN (ACCELERATE)

Procedure	**Screen[a]**	**Randomize**	**Treatment**																		**Early D/C and Safety Follow-up**	
eCRF Visit No.:	V1[b]	V2[c]	V3	V4	V5	V6	V7	V8*	V9	V10*	V11	V12*	V13	V14*	V15	V16*	V17	V18*	V19[d] L/V	U/S Visit	Early D/C	Safety F/U[e]
Months from Randomization			1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	NA	NA	49
Days from Randomization		0	30	90	180	270	360	450	540	630	720	810	900	990	1080	1170	1260	1350	1440	NA	NA	1470
Visit Window (Days)		≤45D fromV1	±5D	±10D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	NA	NA	±7D
Informed Consent Signed	X																					
Medical History	X																					
Pertinent Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X					X				X				X				X	X	X	
Height		X																				
Body Weight		X					X				X				X				X		X	
Serum Creatinine Screening	X																					
Randomization		X																				
Vital Signs: BP/Pulse Rate[f]	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	
ECG[g]		X			X		X				X				X				X		X	
Chem Panel (fasting)[h]		X	X		X		X		X		X		X		X		X		X	X[i]	X[i]	
Hematology Panel		X	X		X		X		X		X		X		X		X		X	X	X	

(continued)

Study Schedule, Protocol I1V-MC-EIAN (ACCELERATE)

Procedure	Screen[a]	Randomize	Treatment																	Early D/C and Safety Follow-up	
eCRF Visit No.:	V1[b]	V2[c]	V3	V4	V5	V6	V7	V8*	V9	V10*	V11	V12*	V13	V14*	V15	V16*	V17	V18*	V19[d] L/V	U/S Visit	Early D/C	Safety F/U[e]
Months from Randomization			1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	NA	NA	49
Days from Randomization		0	30	90	180	270	360	450	540	630	720	810	900	990	1080	1170	1260	1350	1440	NA	NA	1470
Visit Window (Days)		≤45D from V1	±5D	±10D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	NA	NA	±7D
Vitamin E[j]		X		X			X				X								X		X	
Plasma Insulin (fasting)[k]		X		X			X				X								X		X[i]	
Pregnancy Test	X[l]																					
Hemoglobin A1c		X			X		X				X				X				X		X	
Biomarkers (hsCRP)[m]		X		X			X				X								X		X	
Lipid Panel (fasting)[n]		X	X	X	X	X	X		X		X		X		X		X		X	X[i]	X[i]	X[o]
HDL-C/LDL-C/TG screening	X																					
Aldosterone[p]		X	X	X	X	X	X														X	
DNA Storage (PGx)[q]		X																				
Sample Storage (Biomarkers)[r]		X		X			X				X								X		X	
PK Sampling[s]			X	X	X	X	X		X												X[s]	X[o]

(continued)

Study Schedule, Protocol I1V-MC-EIAN (ACCELERATE)

Procedure	**Screen[a]**	**Randomize**	**Treatment**																	**Early D/C and Safety Follow-up**	
eCRF Visit No.:	V1[b]	V2[c]	V3	V4	V5	V6	V7	V8*	V9	V10*	V11	V12*	V13	V14*	V15	V16*	V17	V18*	V19[d] L/V	U/S Visit	Early D/C	Safety F/U[e]
Months from Randomization			1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	NA	NA	49
Days from Randomization		0	30	90	180	270	360	450	540	630	720	810	900	990	1080	1170	1260	1350	1440	NA	NA	1470
Visit Window (Days)		≤45D from V1	±5D	±10D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	±14D	NA	NA	±7D
Adverse Events	X[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Endpoint Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug		X		X	X	X	X		X		X		X		X		X					
Patient Drug Compliance/ Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discontinuation Summary																					X	
Health Econ. Measures:																						
Medical Res. Utilization		X	X	X	X	X	X		X		X		X		X		X		X		X	X
EQ-5D Questionnaire		X			X		X				X				X				X			

(continued)

Abbreviations: BP = blood pressure; D = day; D/C = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; Econ.= economics; EQ-5D = EuroQol-5 dimensions; F/U = follow-up; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IRB = institutional review board; L/V = last visit; LDL-C = low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); NA = not applicable; PGx = Pharmacogenetic; PK = pharmacokinetic; Res. = resource; TG = triglycerides; U/S = unscheduled visit; V = visit.

***Visits will not occur on site.**

a All screening labs will be performed centrally except the pregnancy test, which will be performed locally if applicable.

b Patients who do not meet entry criteria may undergo one repeat screening visit at the investigators discretion. The study window between Visit 1 and Visit 2 can be up to 45 days.

c Visit 2 lab procedures must be completed prior to patient taking study drug. Blood Pressure measurements must be taken before randomization at Visit 2.

d For every patient this represents the last visit (L/V) regardless of duration in the study.

e For every patient this represents the final safety follow-up (F/U) regardless of duration in the study.

f Blood pressure and pulse rate. Three replicate blood pressure and pulse rate measurements should be taken approximately 2 minutes apart and recorded on the eCRF. The same method (or device) should be used to obtain a patient's blood pressure throughout the study (See the MOO for further details). Blood pressure must be taken before randomization at Visit 2.

g Electrocardiograms should be obtained immediately before the single PK sample is collected at a random time point.

h Fasting requires no food or caloric beverage for at least 8 hours prior to sample collection.

i If unscheduled visits or early discontinuation visits are required urgently, patient fasting prior to unscheduled or early discontinuation visits may not be possible.

j Samples will be collected in patients and stored (at select sites), but serum vitamin E levels will only be measured in patients with very low LDL-C levels (<25 mg/dL [<0.6 mmol/L]). Results will remain blinded to investigators and study team.

k Plasma insulin will be collected at select sites.

l Applicable only to women of childbearing potential. Urine or serum tests should be performed at Visit 1 (Screening). Urine or serum tests may be performed at other visits per site discretion. Results analyzed locally.

m Biomarkers (hsCRP) will be collected at select sites.

n Total cholesterol, HDL-C, non-HDL-C, LDL-C, VLDL-C, Triglycerides (TG), Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo B, LP(a). Results will be generally blinded to investigators and study team.

o Will be collected in the first 1000 patients with PK samples collected.

p Aldosterone samples will be collected at select sites at the visits indicated in the schedule for approximately 2,000 patients.

q Where local regulations and IRB approval allow, a blood sample will be collected for potential pharmacogenetic analysis. The sample should be collected at Visit 2. If inadvertently not collected at Visit 2, it may be collected at a later visit.

r Samples will be collected for potential biomarker research unless precluded by local regulations or IRB policy at select sites.

s Single sample will be collected in approximately 2400 patients at the visits indicated at select sites. On Visits 3, 5, and 7 the patients should be instructed to take their study medication prior to the on-site visit, so that the PK sample taken at this visit occurs several hours (optimally within 1 to 12 hours) after their most recent dose. On Visits 4, 6, and 9 the patients should be instructed not to take their study medication until after the on-site visit has occurred, so that the PK sample taken at this visit occurs greater than 18 hours (optimally within 18 to 30 hours) after their most recent dose. Although samples can be taken any time within the specified time windows, the exact time of the sample and prior dose should be recorded. In the case of early D/C, every effort should be made to obtain the sample the evening of the D/C visit.

t Conditions that exist at the screening visit are captured as preexisting conditions at Visit 1.

Attachment 2. Protocol EIAN Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology [b]:	**Clinical Chemistry (Fasting) [b]**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin concentration (MCHC)	Bicarbonate
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented	Direct bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase (ALT/SGPT)
Eosinophils	Aspartate aminotransferase (AST/SGOT)
Basophils	Gamma-glutamyl transferase (GGT)
Platelets	Blood urea nitrogen (BUN)
	Creatinine*
Lipid/Atherosclerosis [b] (Fasting):	Uric acid
Total cholesterol	Calcium
Direct LDL cholesterol*	Glucose, fasting,
HDL cholesterol*	Albumin
Triglycerides*	Total Protein
VLDL cholesterol†	Creatine kinase (CK)
Non-HDL cholesterol†	Vitamin E‡
Apolipoprotein panel (A-I, A-II, C-II, C-III, E, B, Lp(a))	
	HbA1c [b]
Type of Cardiac Biomarkers (local for suspected endpoints) [a]:	
CK	**Aldosterone [b]**
CK-MB	
cTnI and T	
	Plasma Insulin (fasting) [b]
Inflammatory Biomarkers [b]	
hsCRP	
Pregnancy Test (females only) [a, c]	

Abbreviations: C = cholesterol; CK = creatine kinase; CK-MB = creatine kinase-myocardial bands; Cr = creatinine; CRP = C-reactive protein; cTnI and T = Cardiac Troponin I and T; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; hsCRP = high sensitivity C-reactive protein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; RBC = red blood cells; VLDL = very-low-density lipoprotein; WBC = white blood cells.

[a] Local or investigator designated laboratory.

[b] Central laboratory.

[c] Can perform pregnancy test at any time as appropriate (either urine or serum).

* HDL-C, LDL-C, triglycerides (TG), and serum creatinine will also be obtained centrally for screening at Visit 1.

† VLDL-C and non-HDL-C values are calculated from total cholesterol, LDL-C, and HDL-C measurements.

‡ Vitamin E will only be measured in samples if patient levels of LDL-C are <25 mg/dL [<0.6 mmol/L].

Attachment 3. Protocol EIAN Sampling Summary

This table summarizes the maximum number of samples, venipunctures, and volumes for all sampling screening, standard laboratory, PK, pharmacogenetic, biomarker, and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol I1V-MC-EIAN Maximum Estimated Sampling Summary (Based on a 4 year Period) [a]

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening tests	Blood	5 mL	2-3	15 mL
Standard laboratory tests	Blood	10 mL	45	450 mL
Pharmacokinetic samples	Blood	2 mL	7	14 mL
Pharmacogenetic samples	Blood	10 mL	1	10 mL
Nonpharmacogenetic biomarkers, plasma and serum	Blood	9 mL 8.5 mL	7 7	63 mL 59.5 mL
Total rounded to nearest 10	Blood		70	610 mL

[a] Blood volumes may vary, but estimates are provided based on testing volumes needed by a central lab. Additional samples may be drawn if needed for safety purposes or for retests.

Attachment 4. Protocol EIAN Criteria for Newly Detected Type 2 Diabetes Mellitus

Newly detected Type 2 diabetes based on the American Diabetes Association criteria (ADA 2010) as either of the following criteria:

- Fasting plasma glucose ≥126 mg/dL (≥7 mmol/L). Fasting is defined as no caloric intake for at least 8 hours*

  OR

- 2-hour plasma glucose ≥200 mg/dL (≥11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization (WHO 2006), using a glucose load containing the equivalent of 75 g anhydrous glucose in water*

  OR

- Glycated hemoglobin (HbA1c) levels ≥6.5% (≥48 mmol/mol)

*These tests should be confirmed by repeat testing on a second day.

Attachment 5. Protocol EIAN New York Heart Association Congestive Heart Failure Classifications

New York Heart Association Congestive Heart Failure (NYHA CHF) Classifications:

- Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class III: patients with marked limitation of activity; they are comfortable only at rest.
- Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Source: [NYHA] New York Heart Association. 1994.

Leo Document ID = 21160e96-3936-4fb4-9ad0-614db66180d5

Approver: Jeffrey S Riesmeyer (AM\RM98889)
Approval Date & Time: 24-May-2012 12:13:38 GMT
Signature meaning: Approved