Resverlogix Corp.

Protocol Number: RVX222-CS-015

A Phase III Multi-Center, Double-Blind, Randomized, Parallel Group, Placebo-Controlled Clinical Trial in High-Risk Type 2 Diabetes Mellitus (T2DM) Subjects with Coronary Artery Disease (CAD) to Determine Whether Bromodomain Extraterminal Domain (BET) Inhibition Treatment with RVX000222 Increases the Time to Major Adverse Cardiovascular Events (MACE)

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Statistical Analysis Plan

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Prepared by:

PPD
on behalf of Resverlogix Corp.

APPROVAL SIGNATURES

Study Title: A Phase III Multi-Center, Double-Blind, Randomized, Parallel Group, Placebo-Controlled Clinical Trial in High-Risk Type 2 Diabetes Mellitus (T2DM) Subjects with Coronary Artery Disease (CAD) to Determine Whether Bromodomain Extraterminal Domain (BET) Inhibition Treatment with RVX000222 Increases the Time to Major Adverse Cardiovascular Events (MACE)

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List of Abbreviations

ACS	Acute Coronary Syndrome
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
apoA-I	Apolipoprotein A-I
apoB	Apolipoprotein B
API	active pharmaceutical ingredient
AST	Aspartate Aminotransferase
BET	Bromodomain and Extraterminal
BID	twice daily
BMI	Body Mass Index
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CI	Confidence Interval
CK	Creatine Kinase
CRO	Contract Research Organization
CSC	Clinical Steering Committee
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes Mellitus
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D / EQ-5D-5L	EuroQOL five dimensions questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration, US
GGT	Gammaglutamyl Transferase
HbA1c	Glycated Hemoglobin
HBcAb	Hepatitis B Virus Core Protein Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HDL-C	HDL cholesterol
HRQOL	Health Related Quality of Life
hs-CRP/hsCRP	high-sensitivity C-Reactive Protein
IgM	Immunoglobulin M
LDL	Low-Density Lipoprotein
LDL-C	LDL Cholesterol
LVT	Last Visit on Treatment
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed-effect Model Repeat Measures
MOCA/MoCA	Montreal Cognitive Assessment
mRNA	Messenger RNA
PCI	Percutaneous Coronary Intervention
PPS	Per-Protocol Set
RBC	Red Blood Cells

PT INR	Prothrombin International Nomenclature Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SS	Safety Set
T2DM	Type 2 Diabetes Mellitus
TG	Triglyceride
ULN	Upper Limit of Normal Range
WBC	White Blood Cells
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) describes the analyses and data presentation for Resverlogix's protocol RVX222-CS-015 "A Phase III Multi-Center, Double-Blind, Randomized, Parallel Group, Placebo-Controlled Clinical Trial in High-Risk Type 2 Diabetes Mellitus (T2DM) Subjects with Coronary Artery Disease (CAD) to Determine Whether Bromodomain Extraterminal Domain (BET) Inhibition Treatment with RVX000222 Increases the Time to Major Adverse Cardiovascular Events (MACE)." It contains definitions of analysis populations and statistical methods for the efficacy and safety analysis.

The study is an event-based trial and will continue until 250 narrowly defined MACE events (primary events; defined in section 3.2) have occurred. Throughout this SAP, the treatment arms will be referred to as RVX000222 and placebo.

This SAP prospectively lays out statistical approaches in the analysis of study data. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis Software (SAS)® Version 9.2 or higher.

2. Objectives

2.1. Primary Objective

- To evaluate if treatment with RVX000222 as compared to placebo increases time to the first occurrence of narrowly defined MACE. Narrowly defined MACE is defined as a single composite endpoint of CV death or Non-fatal MI or Stroke.

2.2. Secondary Objectives

- To evaluate if treatment with RVX000222 increases time to the first occurrence of broadly defined MACE in comparison to placebo

  Broadly defined MACE is the occurrence of <u>any</u> of the following events:
  - CV death
  - Non-fatal MI
  - Hospitalization for CVD events including:
    - Unstable angina AND evidence of new or presumed new progressive obstructive coronary disease, OR
    - Emergency revascularization procedures at any time and urgent revascularization procedures ≥30 days after the index events prior to randomization
  - Stroke
- To evaluate if treatment with RVX000222 increases time to the first occurrence of fatal or non-fatal MI, or fatal or non-fatal stroke.
- To evaluate treatment group difference in all-cause mortality
- To evaluate changes in lipoprotein concentrations including apoA-I, apolipoprotein B (apoB), LDL-C, HDL-C, and triglyceride (TG) over time within and between treatment groups
- To evaluate changes in DM variables including glycated hemoglobin (HbA1c), fasting glucose, and fasting insulin over time within and between treatment groups
- To evaluate changes in ALP over time within and between treatment groups including isoforms for whole population and quartiles of ALP baseline concentration
- Assess changes in kidney function in population with baseline estimated glomerular filtration rate <60 mL/min/1.7m^2
- To evaluate the safety and tolerability of RVX000222

2.3. Exploratory Objectives

- To evaluate changes in inflammation variables including, but not limited to, high-sensitivity C-reactive protein (hsCRP), fibrinogen, and inflammatory cytokines within and between treatment groups
- To evaluate transcription (messenger RNA [mRNA]) change in whole blood from baseline to 6 weeks of treatment
- To evaluate Health Related Quality of Life (HRQOL) as measured using the EQ-5D-5L
- To evaluate cognition changes in subject >= 70 years as measured using the MoCA scale

3. Investigational Plan

The sub-sections below re-iterate salient features of the investigational plan from the protocol as necessary context prior to the description of general statistical considerations, definitions of analysis populations and the proposed statistical approaches for the analyses of efficacy and safety data.

3.1. Overall Study Design and Plan

This is a double-blind, placebo-controlled, 2 arm parallel-group (allocation ratio 1:1), study of RVX000222 at a dose of 100 mg b.i.d. (total daily dose of 200 mg) or matching placebo in combination with high potency statin therapy administered to T2DM subjects with history of recent CVD event and HDL-C level < 40 mg/dL males or <45 mg/dL females. The high potency statin therapy shall consist of daily dose of either atorvastatin 20-80 mg or rosuvastatin 10-40 mg [20 mg atorvastatin or 10 mg rosuvastatin is only acceptable in circumstances such as advanced age, low body mass, previous intolerance to higher doses or specific drug-drug interactions (e.g. anti-retrovirals).

After an initial screening period of 1 to 2 weeks during which subjects will be treated with standard of care high potency statin therapy, subjects will be randomized to either RVX000222 100 mg b.i.d. or matching placebo with continued statin treatment. This combination treatment period will continue until 250 narrowly defined MACE events have occurred in the study and all surviving subjects have been followed for at least 24 weeks from randomization. Blinded treatment with RVX000222 or matching placebo will then be discontinued. Subjects will remain on standard of care high potency statin therapy for 4 more weeks until the Follow-Up Visit.

The study is an event-based trial and will continue until 250 narrowly defined MACE events have occurred. The study will be monitored by a Data Safety Monitoring Board (DSMB). MACE will be adjudicated by an independent MACE Adjudication Committee (EAC) in an ongoing manner. Study data as indicated on the Schedule of Events (See the study protocol) will be collected at each study visit and recorded in the appropriate sections of the eCRF.

3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint will be time from randomization to the first occurrence of adjudication confirmed MACE narrowly defined as a single composite endpoint of CV Death or Non-fatal MI or Stroke.

3.2.2. Key Secondary Endpoints

The key secondary endpoints will be:

1. Time from randomization to the first occurrence of adjudication-confirmed MACE broadly defined between treatment groups.
   Broadly defined MACE is the occurrence of <u>any</u> of the following events:
   - CV death Non-fatal MI
   - Hospitalization for CVD events which include:
     - Unstable angina AND evidence of new or presumed new progressive obstructive coronary disease, OR

    - Emergency revascularization procedures at any time and urgent revascularization procedures ≥30 days after the index events prior to randomization
  - Stroke
2. Total incidence of Narrow MACE
3. Time from randomization to CV Death or Non-fatal MI
4. Time from randomization to coronary heart disease (CHD) death or Non-fatal MI
5. Time from randomization to Non-fatal MI
6. Time from randomization to CV Death
7. Time from randomization to Stroke
8. All-cause mortality
9. Incidence of hospitalization for congestive heart failure (CHF)

3.2.2.1. Other Secondary Endpoints

- The percent change in apoA-I, apoB, LDL-C, HDL-C, and TG over time within and between treatment groups
- The change from baseline in HbA1c, fasting glucose, and fasting insulin within and between treatment groups
- Changes in ALP within and between treatment groups for all subjects and according to quartiles of ALP baseline concentration
- Changes from baseline in kidney function in subgroup population with estimated glomerular filtration rate <60 mL/min/1.7m^2 within and between treatment groups

3.2.3. Exploratory Endpoints

- The percent change in hsCRP, fibrinogen, and inflammatory cytokines within and between treatment groups
- Change in MoCA score in all and those with baseline MoCA <26 within and between treatment groups
- Transcription/mRNA change in whole blood from baseline to 6 weeks treatment within and between treatment groups
- Change in Health Related Quality of Life (HRQOL) as measured using the EQ-5D-5L

3.2.4. Safety Endpoints

- Safety assessments will include incidence of adverse events (AEs), serious adverse events (SAEs), vital sign measurements, clinical laboratory evaluations, and physical examination findings.

3.3. Study Drugs

RVX000222 is available as a capsule formulation with standard excipients and established stability. Placebo for RVX000222 is available as a capsule formulation free of RVX000222 API. It is comprised of standard excipients and has established stability.

RVX000222 (200 mg BID) will be taken orally with food in the morning and evening, approximately 10-12 hours apart. In certain situations the dose may be decreased to 100 mg daily (50 mg b.i.d.; refer to the protocol). Per protocol, if a dose is missed, subject should take missed dose at the time it is remembered, unless it is within four hours of the next scheduled dose. If within four hours of the next schedule dose,

the missed dose should be skipped. Subjects will take their first dose of study drug while in clinic during Visit 2.

3.4. Study Drug Interruption/Discontinuation

Treatment may be interrupted or discontinued at the discretion of the Investigator and Sponsor, based on AEs, other clinical laboratory data, vital signs measurements, and/or electrocardiogram (ECG) findings.

Subjects discontinuing study drug will continue participation in the study and will complete all remaining study visits. Discontinuation of assigned study drug (RVX000222 or placebo) or high intensity statin therapy should not result in study discontinuation.

3.5. Concomitant Statin Therapy

Protocol defined concomitant treatment in this study is 20-80 mg atorvastatin or 10-40 mg rosuvastatin once daily orally. 20 mg atorvastatin or 10 mg rosuvastatin are acceptable in circumstances such as advanced age, low body mass, or specific drug-drug interactions (e.g. anti-retrovirals).

Subjects will receive concomitant statin therapy as stated in section 6.6 in the protocol.

The statin dose shall be administered daily in the morning at the same time as the RVX000222 dose (or placebo) and within 30 minutes of completion of a meal. Per protocol, if a dose is missed, subject should take missed dose at the time it is remembered, unless it is within four hours of the next scheduled dose. If within four hours of the next schedule dose, missed dose should be skipped.

3.6. Background Therapy

The subject's other background therapy for dyslipidemia and any coexisting conditions such as CAD, hypertension and diabetes should, in the investigator's opinion, adhere to acceptable standards of care and preferably remain unaltered during the treatment period unless clinically indicated.

3.7. Study Visits

After randomization to RVX000222 or placebo, visits will occur every 2 weeks until Week 12. From Week 12 to Week 28, visits will occur every 4 weeks. From Week 28 until the Last Visit on Treatment, visits will occur approximately every 12 weeks. Four weeks after the Last Visit on Treatment, subjects will return for a final Follow-Up Visit. The Schedule of Events can be found in the study protocol. Study treatment will be terminated in all currently participating subjects when it is estimated that 250 subjects have experienced a narrowly defined MACE event. At that time, all subjects actively treated will conduct their Last Visit on Treatment as soon after as possible while ensuring at least 6 months of study therapy and then return 4 weeks after last day of treatment for the Follow-Up Visit. Procedures are defined in the Schedule of Events.

3.8. Dose Adjustment/Modifications

Additional safety lab monitoring will occur and study drug may be interrupted, reduced, and/or permanently discontinued if the subject meets following criteria. If ALT increases >3xULN or serum bilirubin increases >2xULN, subjects will be notified and repeat chemistries obtained as soon as possible.

1. If ALT increase of 3-5xULN is confirmed on repeat measurement (within 3-4 days), subjects will be monitored every 3-4 days until the ALT is <1.5xULN.
2. If ALT increase of >5xULN, study drug will be suspended. If confirmed on repeat measurement (within 3-4 days), study drug will be permanently discontinued and subjects will be monitored every 3-4 days until the ALT is <1.5xULN.
3. If serum bilirubin increase of >2xULN is confirmed on repeat measurement (within 3-4 days), then study drug will be permanently discontinued and subjects will be monitored every 3-4 days until levels are within normal range.

Subjects who have an ALT increase of ≥3xULN will be monitored by liver safety panels [ALT (SGPT), AST (SGOT), GGT, ALP, bilirubin (direct and total)] and have archival serum samples drawn every 3-4 days until ALT is <1.5xULN.

Subjects who have an ALT increase of >5xULN or who have a serum bilirubin increase of >2xULN will be monitored by extended liver safety panels [ALT (SGPT), AST (SGOT), GGT, ALP, bilirubin (direct and total), as well as osteopontin and PT INR] and have archival serum samples drawn every 3-4 days until ALT is <1.5xULN and serum bilirubin levels are in within the normal range.

Per protocol, subjects should continue to follow the protocol-defined assessments according to the Schedule of Events in the protocol until study completion.

If the ALT elevation has cause (e.g. trauma, infection-inflammation, surgery, acetaminophen, clavulanic acid, diclofenac) treatment may be restarted at 50 mg b.i.d. once ALT returns to 1.5 xULN and subjects should continue with all scheduled study visits according to the Schedule of Events and will have additional liver safety panel tests drawn according to the original study schedule:

- Weeks 0-12 after study drug is reinitiated: liver safety panel every 2 weeks (Weeks 0, 2, 4, 6, 8, 10, 12 after re-initiation)
- Weeks 12-28 after study drug is reinitiated: liver safety panel every 4 weeks (Weeks 16, 20, 24 after re-initiation)
- Weeks 28 after investigational drug is reinitiated to end of treatment: liver safety panel approximately every 12 weeks (Weeks 40, 52, 64, 76, 88, 100)

Re-initiation of study drug will be discussed with and approved by the study medical monitor prior to dosing.

4. General Statistical Considerations

4.1. Reporting Conventions and Dates Handling

Derived analysis data sets will be produced from the electronic case report form (eCRF) data, central laboratory data and the electronic adjudication data (EAS) to assist with analysis and summary of both efficacy and safety endpoints. Derived data sets will identify observations selected according to the study window convention described in section 4.5 and values that will be summarized.

The number and percentage of subjects will be used to summarize categorical variables. When count data are presented and the count is zero, the percentage will be suppressed. Unless otherwise specified, the denominator for percentages will be the number of subjects in a given treatment group within the analysis set of interest. Descriptive statistics (number of subjects with non-missing values, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) will be used to summarize continuous variables unless otherwise noted.

In summary tables for categorical data, all categories will be presented if they are specified on the eCRF (eg, discontinuation reason), or if categories are ordered intervals (eg, age groups), regardless of whether or not a subject is found in a given category. For other categorical data (eg, AEs and medications), only categories with at least 1 subject will be presented. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. When no data are available for a table or listing, an empty page with the title will be produced with suitable text (eg, "There are no observations for this table/listing.").

Means and percentiles will be presented to 1 more decimal place than the recorded data. Standard deviations and standard errors will be presented to 2 more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Percentages will be presented to 1 decimal place. Hazard ratios will be presented with 3 decimal places. Confidence intervals (CIs) will be presented using the same number of decimal places as the parameter estimate (eg, LS mean or hazard ratio).

Subjects are uniquely identified by a concatenation of study center number and subject number. All data available from the eCRFs along with some derived variables will be listed. For relevant dates, the actual day relative to start of double-blind treatment will also be listed. Dates will be presented in the format of "DDMMMYYYY.".

4.2. Sample Size Justification*:*

The study design will provide approximately 80% power to declare superiority of RVX000222 arm over Placebo with a hazard ratio of 0.7, a true hazard ratio of 1.0 and at an overall 2-sided 5% significance level.
To calculate the sample size (number of subjects), the following additional information was assumed:

- Total number of narrowly defined MACE events needed: 250
- 10.5% event rate in the placebo arm at 18 months
- 30% relative risk reduction (7.47% event rate at 18 months in the RVX000222 arm)
- Accrual period of 1.7 years (20 months) and a total study duration (including follow-up) of 2.75 years (143 weeks)
- A cumulative drop-out rate of 10% per arm by the end of the study (5% drop out rate per arm by year one)

With the above design and assumptions, a sample size of approximately 2400 randomized subjects enrolled uniformly over 1.7 years with total study duration of 143 weeks and subjects followed until failure, drop out or end of study is estimated to provide the 250 events needed.

The power and sample size for this study was calculated using East 6.2.

4.3. Randomization, Stratification, and Blinding

4.3.1. Randomization

All qualified subjects will be randomly assigned in a ratio of 1:1 to one of the following two treatment arms: RVX000222 200 mg daily or matching placebo. Randomization will be stratified by country and high intensity statin therapy within the country (i.e. atorvastatin or rosuvastatin). Further, randomization will be dynamically restricted to assure that statin therapy imbalance is no greater than 60:40 (or 40:60) within each country. Study participants will only be directed (per informed consent) to switch their statin therapy to rosuvastatin or atorvastatin once randomization limits are reached on either statin to minimize enrollment impact.

A randomization schedule will be generated for the IWRS and will be implemented by the IWRS prior to dosing at Visit 2. The IWRS will allocate the study drug via the prepared randomization scheme and will provide the randomization number and appropriate drug package numbers. The IWRS process to achieve an approximate even split of study participants across the statin levels per country will be described in greater detail in the IWRS specifications. The subject should always be provided study drug with the number allocated by the IWRS.

4.3.2. RVX000222 Treatment Blinding

The blinding is ensured by using double-blind RVX000222 study drug. Placebo capsules will be equally matched in size, shape, and color to RVX000222 and will be packaged in the same manner. The study drug packaging will be labeled with unique identification numbers allocated from the IWRS.

Subjects, investigative staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization. No member of the CSC, the study team at Resverlogix, personnel at study centers, or any clinical research organization (CRO) handling data will have access to the randomization scheme during the course of the study, with the exception of the study personnel generating the randomization scheme, the personnel preparing DSMB data for review, the DSMB itself, the personnel providing IWRS and carrying out the packaging and labelling of investigational products. Unblinding will occur in the case of subject emergencies when knowledge of the treatment assignment would affect subject care and at the conclusion of the study.

4.4. Analysis Set

The following 3 analysis sets will be used.

4.4.1. Full Analysis Set (FAS)

The FAS will include all randomized subjects who receive any amount of study therapy and have at least one measurement of the assessment of interest. All efficacy analyses will be conducted for the FAS. Subjects will be analyzed based on randomized treatment group. Subjects experienced study drug dose adjustment will be included in the FAS and their data will be analyzed according to the randomized treatment group.

4.4.2. Per-protocol Set (PPS)

The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria, and have no major protocol violations. The major protocol violation criteria will be finalized by the Clinical Science and Biostatistics teams as part of the masked data reviews prior to the interim and final database locks. Likewise, whenever possible, subjects belonging to the PPS will be determined prior to the interim and final database locks. Subjects will be analyzed based on the treatments received most often. The list of major protocol violations is provided in section 5.2 of this statistical analysis plan.

4.4.3. Safety Set (SS)

The SS will include all subjects who took at least one dose of double-blind study therapy. In safety summaries, subjects will be analyzed according to the actual treatment received. All safety analyses will use the SS.

4.5. Definition of Time Points, Study Dates, Visit Windows, and Duration

Study Day 1 is defined as the day of randomization when subjects will receive the first dose. Other study days are defined relative to Study Day 1, e.g. the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2. Study days will not be computed for subjects who are not randomized.

All scheduled study visits will be defined relative to Study Day 1. For example, the appropriate day for the scheduled Week 2 visit should be: Day 1 + 14 = Day 15. A windowing convention which will be used to determine the analysis value for a given study visit will be applicable for all by-visit summaries and analyses. The study visit window can be found in the “Schedule of Events” in the study protocol and also presented in the following table below:

Table 1: Visit Windows for Efficacy and Safety Variables

Study Week	Scheduled Day	Study Day Range	
0	Baseline (Day 1)	<=1	
2	15	12	18
4	29	26	32
6	43	40	46
8	57	54	60
10	71	68	74
12	85	82	88
16	113	110	116
20	141	138	144
24	169	166	172
28	197	194	200
40*	281	274	288
52	365	358	372
64	449	442	456
76	533	526	540
88	617	610	624
100	701	694	708
112	785	778	792

*Visits to occur with +/- 7-day window past week 40 every 12 weeks

Study treatment will be terminated in all currently participating subjects when the 250th event occurs and all surviving patients have been followed for at least 24 weeks from randomization. At that time all subjects actively treated will conduct their Last Visit on Treatment. Follow up visit is to be scheduled 4 weeks after last visit on treatment. Last visit on treatment and follow up are subject to +/-7 day window.

The baseline value for a variable is defined as the last observation collected on or before Study Day 1/first dose date & time; it cannot be substituted for any post-baseline value. Unscheduled visits or Study visits that are outside the protocol defined windows will be mapped to the closest study visits. All safety data with incomplete dates will be forwarded to Data Management for query.

One or more results for a particular variable may be obtained in the same visit window due to unscheduled or repeated measurements. In such events, the result with the date closest to the expected visit date (scheduled day) will be used. In the event that 2 observations equidistant from the expected visit date are available, the later observation will be used.

If the CRF dates are needed for variable derivation or calculation and they are missing after querying the sites, the imputation rules below will be employed. However, no results or outcomes will be imputed.

- If the day is missing in the interim data cut, impute missing day as 15th of the month.
- If the month is missing, impute the month as July.
- Additionally, if both day and month are missing, impute to 15JUL.

- If month/year of the onset date is on or after the month/year of Study Day 1, the AE will be considered on-study;
- If month/year of the onset date is equal to the month/year of Study Day 1, and the end date is present, the end date will be used to determine when the AE resolved. If the end date is on or after Study Day 1, the AE will be considered on-study; otherwise, if the AE stopped before Study Day 1, then it will not be on-study; If month/year of the onset date is equal to the month/year of Day 1, and the end date is a partial date, the AE will be considered on-study.

In addition, durations (e.g. treatment duration) will be measured in weeks and will be calculated as:

(End Date – Start Date + 1)/7.

- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:
  WEEKS = DAYS /7.
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:
  MONTHS = DAYS /30.4375.

5. Subject Disposition

5.1. Disposition

Subjects in the analysis sets (FAS, PPS, and SS) and within each of the stratification factors, namely statin use and country, will be presented. Subject disposition (analyses of randomized, treated, discontinued with primary reason for discontinuation) for FAS will be summarized using frequency and percentage by treatment group.

Subjects are free to discontinue participation in the study at any time. A subject's participation may also be discontinued at any time at the discretion of the Investigator. Withdrawn subjects will not be replaced.

Per protocol, discontinuation of study drug should not result in discontinuation of study participation. The frequency and percentage of randomized subjects who were not treated, who discontinued study drug, and who terminated the study early by reason will be summarized. Such subjects will be still included in the study analysis and final vital status will be ascertained if at all possible using recognized methods.

A subject's participation in the study will be discontinued if any of the following applies:

- Adverse Event
- Withdrawn Consent
- Abnormal Lab Value
- Lost to Follow-up
- Protocol Violation
- Death
- Other

Possible reasons for discontinuation of study drug and discontinuation of study include consent withdrawal, AEs, lost to follow-up or safety labs.

Disposition data, inclusion and exclusion criteria, subject eligibility, as well information on stratification will be displayed.

5.2. Significant Protocol Deviations

The Investigator will not deviate from the protocol without prior written approval from Sponsor or its designee, except in medical emergencies. In the instances that protocol deviations do occur, these will be documented and reviewed as stated in generation of the per-protocol set and displayed. The list of major protocol violations is expected to be as follows:

- Patients who had only an elective PCI (percutaneous coronary intervention) as their index event instead of an urgent one that was performed for the presentation of unstable angina or myocardial infarction
- Acute Coronary Syndrome outside the protocol-specified window
- No evidence of T2DM Diabetes recorded in the case report forms
- Use of immunosuppressants as identified in the exclusion criteria of the protocol and other clinical documentation.

6. Demographics and Other Baseline Characteristics

6.1. Demographics

Baseline and demographic information will be summarized for each treatment group and overall. Demographic and baseline characteristics are age in years, age categories (<=65 vs >65 and by quartiles), sex, race, country, height (cm), weight (kg), and body mass index (BMI) (kg/m^2). Summaries of demographic and baseline characteristics will be based on the FAS. No inferential statistics will be presented.

For subjects not in the United States, age in years will be collected directly from the eCRF. Otherwise, age will be calculated as the integer part of

$$\frac{(\text{date of informed consent - date of birth} + 1)}{365.25}$$

and will be summarized using descriptive statistics. The numbers and percentages of subjects in 2 age categories (<=65 vs >65) and by quartiles will also be reported.

The number and percentage of male and female subjects will be summarized.

The number and percentage of subjects in each race category (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other, Pacific Islander, White and Other) will be presented.

Height will be measured at screening only. Weight will be measured during each physical examination. BMI will be calculated using weight and height collected at Screening as follows:

$$\frac{\text{weight in kg}}{((\text{height in cm})/100)^2}.$$

Height, weight, and BMI at Baseline will be summarized using descriptive statistics.

6.2. Baseline Disease Characteristics and Medical History

Baseline disease characteristics such as time since diagnosis of T2DM to randomization, index ACS event type, and time from ACS to randomization will be calculated or extracted from medical history and presented by treatment group.
Medical history will consist of any significant conditions or diseases that stopped at or prior to the date of informed consent. Ongoing conditions will be considered concurrent medical conditions.

Concurrent medical conditions are significant ongoing conditions or diseases present at time of informed consent. These include clinically significant laboratory findings, ECG, or physical examination abnormalities. Summaries of medical history and concurrent medical conditions will be based on the FAS.

Medical history and concurrent medical conditions will be coded using the latest possible version of Medical Dictionary for Drug Regulatory Activities (MedDRA).

7. Treatments and Medications

7.1. Study Treatments

7.1.1. Study Drug Exposure

RVX000222 or matching placebo will be taken orally with meals in the morning and in the evening, 10-12 hours apart.

Table 2: Study Drug Administration Schedule

Treatment Group	Daily dose (mg)	Dose administration b.i.d. (mg)	AM Dose (mg)	PM Dose (mg)	No. of capsules/day
A: RVX000222	200	100	100	100	2
B: Placebo	0	0	0	0	2

As described in section 3.8, if subjects have elevated ALT values they may be administered study drug or matching placebo at a reduced dose of 50 mg b.i.d. This dose change information is to be collected in the eCRF as action taken with study drug when reporting elevated ALT values as an adverse event and subject to confirmation by the medical monitor. Subjects with at least one study treatment dose reduction and those with none will be represented by treatment group on FAS. Information on number of subjects by number of dose reductions will also be summarized by treatment group.

Study drug exposure will begin on the day of the first dose of study drug and end on the day of the last dose of study drug. Duration of study drug exposure in months will be defined as (date of last dose - date of first dose + 1)/30.4.

Study participation will begin on the day of randomization and end on the day of last contact. Duration of study participation in months will be defined as (date of last contact – date of randomization +1)/30.4.

Duration of exposure to study drug and duration of study participation will be summarized for the FAS using descriptive statistics. Duration of study drug exposure and duration of study participation will also be categorically summarized by number and percentage of subjects who had at least 12-weeks, greater than 12 weeks up to 24 weeks, greater than 24 weeks up to 52 weeks, and greater than 52 weeks of study drug exposure and study participation. Duration of drug exposure on subjects with at least one dose reduction will be summarized by the aforementioned categories.

7.2. Prior and Concomitant Medications

Prior and concomitant medications, including antidiabetic medications, will be coded using the latest WHO Drug dictionary Version June, 2010 or higher and classified into the default anatomical therapeutic chemical (ATC) classification system codes provided by the system (the first ATC code by alphabetic order).

Any medication that was stopped prior to the treatment start date will be considered a prior medication. Medication taken at any time between the treatment start date and the date of last contact, inclusive, will be considered concomitant medication. If the medication start or stop dates are missing or partially

missing and the medication is not checked as ongoing, general imputation rules from section 4.5 will be applied. Subject data including prior and concomitant medications including antidiabetic medications will be presented.

7.2.1. Concomitant Statin Therapy

The high potency statin therapy administered to the study participants will be summarized on FAS including the type of statin (Atorvastatin or Rosuvastatin) and doses. Dose adjustments (increase or decrease dose after first dose administered) will be summarized in a manner similar to study drug dose reduction.

8. Efficacy Analysis

All efficacy analyses will use the FAS set. Subjects will be analyzed according to randomized treatment group. Key efficacy analyses will also be performed on the PPS as supportive evidence and to assess the robustness of the efficacy findings. Each table presents the population that the analysis was conducted on.

Time to event analyses for primary and secondary endpoints will use the Kaplan-Meier method to estimate the median survival time and its 2-sided 95% confidence intervals (CIs). A stratified log rank test will be used for calculating the 2-sided p-value for treatment comparisons.

Primary and key secondary endpoint analyses will include presentation of estimated hazard ratios and associated 2-sided CI obtained from a stratified Cox Proportional Hazards (CPH) model. Assessment of proportional hazards assumption for treatment will be assessed through diagnostic checks involving plots of Schoenfeld residuals obtained from CPH model that fit the primary endpoint of narrowly defined MACE.

For the primary, secondary, and exploratory endpoints, time to event will be the time from the date of randomization to the date of first occurrence of any event in the respective endpoint. A subject who did not have an episode of an event for a given endpoint throughout the study, will be censored for that endpoint at the day of last contact. For any interim database cut, a subject who has not discontinued from the study and did not have an episode of an event for a given endpoint will be censored for that endpoint at the date of the interim cutoff.

Statistical tests for comparing RVX000222 arm with Placebo will be conducted for the primary endpoint and other efficacy endpoints described in Section 3.2. The key secondary endpoints will be tested for superiority in order only if superiority is established for primary efficacy endpoint. The key secondary endpoints will be tested sequentially following a pre-specified order as seen in Section 3.2.2.

The multiplicity of the analyses of the primary and key secondary endpoints will be adjusted using a Sequential Gate-Keeping Procedure. This procedure will preserve the Family Wise Error Rate in light of multiple analyses being performed. The analyses will be performed in sequence until one of the analyses has failed to show the significance level of $p = 0.05$. That is, in order to preserve the overall alpha level at 0.05 across the narrowly defined MACE and broadly defined MACE endpoints, formal statistical inference for the broadly defined MACE can only be made if superiority of RVX222 is demonstrated for the primary efficacy endpoint, narrowly defined MACE, at the two-sided 0.05 significance level.

For continuous endpoints pertaining to liver function, lipid profile, kidney function, HbA1c, fasting glucose, and insulin, descriptive statistics (*N*, mean, median, standard deviation, quartiles, minimum and maximum) will be provided by treatment group at specified visits.

Quantitative endpoints that are defined as a (percent) change from baseline will be analyzed using analysis of covariance (ANCOVA) models with treatment group as a factor and the baseline value as a covariate. Mixed-effect model repeated measurements (MMRM) will be used to analyse a subset of secondary outcomes over time.

Subjects will continue to be followed for both primary and secondary endpoints until 250 adjudicated primary endpoints have been observed. Other than the pre-specified sequential testing, no additional alpha adjustments for multiplicity will be made. That is, no multiplicity adjustment is planned for testing regarding the other secondary and exploratory endpoints as these endpoints are considered supportive.

8.1. Adjudication Process of the Key Endpoints

Potential CV events will be identified by comparing all SAE preferred terms to a pre-established list of MedDRA preferred terms. The terms included in the pre-established list are designed to broadly capture

potential CV events from MedDRA SMQs, system organ classes, preferred terms, and lower-level terms specified in the FDA draft guidance document "Endpoints and Standardized Data Collection for Cardiovascular Outcomes Trials", issued July 22, 2009. All reported terms that code to a listed preferred term will be forwarded to the Clinical Events Committee (CEC) for adjudication. The details of CEC operations and the clinical definitions of the CV outcomes are specified in the CEC charter (v3.0 / 08JUN2017).

High level results of the CEC adjudication of potential CV events as entered into PPD PVG EAS (Electronic Adjudication System) will be transferred and maintained in a SAS dataset. All potential CV events and corresponding adjudication outcomes will be summarized. In addition, association of these events with respect to the primary and key secondary endpoints will be flagged for the analyses. The *possible* adjudication outcomes are categorized as follows:

- Deaths
    - Cardiovascular deaths (including coronary heart disease (CHD) deaths)
    - Non cardiovascular deaths
    - Undetermined cause of death
- Non-fatal cardiovascular events
    - Acute myocardial infarction
    - Hospitalization for unstable angina and evidence of new or progressive obstructive coronary disease.
    - Hospitalization for other angina
    - Hospitalization for heart failure
    - Non- Elective (Urgent/Emergency/Salvage) Coronary Revascularization
    - Stroke

8.2. Primary Analysis

The primary analysis will be a time-to-event analysis. The distributions of the primary endpoint within the RVX000222 and placebo groups will be compared using a two-sided stratified log-rank test (LRT) with an alpha = 0.05 level of significance (two sided). Time to first narrowly defined MACE, defined as a single composite endpoint of CV Death or Non-fatal MI or Stroke, will be calculated using randomization date and date of the confirmed event, or date of last contact for censored subjects. For the purpose of the primary analysis and all subsequent analyses involving CV deaths, events within the undetermined cause of death category will be considered CV deaths. All subjects will be followed until drop-out, death, or study closure. Drop-out may be due to withdrawal of consent from further data collection or lost to follow-up. Subjects who drop-out or are alive at study closure will have their event times censored at the time of last contact.

The primary efficacy analysis will be performed on the FAS. The number and percentage of subjects who experienced the narrowly defined MACE, median survival time and corresponding 95% confidence intervals (CIs) will be tabulated and presented by treatment group. A stratified log-rank test and corresponding test statistic, stratifying by country of enrollment and prescribed statin therapy (atorvastatin or rosuvastatin), at a two-sided alpha level of 0.05, will be used to compare the survival rate between the two treatment groups. If stratifying by country results in too many empty cells, stratifying by geographic region may be considered.

As supportive analyses, the primary efficacy analysis will be

1. repeated for the PPS set

2. repeated for FAS set but using just events adjudicated as CV deaths excluding "undetermined cause of death events". This analysis will be outside the analysis hierarchy of the study and will not influence secondary endpoint analyses.

3. performed on the FAS using an unstratified LRT as a supportive analysis.

Kaplan-Meier plots for the primary and key secondary endpoints by treatment groups will be presented. Presentation of primary analyses will include estimated hazard ratios and associated 2-sided CI obtained from Cox Proportional Hazard (CPH) models with treatment as the single factor, stratified by country of enrollment and prescribed statin therapy (atorvastatin or rosuvastatin).

Subgroup analyses will be conducted for the primary endpoint based on the following categorizations:

- Subjects receiving rosuvastatin and those receiving atorvastatin
- Index acute coronary syndrome $\leq$ 30 days and > 30 days pre randomization
- LDL/HDL/TG's above and below median value for the study sample
- HbA1c above and below median value for the study sample
- GFR $\geq$60 mL/min and < 60 mL/min as calculated at baseline
- hs-CRP $\geq$ and below the median, as collected at Visit 2
- ALP above and below median as collected at screening,
- Males and Females

8.3. Key Secondary Analysis

Similar to the primary analysis, the key secondary endpoints (listed in section 3.2.2) are also time-to-event variables and will be analyzed using time-to-event models and the stratified log rank test, as described for the primary analysis.

The key secondary analysis will be performed on FAS. The number and percentage of subjects experienced the broadly defined MACE, median survival time and corresponding 95% confidence intervals (CI) will be tabulated and presented by treatment group. A stratified log-rank test and corresponding test statistic, stratifying for country of enrollment and prescribed statin therapy (atorvastatin or rosuvastatin), at a two-sided alpha level of 0.05, will be used to compare the survival rate between the two treatment groups. For the purpose of all subsequent analyses listed below involving CV deaths, events within the "undetermined cause of death" category will be considered CV deaths.

No adjustment for multiplicity is needed for the primary hypothesis as there is no provision to terminate the trial for efficacy. A sequential gate-keeping approach will be used to control the overall Type I error rate when testing for the key secondary endpoints only if superiority is established for primary efficacy endpoint.
The key secondary endpoints will be tested sequentially following a pre-specified order as stated in section 3.2.2 and re-emphasized below:

1. Time from randomization to the first occurrence of adjudication-confirmed MACE broadly defined between treatment groups.

2. Total incidence in narrow MACE (CV Death or Non-fatal MI or Stroke)
3. Time from randomization to CV Death or Non-fatal MI
4. Time from randomization to coronary heart disease (CHD) death or Non-fatal MI
5. Time from randomization to Non-fatal MI
6. Time from randomization to CV Death
7. Time from randomization to Stroke
8. All-cause mortality
9. Incidence of hospitalization for congestive heart failure (CHF)

The analysis of the key secondary endpoint will be repeated for the PPS set as the supportive analysis. Presentation of key secondary analyses will include estimated hazard ratios and associated 2-sided CI obtained from Cox Proportional Hazards (CPH) model with treatment as a factor, stratified by country of enrollment and prescribed statin therapy (atorvastatin or rosuvastatin).

Endpoints such as incidence of narrow MACE or incidence of CHF will allow consideration of recurrent events and will be evaluated using Andersen-Gill methodology in a proportional hazards model. Hazard ratios, confidence intervals, and p values will be presented as appropriate. Event rate and corresponding hazard ratios will be provided for all-cause mortality.

8.4. Other Secondary and Exploratory Analysis

Other secondary and exploratory endpoints are listed in sections 3.2.2.1 and 3.2.3. Quantitative endpoints that are defined as a (percent) change from baseline will be analyzed using analysis of covariance (ANCOVA) models with treatment group, baseline value, and strata as covariates. Descriptive statistics for (percent) change from baseline at each post-baseline visit will be summarized using the FAS.

Descriptive statistics (number of subjects with non-missing values, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) will be used to summarize continuous variables by treatment group for the FAS set.

Least squares (LS) means and difference in LS means between RVX000222 and Placebo with standard errors (SEs) and 2-sided 95% CI and p-values obtained from ANCOVA model will be presented at each applicable post baseline visit.

Mixed-effects model repeated measures analysis will be used to model percent change in measurements over time at the last visit on treatment (LVT). An unstructured covariance matrix will be used to fit the underlying MMRM model. Subject and error will be considered random effects; all effects that include treatment, strata and baseline value will be considered fixed.

The pattern of change from baseline over time will also be displayed graphically in Figures for some endpoints. No multiplicity adjustment is planned to test the other secondary and exploratory endpoints. Since most of the other secondary endpoints are clinical laboratory tests, they are also summarized under safety analysis in section 9.

Analyses will summarize EQ-5D-5L scale and subscale scores at each visit and change from baseline at each visit.

Analyses will address mean differences by treatment group on MOCA scale and differences for subjects with a baseline score indicative of cognitive impairment (Baseline MoCA < 26)

9. Safety Analysis

Safety data such as clinical laboratory results, vital signs, findings from physical examinations will be listed and/or summarized by treatment group where appropriate. No inferential hypothesis testing will be performed on the safety variables.

The assessment of safety will be based on the frequency, intensity, and types of AEs and for change and from Baseline in the clinical laboratory variables, and vital sign measurements.

9.1. Adverse Events

Adverse events will be summarized using the safety set. Adverse events will be coded using MedDRA (version 17.0 or higher), summarized by frequency, severity, relationship to study drug, and number of subjects per treatment and by the preferred term and system organ class. Data will be summarized using preferred term and primary system organ class. The coded events will be summarized by treatment group, in subsets of all treatment-emergent AEs, all treatment-related AEs, and serious treatment emergent AEs.

9.1.1. Incidence of Adverse Events

A Treatment-Emergent AE (TEAE) will be defined as any AEs, regardless of relationship to study drug, that occur after the first dose of double-blind study drug and within 14 days after the last dose of double-blind study drug. An AE with a reported onset date after the subject has signed the informed consent document and before the date of randomization (or the date of first dose of study drug if a subject was treated but no randomized) will be considered a pre-study event. AEs with missing onset dates will be considered on-study events.

If the day of onset of an AE is missing, and if the month and year of an onset date are on or after Day 1, general imputation rules from section 4.5 will be applied.

If, despite implementing the above conventions, the onset date of the AE cannot be placed before, on, or after Day 1, then the event will be considered on-study.

All AEs will be coded using the MedDRA Version 17.0 or higher coding system. In this dictionary, each diagnosis is mapped to a lower level term and then to a preferred MedDRA term, which is then mapped to a system organ class.

TEAEs will be summarized by treatment group and overall for the SS. Summaries of TEAEs will be displayed by descending overall frequency for system organ class and preferred term. Treatment-Emergent AEs and SAEs will include events per 100 subject-years of study drug exposure. In addition, TEAEs leading to Study Drug Discontinuation, Serious TEAEs and TEAEs resulting in Deaths will be presented.

9.1.2. Relationship of Adverse Events to Study Drug

Numbers and percentages of subjects with TEAEs by causality and study drug-related TEAEs will be summarized by system organ class and preferred term; TEAE with missing relationship to study drug will be considered as study drug-related and included. However, the TEAE will be presented with a missing relationship. Drug-related TEAEs will be defined as any TEAE that the investigator considers related to study drug. If a subject reported multiple occurrences of the same AE, only the

related occurrence will be presented. Therefore, these summaries will not include events per 100 subject-years of study exposure.

9.1.3. Intensity of Adverse Event

Numbers and percentages of subjects with TEAEs by intensity, system organ class and preferred term will be summarized; AEs with missing intensity will be imputed. If a subject reported multiple occurrences of the same AE, only the most severe occurrence will be presented. Therefore, these summaries will not include events per 100 subject-years of study exposure.

9.1.4. Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (life threatening refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect; or
- Is medically significant, and though not included in the above list, is an important medical event that may jeopardize the subject or require medical intervention to prevent one of the outcomes listed above. Discontinuation of study drug or conduct of additional diagnostic evaluations, will not, by themselves, satisfy the criterion for a medically significant event.

9.1.5. Hospitalization

Adverse events reported from clinical trials associated with hospitalization or prolongations of hospitalization are considered serious and will be included in SAEs.

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care
- Skilled nursing facilities
- Nursing home
- Routine emergency room admission
- Same day surgeries (as outpatient/same day/ambulatory procedures)

9.1.6. Adverse Events Leading to Study Drug Discontinuation

AEs leading to study drug withdrawal will be recorded on the eCRF with a study drug action taken as "Drug Withdrawn". Numbers and percentages of subjects with AEs leading to study drug withdrawal will be summarized by system organ class and preferred term. All AEs leading to study drug withdrawal will also be summarized.

9.1.7. Death

All deaths during this study will be reported. Data presented will include, where applicable, date of first dose, AE type, date of death, days relative to the date of randomization, date of last dose, study day, cause of death, and relationship of cause of death to study drug.

9.2. Clinical Laboratory Evaluations

Clinical laboratory samples (fasting lipid panel, hematology, chemistry, hepatitis serology, liver safety, lipoproteins, and inflammation panel) will be collected according to the study Schedule of Events shown in the protocol.

Evaluation of clinical laboratory samples collected for safety will include standard hematology, serum chemistry, and urinalysis. All summaries of clinical laboratory variables will be performed using the SS. No inferential statistics will be provided.

Change from baseline in continuous safety laboratory variables will be summarized by treatment group. Standard units will be reported for all lab tests.

In the event that 2 or more observations equidistant from the expected visit date are available, the later observation will be used. A subject who has multiple test results for a particular test at a particular visit and at least 1 of them is markedly abnormal; the subject will be classified as having a markedly abnormal result at that visit and values from all visits will be listed. All descriptive statistics will be based on data selected according to the window convention outlined in Section 4.5.

9.2.1. Fasting Lipid Profile

Fasting blood work will be collected for lipid profile (total cholesterol, LDL-C, HDL-C, and TGs), at visits indicated on the Schedule of Events in the study protocol.

A summary of descriptive statistics of lipid profile values for baseline, each post-baseline scheduled visit, and change from baseline to each post-baseline scheduled visit will be presented.

9.2.2. Hematology

Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count, and HbA1c will be measured at visits indicated on Schedule of Events in the study protocol.

A summary of descriptive statistics of hematology values for baseline, each post-baseline scheduled visit, and change from baseline to each post-baseline scheduled visit will be presented.

9.2.3. Chemistry

Albumin, blood urea nitrogen, creatine kinase (CK), serum creatinine, fasting glucose, ALP, calcium, phosphate, potassium, sodium, and total protein will be measured at visits indicated on the Schedule of Events in the study protocol.

Estimated glomerular filtration rate will be calculated by the lab using serum creatinine values and the Cockcroft-Gault formula.

A summary of descriptive statistics of serum chemistry values for baseline, each post-baseline scheduled visit, and change from baseline to each post-baseline scheduled visit will be presented.

9.2.4. Hepatitis Serology

Blood samples will be collected at Screening to test for antibody to hepatitis A (IgM), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B virus core protein antibody (HBcAb), hepatitis C (HCV). Subjects with evidence, in the opinion of the Investigator, of active hepatitis will be excluded from participation in this study. Since these tests are only collected at screening only, the data will be available upon request.

9.2.5. Liver Safety Panel

ALT (SGPT), AST (SGOT), gammaglutamyl transferase (GGT), ALP, and bilirubin (direct and total) will be measured at each visit as indicated on the Schedule of Events in the study protocol.

As defined in the protocol, subjects who have an ALT increase of ≥3xULN will be monitored by liver safety panels and have archival serum samples drawn every 3-4 days until ALT values return to <1.5xULN and subjects who have an ALT increase of >5xULN or who have a serum bilirubin increase of >2xULN will be monitored by extended liver safety panels and have archival serum samples drawn every 3-4 days until ALT values return to <1.5xULN or serum bilirubin values return to within normal range.

The Extended Liver Panel includes ALT (SGPT), AST (SGOT), GGT, ALP, bilirubin (direct and total), as well as osteopontin and PT/INR.

9.2.6. Biomarker Laboratory Tests

A subset of up to 600 subjects in selected countries will have additional biomarker samples collected for lipoprotein, fasting insulin, and an inflammation panel analysis as described below (Sections 9.2.6.1 through 9.2.6.3) at visits indicated on the Schedule of Events in the study protocol.

9.2.6.1 Lipoproteins

Fasting blood work will also be collected from a selected subset of subjects for apoA-I and apoB at visits indicated on the Schedule of Events in the study protocol. Summary statistics for apoA-I and apoB values at baseline, each post-baseline scheduled visit, and change from baseline to each post-baseline scheduled visit will be presented.

9.2.6.2 Fasting Insulin

Fasting insulin will be measured in a selected subset of subjects at visits indicated on Schedule of Events in the study protocol. A summary of descriptive statistics for fasting insulin values at baseline, each post-baseline scheduled visit, and change from baseline to each post-baseline scheduled visit will be presented.

9.2.6.3 Inflammation Panel

hsCRP, fibrinogen, and inflammatory cytokines will be measured in a selected subset of subjects at visits indicated on Schedule of Events in the study protocol. Summary statistics of hsCRP, fibrinogen, and inflammatory cytokines values at baseline, each post-baseline scheduled visit, and change from baseline to each post-baseline scheduled visit will be presented.

9.3 Montreal Cognitive Assessment (MOCA).

The MOCA will be performed on subjects 70 years of age and older at visits indicated on the Schedule of Events to measure any cognitive changes from baseline. Descriptive statistics of the assessment and changes from baseline at visits will be presented. Analyses will also address mean differences for subjects with a baseline score indicative of cognitive impairment (Baseline MoCA < 26).

9.4 Vital Sign Measurements

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature) will be measured according to the Schedule of Events in the study protocol.

Vital signs measured are systolic and diastolic blood pressure in mmHg, pulse rate in beats per minute, and weight in kg. A summary of descriptive statistics for vital sign measurements at baseline, each post-baseline scheduled visit, interim last value, and the last observed value, and change from baseline to each post-baseline scheduled visit using the SS will be presented.

9.5 Electrocardiogram

A standard 12-lead ECG will be performed at Screening (Visit 1).

The number and percentage of subjects in each overall ECG interpretation category (normal, clinically significant abnormal, non-clinically significant abnormal) will be summarized using the SS. Percentages will be based on the number of subjects with values at each visit.

Schedule of Events

	Screen	Treatment																		Follow Up (ET)
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 to end of study	LVT[1]	FU
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100	112, then every 12wks	end of study	LVT + 4wks[2]
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed Consent	X																				
Randomization		X																			
Inclusion / Exclusion	X	X																			
Medical History/Demographics	X																				
ECG	X																				
Vital Signs	X	X									X			X		X		X		X	X
Physical Exam[3]	X																	X		X	X
Central Laboratory:																					
Fasting Lipid profile[4]	X										X			X		X		X		X	X
Hematology[5], HbA1c	X										X			X		X		X		X	X
Chemistry[6]	X										X			X		X		X		X	X
Urinalysis[7]	X										X			X		X		X		X	X
Hepatitis Serology[8]	X																				
Liver Safety Panel[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker Laboratory Tests[10]																					
Lipoproteins[11], fasting insulin		X									X			X		X		X		X	X
Inflammation Panel[12]		X						X						X							
Serum/Plasma Archive[13]		X						X						X							
Pharmacogenomic[14]		X			X																
MOCA[15]		X												X				X		X	
EQ-5D-5L		X									X			X		X		X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior / Con. Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispense/Account.	X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Study treatment will be terminated in all currently participating subjects when the 250th event occurs and all surviving patients have been followed for at least 24 weeks from randomization. At that time all subjects actively treated will conduct their Last Visit on Treatment.
[2] 4 weeks after Last Visit on Treatment (LVT).
[3] Physical Exam: height will be recorded only at Visit 1
[4] Lipid profile includes: TC, LDL-C, HDL-C, TG
[5] Hematology includes: platelet count, hemoglobin, hematocrit, RBC, WBC with differential
[6] Chemistry includes: albumin, blood urea nitrogen, creatine kinase, serum creatinine, fasting glucose, calcium, phosphate, potassium, sodium, total protein
[7] Including urine HCG at screening for subjects of childbearing potential. Dipstick tests performed and results maintained at investigational sites.
[8] Hepatitis Serology: hepatitis A (IgM), B by HBs-Ag, Anti-HBs, Anti-HBc , C (HCV)
[9] Liver Safety Panel: ALT (SGPT), AST (SGOT), GGT, ALP, bilirubin (direct and total)
[10] Additional biomarker laboratory test samples will be collected on a selected subset of subjects
[11] Lipoproteins include: apoA-I and apoB
[12] Inflammation Panel includes: hsCRP, fibrinogen, and inflammatory cytokines
[13] Serum/plasma samples for future biomarker analysis in lipid/inflammation
[14] Optional: whole blood will be collected for DNA analysis (Visit 2 only) and mRNA analysis (both Visit 2 and 5) if consent obtained.
[15] **Montreal Cognitive Assessment (MOCA)** will be performed on subjects ≥70 years of age at randomization
[16] Only statin will be dispensed at screening visit and LVT.