BETonMACE

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)

Protocol Number:	RVX222-CS-015
Investigational Product:	RVX000222 Oral, 100 mg Capsule
EudraCT Number: ClinicalTrials.gov Identifier:	2015-002040-14 NCT02586155
Sponsor:	Resverlogix Corp. 300, 4820 Richard Road SW Calgary, Alberta, T3E 6L1 CANADA Phone: 403.254.9252 Fax: 403.256.8495
Medical Monitor:	Michael Sweeney, M.D. Resverlogix Corp.
Protocol Version / Date:	Version3A / 31 October 2017

Clinical Development Approval:

Michael Sweeney, M.D
Senior VP of Clinical Development
Resverlogix Corp.

Date

PROTOCOL REVIEW AND SIGNATURE FORM

Sponsor:	Resverlogix Corp.
Protocol 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)
Protocol Number:	RVX222-CS-015
Protocol Version / Date:	Version 3A / 31 October 2017

I have read the above-mentioned protocol. I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and other applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Principal Investigator Signature	Date

Principal Investigator Name (print)

CLINICAL STUDY RVX222-CS-015 PROTOCOL SYNOPSIS

Title	BETonMACE: 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)
Protocol No.	RVX222-CS-015
Study Centers	Multiple, global investigative sites
Indication	Secondary cardiovascular disease (CVD) prevention in type 2 diabetes mellitus (T2DM) subjects with low high-density lipoprotein cholesterol (HDL-C) at high risk for MACE.

Objectives	**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.
	
	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 any of the following events:
	  • CV death
	  • Non-fatal Myocardial Infarction (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 event as defined by Hicks et al.
	  • 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), low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglyceride (TG) over time within and between treatment groups
	• To evaluate changes in diabetes mellitus variables including glycated hemoglobin (HbA1c), fasting glucose, and fasting insulin over time within and between treatment groups
	• To evaluate changes in alkaline phosphatase (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 (eGFR) <60 mL/min/1.7m^2 • To evaluate the safety and tolerability of RVX000222 **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
Study Design	This design 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 intensity statin therapy administered to T2DM subjects with history of recent CAD event and HDL-C level <40 mg/dL males or <45 mg/dL females. High intensity statin therapy shall consist of a daily dose of either atorvastatin 40-80 mg or rosuvastatin 20-40 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 high intensity 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 patients 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 high intensity 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, treatment-blinded MACE Clinical Events Committee (CEC) in an ongoing manner.
Target Population	Male or female subjects with T2DM and high risk CAD treated with high intensity statin therapy and with a low level of HDL-C of <40 mg/dL males or <45 mg/dL females.
Length of Study	Total subject participation: • Screening period of 1-2 weeks • Treatment period of time until study reaches 250 narrowly defined MACE events or a minimum of 24weeks • Follow-up period of 4 weeks

Selection Criteria	**Inclusion Criteria:** 1. Male and female subjects age 18 and over with documented diagnosed T2DM and a CAD event of either unstable angina or myocardial infarction, not less than 7 days and no more than 90 days prior to Visit 1. In order to have sufficient number of clinical events, the number of subjects with unstable angina will be limited to 25% of the total number of subjects. • Unstable angina: for a qualifying unstable angina event, each of components (a), (b), and (c) must be satisfied: a. Characteristic ischemic pain or discomfort in chest or associated referral areas, occurring at rest or with minimal exertion b. ECG changes consistent with acute myocardial ischemia based upon at least one of the following: i. new or presumed new ST elevation ii. new or presumed new ST depression iii. new or presumed new T-wave inversion c. Objective evidence of obstructive coronary artery disease based upon at least one of the following: i. new or presumed new evidence of myocardial ischemia or infarction by perfusion imaging ii. new or presumed new regional wall motion abnormality iii. current evidence of at least one epicardial coronary artery stenosis ≥70% by coronary angiography iv. need for coronary revascularization for the index ACS event, including a percutaneous coronary intervention (PCI) with or without coronary stenting • Previous MI 7-90 days before screening, treated with or without a percutaneous coronary intervention (PCI). For a qualifying event of MI, **two of the following three criteria must be satisfied**: a. Characteristic ischemic chest pain or pain in associated referral areas b. Dynamic elevation of troponin T or I or CKMB, if troponin T or I is unavailable at the local lab (at least above the upper limit of normal for the laboratory) c. Development of new Q-waves in at least two adjacent electrocardiogram (ECG) leads or development of a new dominant R wave in V1 2. Documented diagnosis of T2DM (one or more of the following criteria must be met): • Documented history of T2DM • History of taking diabetes medication • HbA1c ≥6.5% at Visit 1 3. For males HDL-C of <40 mg/dL (1.04 mmol/L) and for females HDL-C of <45 mg/dL (1.17 mmol/L) at Visit 1. 4. In the opinion of the Investigator, subjects currently not on high intensity statin therapy will be able to start rosuvastatin according to the protocol at Visit 1.

5. In the opinion of the Investigator, subjects currently on statin therapy other than atorvastatin or rosuvastatin can be switched to rosuvastatin according to the protocol at Visit 1. High intensity statin therapy doses should remain unchanged during the study period if at all possible.
6. Female subjects must meet one of the following:
   - If of childbearing potential, female subjects must have a negative urine pregnancy test and be willing and able to use medically acceptable non-hormonal method of birth control (non-hormonal intrauterine device, condom, or diaphragm) or remain abstinent from Screening until Follow-up Visit.
   - Be of non-child-bearing potential: post-surgical sterilization or post-menopausal.
7. Have given signed informed consent to participate in this study.

Exclusion Criteria:

1. Heart disease which, in the opinion of the investigator, will within 90 days of Visit 1 likely require coronary bypass, PCI, cardiac transplantation, surgical repair and/or replacement.
2. Previous or current diagnosis of severe heart failure (New York Heart Association Class IV) or a documented left ventricular ejection fraction (LVEF) of <25% as determined by contrast left ventriculography, radionuclide ventriculography or echocardiography. The absence of a LVEF measurement in a subject without a previous or current diagnosis of heart failure does not prohibit entry into the study.
3. Subjects with evidence of cardiac electrophysiologic instability including a history of uncontrolled ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardias with a ventricular response heart rate of >100 beats per minute at rest within 4 weeks prior to Visit 1.
4. Coronary artery bypass grafting (CABG) within 90 days prior to Visit 1.
5. Evidence of severe renal impairment as determined by <u>any one</u> of the following:
   - an eGFR <30 mL/min/1.7m^2 at Visit 1
   - a current need for dialysis
6. Uncontrolled hypertension defined as 2 consecutive measurements of sitting blood pressure of systolic >180 mm Hg or diastolic >100 mm Hg at Visit 1.
7. Subjects at risk of immunosuppression, including current or recent (within 12 months prior to Visit 1) treatment with immunosuppressants (e.g., cyclosporine).
8. Use of fibrates at any dose or niacin/nicotinic acid 250 mg or more within 30 days prior to Visit 1.
9. A known allergy or sensitivity to any ingredient in the investigational medicinal product.
10. History of intolerance to atorvastatin or rosuvastatin. This exclusion criterion applies to subjects with a history of intolerance to the statin to which they would be assigned at screening.
11. Triglycerides >400 mg/dL (4.52 mmol/L) at Visit 1.
12. Any medical or surgical condition which might significantly alter the absorption, distribution, metabolism or excretion of medication including, but not limited to any of the following: untreated or incompletely treated thyroid dysfunction, cholecystitis, Crohn's disease, ulcerative colitis, or any gastric bypass alteration.

	13. Evidence of cirrhosis from liver imaging or biopsy, a history of hepatic encephalopathy, esophageal or gastric varices, active hepatitis, or prior porta-caval shunt procedure, or a Child-Pugh score of at least 5 points (Appendix A). • Any one of the following liver enzymes that is >1.5x the upper limit of normal range (ULN) by central lab at Visit 1 a. Alanine aminotransferase (ALT) b. Aspartate aminotransferase (AST) 14. A total bilirubin that is >ULN by central lab at Visit 1. 15. History of malignancy of any organ system, treated or untreated, within the past 2 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. 16. History or evidence of drug or alcohol abuse within 12 months of Visit 1, in the opinion of the investigator. 17. Female subjects who are pregnant. 18. Any condition which, in the opinion of the investigator, may place the subject at higher risk from his/her participation in the study, or is likely to prevent the subject from complying with the requirements of the study or completing the study, including subjects at risk of immunosuppression. 19. Use of other investigational drugs and devices within 30 days or 5 half-lives of Visit 1, whichever is longer. 20. History of noncompliance with medical regimens or unwillingness to comply with the study protocol. 21. Any condition that, in the opinion of the investigator, would confound the evaluation and interpretation of efficacy and/or safety data. 22. Persons directly involved in the execution of this protocol.
Study Procedures	After informed consent is signed at the Screening Visit (Visit 1), laboratory samples will be collected, and subjects currently receiving high intensity statin therapy of 40-80 mg atorvastatin or 20-40 mg rosuvastatin will continue on the same statin as they are currently receiving. Subjects who are currently receiving atorvastatin or rosuvastatin at doses other than the protocol-defined dosage will, if clinically appropriate in the investigator's opinion, begin treatment with atorvastatin at the 40-80 mg dose or rosuvastatin at the 20-40 mg dose. [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).] Subjects not currently receiving high intensity statin therapy of atorvastatin or rosuvastatin, will begin treatment with 20-40 mg rosuvastatin and discontinue use of any other statin previously prescribed. Randomization will be stratified by the participating country and high intensity statin therapy (atorvastatin or rosuvastatin) within the country. Further, randomization will be dynamically restricted to assure that statin therapy imbalance is no greater than 60:40 (or 40:60) within each country. After 1 to 2 weeks of study qualification and demonstrated tolerance of high intensity statin therapy treatment during screening phase, subjects will return to the clinic for Visit 2 at which adverse events (AEs) will be recorded. Upon confirmation of tolerance of high intensity statin therapy and satisfaction of inclusion and exclusion criteria based on the Visit 1 central laboratory results, subjects will be randomized and treatment-blinded investigational drug will be dispensed. Atorvastatin or rosuvastatin dose may be adjusted if indicated clinically during the study.

Clinical safety will be evaluated at each visit. Assessments can include physical examinations, vital sign measurements and clinical laboratory measurements including lipid analysis, biomarkers of cardiovascular (CV) risk and safety laboratories. All CV events including hospitalizations and deaths will be adjudicated by a CEC. A DSMB will monitor the study regularly.

	Screen											**Treatm**
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Informed Consent	X											

After randomization to RVX000222 or placebo, visits will occur every 2 weeks until Week 12. From Week 12 to 28, visits will occur every 4 weeks. From Weeks 28 until the Last Visit on Treatment visits will occur approximately every 12 weeks. Four to sixteen weeks after Last Visit on Treatment, patients will return for a final Follow-Up Visit. Study treatment will be terminated in all currently participating subjects when 250 narrowly defined MACE events have occurred in the study and all surviving patients have been followed for at least 24 weeks from randomization. At that time, all subjects will conduct their Last Visit on Treatment. Subjects will continue to take atorvastatin or rosuvastatin and will return 4 weeks after Last Visit on Treatment for the Follow-Up Visit. Procedures are defined in

Randomization		X										
Inclusion / Exclusion	X	X										
Medical History/Demographics	X											
ECG	X											
Vital Signs	X	X									X	
Physical Exam	X											
Central Laboratory:												
Fasting Lipid profile	X										X	
Hematology, HbA1c	X										X	
Chemistry	X										X	
Urinalysis	X										X	
Hepatitis Serology	X											
Liver Safety Panel	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker Laboratory Tests												
Lipoproteins, fasting insulin		X									X	
Inflammation Panel		X						X				
Serum/Plasma Archive		X						X				
Pharmacogenomic		X			X							
MOCA		X										
EQ-5D-5L		X									X	
Adverse Events	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
Drug Dispense/Account.	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Events. The same visit schedule will apply to subjects who remain on assigned study treatment until the Last Visit on Treatment and to subjects who have prematurely discontinued study medication prior to the Last Visit on Treatment.

Liver safety:

a) If ALT increase of >3 and ≤5xULN is confirmed on repeat measurement (within 3-4 days), subjects will be monitored every 3-4 days until the ALT is <1.5xULN.
b) If ALT increase of >5xULN, investigational drug will be suspended. If confirmed on repeat measurement (within 3-4 days), investigational drug will be discontinued and subjects will be monitored every 3-4 days until ALT is <1.5xULN.
c) If serum bilirubin increase of >2xULN, investigational drug will be suspended. If confirmed on repeat measurement (within 3-4 days), investigational drug will be 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 osteopontin and PT INR] and have archival serum samples drawn every 3-4 days until ALT is <1.5xULN and serum bilirubin is within the normal range.

If the ALT or serum bilirubin elevation has a likely cause other than investigational drug (e.g. trauma, infection-inflammation, surgery, acetaminophen, clavulanic acid, diclofenac), investigational drug may be restarted at 50 mg b.i.d. once ALT returns to 1.5xULN. Subjects should continue with all scheduled study visits with additional liver safety panel tests drawn as defined in Section 6.10.1. All re-initiations of study therapy must be discussed with and approved by the study medical monitor.

Investigational drug	RVX000222 will be administered orally with food at a dose of 200 mg daily (100 mg b.i.d.). In certain situations the dose may be decreased to 100 mg daily (50 mg b.i.d.)
Concomitant Statin Therapy	Protocol-defined concomitant statin therapy in this study is a tolerable atorvastatin daily dose of 20-80 mg or rosuvastatin daily dose of 10-40 mg. [Doses of 20 mg atorvastatin and 10 mg rosuvastatin are 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).]
Efficacy Assessments	**Primary Endpoint:** 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. **Key Secondary Endpoints:** 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: o Unstable angina AND evidence of new or presumed new progressive obstructive coronary disease, OR o Emergency revascularization procedures at any time and urgent revascularization procedures ≥30 days after the index events prior to randomization • Stroke 2. Time from randomization to fatal or non-fatal MI, or fatal or non-fatal stroke 3. Time from randomization to CV Death or Non-fatal MI 4. Time from randomization to Non-fatal MI 5. Time from randomization to CV Death 6. Time from randomization to Stroke 7. All-cause mortality **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/1.7 m^2 within and between treatment groups **Exploratory Endpoints:** • The percent change in hsCRP, fibrinogen, and inflammatory cytokines 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
Safety Assessments	Safety assessments will include incidence of AEs, serious AEs (SAEs), vital sign measurements, clinical laboratory evaluations, and physical examination findings. For subjects ≥70 years at randomization, a Montreal Cognitive Assessment (MOCA) test will be completed.

Data Safety Monitoring Board	An independent DSMB will be appointed to monitor the subject safety data on an ongoing basis at quarterly meetings during the course of the study. The ongoing DSMB safety review will include review of adverse events of special interest, including all opportunistic infections and serious infections. In addition to ongoing safety assessments, the DSMB will review and interpret the planned interim efficacy analysis to assess futility and sample size, if indicated, when 75% (i.e. 188) of the 250 narrowly defined MACE have been confirmed by CEC. The statistical methodology for SSA that preserves the overall Type I error will be described in greater detail in the DSMB interim futility / sample size adjustment analysis plan.
Sample Size	It is estimated that enrollment of approximately 2400 subjects will be needed to reach the 250 narrowly defined MACE in this event based trial.
Statistical Consider-ations	**Sample Size Justification:** A sample size of 2400 randomized subjects will yield approximately 80% power for the primary analysis under the following assumptions: 1. Total number of events: 250 2. 2-sided type 1 error rate of α=5% 3. 10.5% event rate in the placebo arm at 18 months 4. 30% relative risk reduction (7.47% event rate at 18 months in the RVX000222 arm) 5. A cumulative drop-out rate of 10% per arm by the end of the study (5% drop out rate per arm by year 1) 6. Provision for an interim analysis to terminate the trial for futility (non-binding) when approximately 75% of the 250 events have occurred **Primary Analysis:** The primary analysis of time to the first occurrence of MACE narrowly defined will be completed following the occurrence of the 250th adjudication-confirmed primary endpoint event. The RVX000222 and placebo groups will be compared using a two-sided stratified log-rank test with an alpha = 0.05 level of significance. **Secondary and Exploratory Analyses:** Endpoints that are defined as time-to-event variables will be analyzed using the stratified log-rank test, as described for the primary analysis. Quantitative endpoints that are defined as a 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. 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. No multiplicity adjustment is planned to test the other secondary and exploratory endpoints.

Table 1: 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.

List of Abbreviations

ACS	Acute Coronary Syndrome
AE	Adverse Event
AESI	Adverse Event of Special Interest
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
ASSERT	apoA-I Synthesis Stimulation Evaluation in Patients Requiring Treatment for Coronary Artery Disease
ASSURE	ApoA-I Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation
AUC	Area under time curve
BET	Bromodomain and Extraterminal
BID	twice daily
BMI	Body Mass Index
BRD	Bromodomain
BRD4	BET protein 4
CABG	Coronary Artery Bypass Grafting
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
CYP7A1	cholesterol 7-alpha hydroxylase
DM	Diabetes Mellitus
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
EQ-5D-5L	EuroQOL five dimensions questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration, US
FXR	Farnesoid X Receptor
GGT	Gammaglutamyl Transferase
HbA1c	Glycated Hemoglobin
HBcAb	Hepatitis B Virus Core Protein Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HDL-C	HDL cholesterol
HIV	Human Immunodeficiency Virus
HRQOL	Health Related Quality of Life
hs-CRP	high-sensitivity C-Reactive Protein

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
LDL	Low-Density Lipoprotein
LDL-C	LDL Cholesterol
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed Model Repeat Measures
MOCA	Montreal Cognitive Assessment
mRNA	Messenger RNA
NOAEL	No Observable Adverse Effect Level
PCI	Percutaneous Coronary Intervention
PPS	Per-Protocol Set
RBC	Red Blood Cells
PT INR	Prothrombin International Nomenclature Rate
RCT	Reverse Cholesterol Transport
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SS	Safety Set
SSA	Sample Size Adjustment

SUSAR	Suspected Unexpected Serious Adverse Reaction
SUSTAIN	Study of qUantitative Serial Trends in lipids with ApoliproteIn A-I stimulatioN
T2DM	Type 2 Diabetes Mellitus
TG	Triglyceride
ULN	Upper Limit of Normal Range
WBC	White Blood Cells

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1.0 BACKGROUND AND STUDY RATIONALE

The majority (75%) of deaths in subjects with diabetes mellitus (DM) are due to atherosclerotic cardiovascular disease (CVD). In the United Kingdom Prospective Diabetes Study, after 9 years of follow-up, fatal CVD events were 70 times more frequent than fatal microvascular complications. High residual risk of CVD events remains, even in subjects with controlled low-density lipoprotein cholesterol (LDL-C). Recent studies suggest a major adverse cardiovascular event (MACE) rate of >11% over 18 months in type 2 diabetes mellitus (T2DM) despite a baseline LDL-C of <2.1 mmol/L. There is, therefore, an urgent need for new approaches to reduce MACE in subjects with CVD, especially for T2DM subjects.

Bromodomains (BRDs) are a family of evolutionary conserved protein-interaction modules that play key functions in chromatin organization and regulation of gene transcription. One recognized family of bromodomain-containing proteins is the bromodomain and extra-terminal (BET) family. BET inhibition represents a novel, epigenetic approach to treat CVD. RVX000222 is the first oral agent in the BET inhibitor class that preferentially targets BET protein 4 (BRD4) thereby regulating gene activity. RVX000222 affects biological processes important in atherosclerosis and acute coronary events via selective inhibition of BET proteins. RVX000222 selectively binding to the bromodomains (BD1/2) of the BET proteins with a 20-fold higher affinity to the second domain (BD2) versus the first (BD1). This feature of RVX000222 differentiates it from all other known BET inhibitors that have equal affinity of binding to either BD1/2. RVX000222 affects a single target (the second domain [BD2] of the bromodomain system) with multiple biological actions. The discovery of RVX000222 in 2006 stemmed from the screening of chemical compounds that had the ability to increase apolipoprotein A-I (ApoA-I) gene expression when exposed to human hepatoma cells. Initial cellular assays involving treatment with RVX000222 led to a rapid but direct effect in reducing IL-6 and VCAM-1 mRNA by 4 hours. In contrast, induction of ApoA-I mRNA and protein production required 24-48 hours suggesting an indirect effect. During the course of RVX000222 development, studies into the mechanism of action further demonstrated that its activity on atherosclerosis extended beyond its effects on ApoA-I/HDL. We now know that the lipid modifying effects are likely a minor contributor to efficacy of the compound. Indeed, current studies of RVX000222 show that it has effects on vascular inflammation, the complement and coagulation cascades, and acute phase response pathways all of which have known roles in cardiovascular disease and acute cardiac events. Gene expression regulation by BET proteins appears to be at the root of the pathogenesis of cardiac events. The effect of selective BET inhibition on all of the pathways outlined above underlies the potential benefit of using RVX000222 in treating CVD risk and for the prevention of recurrent acute events.

RVX000222 is available as a capsule formulation with standard excipients and established stability.

A total of 985 subjects have participated in completed trials, of which 706 received treatment with RVX000222 including 130 healthy volunteers and 576 subjects with stable coronary artery disease (CAD) and/or dyslipidemia on standard of care therapy. Three Phase 2 studies in subjects with CVD have been completed: a 12-week study (RVX222-CS-005; ASSERT) in which 299 subjects with stable CAD on standard of care therapy were enrolled, coupled with 24-week (RVX222-CS-008; SUSTAIN) and 26-week (RVX222-CS-007; ASSURE) studies in statin treated subjects with stable CAD and/or dyslipidemia, with low baseline HDL-C concentrations. The latter two studies enrolled 176 and 323 subjects, respectively. An additional Phase 2 study in subject with pre-diabetes (RVX222-CS-010) that enrolled 20 subjects was also completed.

The metabolism and disposition of RVX000222 after oral administration in humans, is similar to what occurs in animals. The parent molecule is metabolized to the same two inactive primary metabolites (RVX000288 [carboxylic acid] and RVX000404 [glucuronide]), with only about one-tenth of the dose excreted in the urine as a combination of parent and metabolite. It appears to be reasonably well absorbed, and exhibited dose-proportional increases in exposure (area under time curve [AUC]) between 1 and 4 mg/kg. The terminal half-life of the drug is about 11 hours. An increase in bioavailability of approximately 60% when given with food led to a recommendation that dosing with meals is required for further clinical studies. On a b.i.d. treatment schedule, steady-state kinetics were achieved within about 1

day of treatment. RVX000222 is expected to have low risk for producing drug-drug interactions, based on available data related to inhibition or induction of cytochrome P450 enzymes.

Positive changes in CVD biomarkers were seen in both normal volunteer and subject studies and led to the identification of a total daily dose of 200 mg (100 mg b.i.d taken with meals) as the optimum balance of efficacy and adverse events (AEs). The changes in biomarkers observed in the longer term Phase 2 studies are shown in Table 2.

Table 2: Effects of RVX000222 on Biomarkers of CV Risk – Lipids and Inflammation (ASSURE and SUSTAIN Trials)

Biomarker	Placebo (n=166)		RVX000222 (n=331)		p value vs. placebo
	Percent Change	p value vs. baseline	Percent Change	p value vs. baseline	
HDL Cholesterol, (mg/dL)	0	0.59	7.69	<0.0001	0.0003
ApoA-I, (mg/dL)	3.8	0.0003	10.3	<0.0001	0.005
Total HDL particles, (µmol/L)	0.4	0.61	6.51	<0.0001	0.07
HDL particle size, (nm)	0	0.3	1.16	<0.0001	0.049
Large HDL particles, (µmol/L)	4.11	0.02	30.71	<0.0001	0.03
hs-CRP, (mg/L)	-22.4	0.0002	-28.4	<0.0001	0.67
ALP, (U/L)	-3.23	0.03	-11	<0.0001	<0.001

Results expressed as median percentage change from baseline. Source: RVX000222 data on file. Modified intention to treat population, 2-sided van Elteren test of RVX000222 vs. placebo, stratified by trial. Wilcoxon signed-rank test for within group comparison vs. baseline.

The data from all three individual Phase 2 studies in CVD patients showed independent, consistent trends for fewer MACE in RVX000222-treated subjects versus subjects receiving placebo. In the ASSERT study, 2.2% of subjects treated with RVX000222 experienced a MACE compared to 2.7% of placebo-treated subjects during 12 weeks of therapy. In the SUSTAIN study, MACE occurred in 7.5% of placebo-treated subjects and only 0.4% of RVX000222-treated subjects (p <0.06) after 24 weeks of therapy. This trend was also observed in the ASSURE trial, with 14.3% of placebo-treated subjects experiencing MACE compared to 7.5% of subjects in the RVX000222-treated group after 26 weeks of therapy, an approximately 48% difference (p <0.1).

Given the promising findings of reduced MACE from these three studies, a post-hoc meta-analysis was conducted using the pooled data (n = 798). Collectively, there was a statistically significant (p = 0.023) reduction in MACE as defined by death, myocardial infarction (MI), coronary revascularization, or cardiovascular hospitalization (CV) as shown in Figure 1. Subjects receiving RVX000222 were 44% less likely to experience a MACE compared to placebo with only 5.9% of RVX000222-treated subjects experiencing any MACE compared to 10.4% for placebo-treated subjects. Approximately 80% of subjects were treated with high intensity statin therapy (atorvastatin and rosuvastatin).

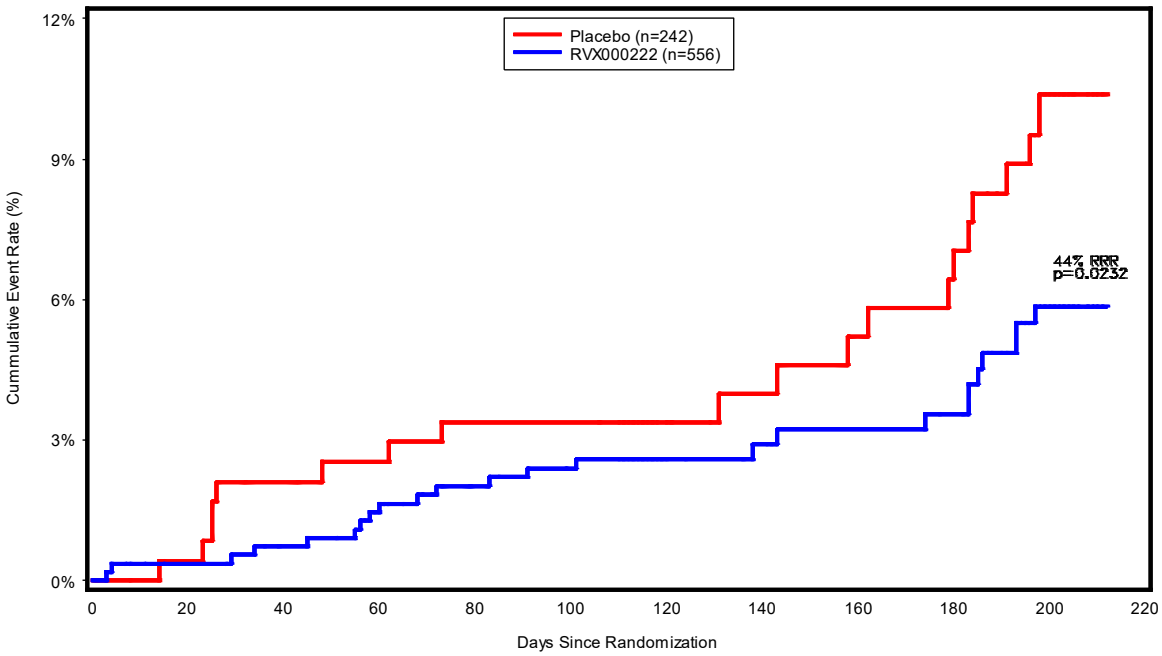


Figure 1: MACE in Subjects Treated in RVX000222 Phase 2 Studies

Overall, RVX000222 was generally well tolerated and AEs were mild with little discernible difference between placebo- and the RVX000222-treated subjects. The dose-limiting toxicity for RVX000222 is a generally non-symptomatic elevation in serum transaminases (alanine aminotransferase [ALT] and in some cases aspartate aminotransferase [AST]), without adversely affecting total bilirubin values in any subject. There was no increase in alkaline phosphatase (ALP) observed. There was an overall incidence of 7-8% of subjects with ALT >3x the upper limit of normal range (ULN). There was often confounding with use of drugs known to increase ALT (diclofenac and clavulanic acid) or prior history of hepatitis. Raised enzymes return promptly to within the normal transaminase range (approximately 15 days for ALT >5xULN), suggesting that any hepatocellular effect can be reversed by suspending treatment with investigational drug. For subjects with elevations >3xULN and <5xULN, treatment was continued and all returned to normal levels. Subjects with ALT elevations >5x and <8xULN were dose interrupted, re-challenged at a lower dose and the majority successfully completed the studies. Drug-induced ALT elevations >3xULN were observed between weeks 4-12 across all 4 completed Phase 2 trials, with one exception. One subject with elevated ALT and AST at Week 20 due to cholecystitis was noted in RVX222-CS-007. No cases of Hy's Law have been detected.

A possible mechanism implicated in the elevation of serum transaminases is the effect of BET inhibition on hepatic bile acids through changes in expression of the farsenoid X receptor (FXR) and cholesterol 7-alpha hydroxylase (CYP7A1). Hepatocyte cell culture studies show that RVX000222 represses FXR expression. Increased expression of CYP7A1, a rate limiting enzyme in bile acid synthesis, is observed in select donors of primary hepatocytes as a consequence of FXR repression. Increased CYP7A1 expression predicts increased bile acid synthesis. Intracellular concentrations of bile acids may be further augmented through downregulation of BSEP, a bile acid export pump. Increased bile acid synthesis, combined with a decrease in BSEP-mediated biliary excretion of bile acids, may mediate ALT elevations in select patients where CYP7A1 is induced. In healthy volunteers or CVD patients taking RVX000222, serum bile acids appear to track with ALTs. Elevation of serum bile acids preceded serum ALT elevation, suggesting that the bile acid-mediated mechanism is plausible. However, other markers of liver damage such as bilirubin or LDH are not elevated and serum bile acids although increased from baseline remain in a normal range.

Minimizing residual risk of MACE in T2DM subjects' post-acute coronary syndrome (ACS) addresses an important unmet medical need. RVX000222 and BET inhibition represent a potential new treatment mechanism for subjects at high risk for CVD. Based on the data above, the BETonMACE study (RVX222-CS-015) will focus on prevention of subsequent MACE in subjects with CAD and DM with high intensity statin therapy as co-medication.

2.0 STUDY 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.

  Criteria for the evaluation of individual events will be defined in the MACE Clinical Events Committee (CEC) charter and will be based on the CDISC standardized definitions for Cardiovascular and Stroke Endpoint Events[1].

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 event as defined by Hicks et al.
  - 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

3.0 STUDY ENDPOINTS

3.1 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 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. Time from randomization to fatal or non-fatal MI, or fatal or non-fatal stroke
3. Time from randomization to CV Death or Non-fatal MI
4. Time from randomization to Non-fatal MI
5. Time from randomization to CV Death
6. Time from randomization to Stroke
7. All-cause mortality

3.3 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

3.4 Exploratory Endpoints

- The percent change in hsCRP, fibrinogen, and inflammatory cytokines 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

3.5 Safety Endpoints

- Safety assessments will include incidence of adverse events (AEs), serious adverse events (SAEs), vital sign measurements, clinical laboratory evaluations, Montreal Cognitive Assessment (MOCA) (for subjects ≥ 70 years of age at randomization) and physical examination findings

4.0 STUDY DESIGN

This is a double-blind, placebo-controlled, 2-arm parallel-group (allocation ratio 1:1), study of RVX000222 at a daily dose of 100 mg b.i.d. (total daily dose of 200 mg) or matching placebo in combination with high intensity statin therapy administered to T2DM subjects with history of recent CAD event and HDL-C level <40 mg/dL in males or <45 mg/dL in females.

After an initial screening period of 1 to 2 weeks during which subjects will demonstrate tolerance of high intensity 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 patients 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 high intensity statin therapy for 4 more weeks until the Follow-Up Visit.

The study is an event-based trial and will continue until 250 primary endpoint events have occurred. Study treatment will be terminated after the 250th adjudicated event occurs. At that time, all subjects actively treated will conduct their Last Visit on Treatment and then be discontinued from investigational drug. Subjects will then return 4 weeks after last day of treatment for the Follow-Up Visit.

A Clinical Steering Committee (CSC) will oversee the conduct of the study. A Data Safety Monitoring Board (DSMB) will oversee the safety data for this study and independent CEC will adjudicate all suspected MACE composite events in an ongoing manner. An independent team (including an independent statistician) will perform the prospective unblinded analyses described in Section 10.8 (Data Safety Monitoring Board) and will report the results to the DSMB. Each committee will develop a charter to describe their activities and responsibilities prior to initiation of the study.

5.0 STUDY POPULATION

5.1 Number of Subjects

It is estimated that enrollment of approximately 2400 male or female subjects with T2DM and high-risk CAD treated with high intensity statin therapy (atorvastatin 20-80 mg or rosuvastatin 10-40 mg) and with a low level of HDL-C of <40 mg/dL in males or <45 mg/dL in females at multiple investigational sites globally will be needed to reach the 250 MACE needed for this event-based trial.

5.2 Inclusion Criteria

Subjects who meet the following criteria may be enrolled:

1. Male and female subjects age 18 and over with documented diagnosed T2DM and a CAD event of either unstable angina or myocardial infarction, not less than 7 days and no more than 90 days prior to Visit 1. In order to have sufficient number of clinical events, the number of subjects with unstable angina will be limited to 25% of the total number of subjects.

- Unstable angina: for a qualifying unstable angina event, each of components (a), (b), and (c) must be satisfied:
    a. Characteristic ischemic pain or discomfort in chest or associated referral areas, occurring at rest or with minimal exertion
    b. ECG changes consistent with acute myocardial ischemia based upon at least one of the following:
        i. new or presumed new ST elevation
        ii. new or presumed new ST depression
        iii. new or presumed new T-wave inversion
    c. Objective evidence of obstructive coronary artery disease based upon at least one of the following:
        i. new or presumed new evidence of myocardial ischemia or infarction by perfusion imaging
        ii. new or presumed new regional wall motion abnormality
        iii. current evidence of at least one epicardial coronary artery stenosis ≥ 70% by coronary angiography
        iv. need for coronary revascularization for the index ACS event, including percutaneous coronary intervention (PCI) with or without coronary stenting

- Previous MI 7-90 days before screening, treated with or without a percutaneous coronary intervention (PCI). For a qualifying event of MI, **two of the following three criteria must be satisfied**:
    a. Characteristic ischemic chest pain or pain in associated referral areas
    b. Dynamic elevation of troponin T or I or CKMB, if troponin T or I is unavailable at the local lab (at least above the upper limit of normal for the laboratory)
    c. Development of new Q-waves in at least two adjacent ECG leads, or development of a new dominant R wave in V1

2. Documented diagnosis of T2DM (one or more of the following criteria must be met):
    - Documented history of T2DM
    - History of taking diabetes medication
    - HbA1c ≥6.5% at Visit 1
3. For males HDL-C of <40 mg/dL (1.04 mmol/L) and for females HDL-C of <45 mg/dL (1.17 mmol/L) at Visit 1.
4. In the opinion of the Investigator, subjects currently not on high intensity statin therapy will be able to start rosuvastatin according to the protocol at Visit 1.
5. In the opinion of the Investigator, subjects currently on statin therapy other than atorvastatin or rosuvastatin can be switched to rosuvastatin according to the protocol at Visit 1. High intensity statin therapy doses should remain unchanged during the study period if at all possible.
6. Female subjects must meet one of the following:
    - If of childbearing potential, female subjects must have a negative urine pregnancy test and be willing and able to use medically acceptable non-hormonal method of birth control (non-hormonal intrauterine device, condom, or diaphragm) or remain abstinent from Screening until Follow-up Visit.
    - Be of non-child-bearing potential: post-surgical sterilization or post-menopausal.
7. Have given signed informed consent to participate in this study.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will not be enrolled:

1. Heart disease which, in the opinion of the investigator, will within 90 days of Visit 1 likely require coronary bypass, PCI, cardiac transplantation, surgical repair and/or replacement.
2. Previous or current diagnosis of severe heart failure (New York Heart Association Class IV) or a documented left ventricular ejection fraction (LVEF) of <25% as determined by contrast left ventriculography, radionuclide ventriculography or echocardiography. The absence of an LVEF measurement in a subject without a previous or current diagnosis of heart failure does not prohibit entry into the study.
3. Subjects with evidence of cardiac electrophysiologic instability including a history of uncontrolled ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardias with a ventricular response heart rate of >100 beats per minute at rest within 4 weeks prior to Visit 1.
4. Coronary artery bypass grafting (CABG) within 90 days prior to Visit 1.
5. Evidence of severe renal impairment as determined by <u>any one</u> of the following:
   - an estimated Glomerular Filtration Rate less than 30 mL/min/1.7m^2 at Visit 1
   - a current need for dialysis
6. Uncontrolled hypertension defined as 2 consecutive measurements of sitting blood pressure of systolic >180 mm Hg or diastolic >100 mm Hg at Visit 1.
7. Subjects at risk of immunosuppression, including current or recent (within 12 months prior to Visit 1) treatment with immunosuppressants (e.g., cyclosporine).
8. Use of fibrates at any dose or niacin/nicotinic acid 250 mg or more within 30 days prior to Visit 1.
9. A known allergy or sensitivity to any ingredient in the investigational medicinal product.
10. History of intolerance to atorvastatin or rosuvastatin. This exclusion criterion applies to subjects with a history of intolerance to the statin to which they would be assigned at screening.
11. Triglycerides >400 mg/dL (4.52 mmol/L) at Visit 1.
12. Any medical or surgical condition which might significantly alter the absorption, distribution, metabolism or excretion of medication including, but not limited to, any of the following: Untreated or incompletely treated thyroid dysfunction, cholecystitis, Crohn's disease, ulcerative colitis, or any gastric bypass alteration.
13. Evidence of cirrhosis from liver imaging or biopsy, a history of hepatic encephalopathy, esophageal or gastric varices, active hepatitis, or prior porta-caval shunt procedure, or a Child-Pugh score of at least 5 points (Appendix A).
    - <u>Any one</u> of the following liver enzymes that is >1.5xULN by central lab at Visit 1
      a. ALT
      b. AST
14. A total bilirubin that is >ULN by central lab at Visit 1.
15. History of malignancy of any organ system, treated or untreated, within the past 2 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
16. History or evidence of drug or alcohol abuse within 12 months of Visit 1, in the opinion of the investigator.
17. Female subjects who are pregnant.
18. Any condition which, in the opinion of the investigator, may place the subject at higher risk from his/her participation in the study, or is likely to prevent the subject from complying with the

requirements of the study or completing the study, including subjects at risk of immunosuppression.

19. Use of other investigational drugs and devices within 30 days or 5 half-lives of Visit 1, whichever is longer.
20. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
21. Any condition that, in the opinion of the investigator, would confound the evaluation and interpretation of efficacy and/or safety data.
22. Persons directly involved in the execution of this protocol.

6.0 STUDY TREATMENT

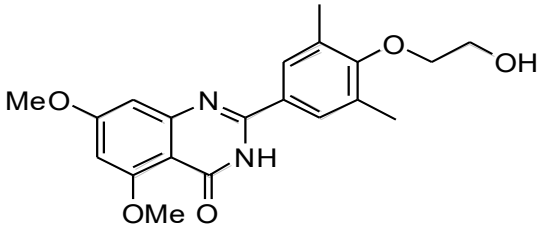
6.1 Investigational Drug (RVX000222, Oral and Placebo for RVX000222, Oral)

6.1.1 RVX000222, Oral

RVX000222 is available as a capsule formulation with standard excipients and established stability.

Active Pharmaceutical Ingredient (API)

Chemical Structure



Molecular Weight	370.41 g/mol
Molecular Formula	$C_{20}H_{22}N_2O_5$
Appearance	White, off-white to tan solid
Solubility	RVX000222 has a solubility of 15-25 mcg/mL in water and 3-3.5 mg/mL in 0.1 N HCl
Capsule Formulation	A free base immediate release capsule dosage form. This capsule formulation is a dry blend formulation comprised of Avicel, colloidal silicone dioxide, sodium starch glycolate and magnesium stearate. The capsule is a hard shell gelatin white, opaque size 1 capsule.

6.1.2 Placebo for RVX000222, Oral

Placebo for RVX000222, Oral is available as a capsule formulation free of RVX000222 API. It is comprised of standard excipients and has established stability. The capsule formulation is the same as that used for RVX000222, Oral (described in Section 6.1.1).

6.2 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 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 investigational 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 investigational drug with the number allocated by the IWRS. Procedures for this will be described in the IWRS user manual.

6.3 RVX000222 Treatment Blinding

The blinding is ensured by using double-blind RVX000222 investigational drug. Placebo capsules will be equally matched in size, shape, and color to RVX000222 and will be packaged in the same manner. The investigational drug packaging will be labelled 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 unblinded analyses for review, the DSMB itself, the personnel providing IWRS and carrying out the packaging and labeling of investigational products. Unblinding will occur in the case of subject emergencies when knowledge of the treatment assignment would affect subject care (Section 6.10.2) and at the conclusion of the study.

6.4 Study Drug Supply, Storage, and Tracking

RVX000222 capsules, atorvastatin, and rosuvastatin will be shipped to the Investigator as labeled drug. All study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and qualified personnel have access. RVX000222 should be stored at ambient temperature, 15˚ to 30˚C (59˚ to 86˚F). Atorvastatin and rosuvastatin should be stored according to the respective SmPC (refer to the study manual for these documents).

Study drug packaging will be subject-specific. Each subject will be allocated enough study drug at each visit to cover at least the time period until the next scheduled visit plus the visit window.

Investigators must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Subjects will be asked to return all unused study drug and packaging, including concomitant statin therapy, if provided by sponsor, at each visit, the end of the study, or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger.

Procedures for drug dispensing and drug accountability are described in the study manual.

6.5 RVX000222 Investigational Drug Administration

RVX000222 or matching placebo will be taken orally with meals in the morning and in the evening, 10-12 hours apart. 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. Subjects will take their first dose of investigational drug while in clinic during Visit 2.

Table 3: Investigational 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

If subjects have elevated ALT values (see Section 6.10.1) they may be administered investigational drug or matching placebo at a reduced dose of 50 mg b.i.d, subject to confirmation by the medical monitor.

6.6 Concomitant Statin Therapy

Protocol defined concomitant treatment in this study is 40-80 mg atorvastatin or 20-40 mg rosuvastatin once daily orally. 20 mg atorvastatin or 10 mg rosuvastatin are only 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 follows:

Subjects who, at Visit 1, are currently receiving high intensity statin therapy of atorvastatin 40-80 mg or rosuvastatin 20-40 mg will continue on the same statin as they are currently receiving.

If clinically appropriate, in the investigator's opinion, subjects who, at Visit 1, are currently receiving atorvastatin or rosuvastatin at doses other than the protocol-defined dosage (10 mg dose of atorvastatin or 5 mg dose of rosuvastatin) should be transitioned to a 40-80 mg dose of atorvastatin or 20-40 mg dose of rosuvastatin.

Subjects not currently receiving high intensity statin therapy of atorvastatin or rosuvastatin will be prescribed rosuvastatin 20-40 mg as concomitant therapy at Visit 1 and will discontinue use of any other statin previously prescribed.

A country level stratification will be applied to ensure that subjects are allocated evenly (no greater than 60:40 imbalance within each country) between atorvastatin and rosuvastatin. In the event that the atorvastatin or rosuvastatin strata is full, subjects may be transitioned at Visit 1 to the other protocol defined statin therapy.

The dose and transition plan for statin administration will be monitored and accounted through the IWRS.

High intensity statin therapy dose may be reduced if clinically indicated. Otherwise, dosing should remain unchanged during the course of the study if at all possible.

Subjects will continue taking high intensity statin therapy until the Follow-Up Visit (final study visit).

The statin dose shall be administered once daily at the same time as one of the two RVX000222 doses (or placebo) and within 30 minutes of completion of a meal. 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.

6.7 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.

Ezetimibe use is not prohibited at screening, randomization or during the study treatment phase. However, LDL-lowering should be addressed with high intensity statins.

6.8 Prohibited Concomitant Medications and Excluded Therapies

The use of the following treatments is NOT allowed beginning at Visit 1 until the end of the study, as these medications may interfere with the evaluation of safety, tolerability and/or efficacy. Subjects who may require any of the following medication(s) during the course of the study should be excluded.

1. Cyclosporine. The initiation of cyclosporine therapy during the study constitutes a mandatory reason for permanent discontinuation of investigational drug.
2. Fibrates at any dose
3. Niacin/nicotinic acid >250 mg per day
4. Clavulanic acid
5. Diclofenac (Topical diclofenac is acceptable with intermittent use, but not with daily use for any period >7 days.)
6. Acetaminophen >1g/day
7. Hormonal Contraceptives or Hormone Replacement Therapy (see Section 6.9)

Patients whose clinical condition during the study warrants clavulanic acid, diclofenac, or acetaminophen >1g/day should suspend study medication from the day these treatments are initiated until three days after they are completed.

The investigator should instruct the subject to notify the study site about any new medications he/she takes after the start of the study drug, including concomitant statin therapy. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with study drug must be listed on the concomitant medications/significant non-drug therapies section of the electronic case report form (eCRF) after start of study drug.

6.9 Contraception / Hormone Replacement Therapy

Hormonal contraceptives are not allowed during study participation by study subjects. All female subjects of childbearing potential will be asked to practice appropriate non-hormonal contraception (non-hormonal intrauterine device, condom, or diaphragm) or practice abstinence for the duration of the study.

Subjects who take hormone replacement therapy must be willing to discontinue their hormonal therapy if it is medically appropriate. To be eligible for study participation, they must agree to remain off their hormonal replacement therapy for the duration of the study.

6.10 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 investigational drug (RVX000222 or placebo) or high intensity statin therapy should not result in study discontinuation. Subjects discontinuing investigational drug (RVX000222 or placebo) should be encouraged to continue on study-supplied high intensity statin therapy. For subjects who discontinue both investigational drug and study-supplied concomitant statin therapy, record alternative statin/lipid lowering therapy, if applicable.

	Screen	Treatment

6.10.1 Additional Safety Lab Monitoring/Dose Adjustment

Additional safety lab monitoring will occur and investigational drug (RVX000222 or placebo) may be interrupted, reduced, and/or discontinued if the subject meets following criteria. If ALT increases >3xULN or serum bilirubin increases >2xULN, subjects should be notified and repeat chemistries obtained as soon as possible.

1. If ALT increase of >3 and ≤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, investigational drug will be suspended. If confirmed on repeat measurement (within 3-4 days), investigational drug will be discontinued and subjects will be monitored every 3-4 days until the ALT is <1.5xULN.
3. If serum bilirubin increase of >2xULN, investigational drug will be suspended. If confirmed on repeat measurement (within 3-4 days), investigational drug will be 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.

Subjects should continue to follow the protocol-defined assessments according to the Schedule of Events (

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

Table 1) until study completion.

If the ALT or serum bilirubin elevation has a likely cause other than investigational drug (e.g. trauma, infection-inflammation, surgery, acetaminophen, clavulanic acid, diclofenac) investigational drug may be restarted at 50 mg b.i.d. once ALT returns to 1.5 xULN. Subjects should continue with all scheduled study visits according to the Schedule of Events (

Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin		x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic		x			x													
MOCA		x												x				x
EQ-5D-5L		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1) and will have additional liver safety panel tests drawn according to the original study schedule:

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

Any re-initiation of investigational drug must be discussed with and approved by the study medical monitor prior to dosing.

6.10.2 Emergency Un-blinding of Treatment Assignment

Emergency un-blinding should only be undertaken when it is essential for effective treatment of the subject. Most often, investigational drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Individual treatment codes indicating the treatment randomization for each randomized subject will be available to the investigator. Procedures for this will be described in the IWRS user manual. The Investigator will notify the Medical Monitor as soon as possible of any situation resulting in treatment un-blinding of any subject.

6.10.3 Subject Withdrawal / Discontinuation from Study

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. However, discontinuation of study drug should not result in discontinuation of study participation.

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

- Withdrawal of informed consent
- Subject experiences AEs sufficiently severe to contraindicate continuing the study
- Subject's general condition, in the opinion of the Investigator, contraindicates continuing in the study
- Subject refuses to cooperate; or
- Sponsor elects to end the study, or any portion thereof, for any reason

When a subject decides to discontinue participation in the study, or is lost to follow-up (those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), a reasonable attempt will be made to contact the subject about the reasons for discontinuation and any AEs. All AEs will be followed until resolved or a stable condition has been established. Subjects withdrawn due to an AE or abnormal laboratory test will be followed until the AE or abnormal laboratory

	Screen	Treatment

test resolves, or there is an adequate explanation that the AE or abnormal laboratory test was not related to study drug.

For subjects who are lost to follow-up, the Investigator should show “due diligence” by documenting in the source documents the steps taken to contact the subject.

Should a subject request to be withdrawn from the study, the following options should be offered to him/her regarding continued participation:

1. Continued study site visits and procedures following the visit schedule, without medication being dispensed.
2. Telephone (or other communication) contact at regular scheduled study visits. Last visit on treatment and follow-up visit would be at clinic, if at all possible. Concomitant medications, updated contact information, and SAE assessments should be collected at each telephone visit.
3. On-site and/or telephone (or other communication) contact at less than scheduled visit intervals (at a minimum, at least approximately at the calculated timeframe for the follow-up visit). If telephone contact, collect concomitant medications, update contact information, and SAEs at each telephone visit.
4. Indirect Method: Subject is not willing to have Principal Investigator or staff contact them. However, allows Primary Care Physician/Designated Contact at approximately the calculated timeframe for the follow-up visit.
5. Indirect Method: Subject is not willing to have Principal Investigator or staff contact them. However, allows review of vital status checks throughout the study. Vital status will be checked using appropriate available information sources such as public records or contact with family members.
6. No further contact/full withdrawal of consent, in writing.

The subject’s continued level of participation should be clearly documented and updated in the subject’s source documents. Should a subject no longer wish any further contact, the primary reason for termination must be recorded as well. In addition, efforts should be made to perform all procedures scheduled for the last visit on treatment and follow-up visit.

The Investigator, in discussion with the Sponsor, may decide to withdraw a subject or prematurely end the study for clinical safety reasons.

7.0 VISIT SCHEDULE AND ASSESSMENTS

	Screen	Treatment																
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±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
Physical Exam	x																	x
Central Laboratory:																		
Fasting Lipid profile	x										x			x		x		x
Hematology, HbA1c	x										x			x		x		x
Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin		x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic		x			x													
MOCA		x												x				x
EQ-5D-5L		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1: Schedule of Events lists all of the assessments and indicates with an “x” the visits when they are performed.

Subjects should be seen for all visits on the designated day. Visit dates should be adhered to as closely as possible. Target visit dates will be generated for each subject based on the Visit 2 date.

7.1 Safety Evaluations

Safety and tolerability will be determined by symptoms, signs, severity, and causality of AEs, clinical laboratory test results, vital sign measurements, and changes in physical examination findings.

7.1.1 Electrocardiograms

A standard 12-lead ECG will be performed at Screening (Visit 1). Each ECG tracing should be kept in the source documents at the study site. Interpretation of the tracing must be made by a qualified physician and documented in the source documentation. This interpretation will be collected in the eCRF. Only clinically significant abnormalities should be reported on this page. Clinically significant abnormalities should also be recorded on the relevant medical history/current medical conditions eCRF page.

7.1.2 Vital Signs

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

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

Table 1). All measurements will be recorded in the subject's source documents and eCRF.

Blood pressure will be measured in the sitting position at all time points. Blood pressure will be measured in the subject's dominant arm (if possible), with the arm supported at the level of the heart, and recorded to the nearest 1 mm Hg. Screening blood pressure may be retested up to 3 times at intervals of no less than 5 minutes between each measurement. The final blood pressure measurement should be recorded in the eCRF.

The use of automated devices for measuring blood pressure and heart rate is acceptable. When done manually, heart rate will be measured in the brachial or radial artery for at least 30 seconds.

7.1.3 Physical Examinations

Physical examinations will occur as shown in the Schedule of Events (

	Screen	Treatment																
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent	X																	
Randomization		X																
Inclusion / Exclusion	X	X																
Medical History/Demographics	X																	
ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X									X			X		X		X
Physical Exam	X	X																X
Central Laboratory:																		
Fasting Lipid profile	X										X			X		X		X
Hematology, HbA1c	X										X			X		X		X
Chemistry	X	X									X			X		X		X
Urinalysis	X	X									X			X		X		X
Hepatitis Serology	X																	
Liver Safety Panel	X																	
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin	X	X									X			X		X		X
Inflammation Panel		X						X						X				X
Serum/Plasma Archive																		
Pharmacogenomic	X	X			X						X			X		X		X
MoCA	X	X									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
Prior / Con. Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispense/Account.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1). Height will be measured at screening only. Weight will be measured during each physical exam. Physical examinations will include but not be limited to the examination of general appearance, skin, head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, endocrine metabolic, genito-urinary, blood/lymphatic, and musculoskeletal systems.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the relevant Medical History/Current Medical Conditions screen on the subject's eCRF. Significant findings after signing of the informed consent, which meet the definition of an AE, must be recorded on the AE eCRF.

7.1.4 Clinical Laboratory Tests

Clinical laboratory samples (fasting lipid panel, hematology, chemistry, infectious serology, and urinalysis) will be collected as shown in the Schedule of Events (

	Screen	Treatment																
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin	x										x			x		x		x
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
+No Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Pharmacogenomic		x			x													
Informed Consent	x																	
MOCA		x												x				x
Randomization		x																
EQ-5D-5L		x									x			x		x		x
Inclusion / Exclusion	x	x																
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medical History/Demographics	x																	
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x																	
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1).

A central laboratory will be used for analysis of all specimens collected, except dipstick tests for urinalysis. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to the investigators in the laboratory manual. All laboratory results (excluding biomarker and pharmacogenomics results) will be communicated to the investigators. Dipstick tests for urinalysis will be performed and results maintained at investigational sites.

For fasting laboratory tests, blood should be collected after a period of 9 to 12 hours with no oral intake except for water and medications. If a subject attends a study visit in a non-fasting state, labs should be collected nonetheless and the non-fasting condition should documented.

7.1.4.1 Fasting Lipid Profile

Fasting bloodwork will be collected for lipid profile (total cholesterol, LDL-C, HDL-C, and TGs), at visits indicated on the Schedule of Events (

	Screen	Treatment																
Vital Signs	x	x									x			x		x		x
Physical Exam	x																	
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Central Laboratory:																		
Fasting Lipid profile	x										x			x		x		x
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
Hematology, HbA1c	x										x			x		x		x
± Nr. Day	x		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Chemistry																		
Urinalysis	x										x			x		x		x
Informed Consent	x																	
Hepatitis Serology	x	x																
Randomization																		
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Inclusion / Exclusion	x	x																
Biomarker Laboratory Tests																		
Medical History/Demographics	x																	
Lipoproteins, fasting insulin		x									x			x		x		x
ECG	x																	
Inflammation Panel		x						x						x				
Vital Signs	x	x									x			x		x		x
Serum/Plasma Archive		x						x						x				
Physical Exam	x																	
Pharmacogenomic		x			x													x
Central Laboratory:																		
MOCA																		
Fasting Lipid profile	x	x									x			x		x		x
EQ-5D-5L											x			x		x		x
Hematology, HbA1c	x																	
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	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
Urinalysis	x										x			x		x		x
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1).

7.1.4.2 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 (

	Screen	Treatment																
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin	x										x			x		x		x
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
+No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Pharmacogenomic		x			x													
Informed Consent	x																	
MOCA		x												x				x
Randomization		x																
EQ-5D-5L		x									x			x		x		x
Inclusion / Exclusion	x	x																
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medical History/Demographics	x																	
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x																	
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	x	x									x			x		x		x
Physical Exam	x																	x
Central Laboratory:																		
Fasting Lipid profile	x										x			x		x		x

Table 1).

7.1.4.3 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 (

	Screen	Treatment																
Hematology, HbA1c	x										x			x		x		x
Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Lipoproteins, fasting insulin	x	x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic	x	x			x													
Medical History/Demographics	x	x												x				x
ECG	x	x									x			x		x		x
EQ-5D-5L																		
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	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
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior / Con. Medication																		
Central Laboratory:																		
Drug Dispense/Account.																		
Fasting Lipid profile	x										x			x		x		x

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent	x																	
Randomization		x																
Inclusion / Exclusion		x			x													
MOCA		x												x				x
EQ-5D-5L											x			x		x		x
Adverse Events		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

Table 1).

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

7.1.4.4 Urinalysis

Urinalysis consisting of visual description, a dipstick test (specific gravity, pH, protein [qualitative], glucose, ketones, bilirubin, and blood) will be done at visits indicated on Schedule of Events (

	Screen	Treatment																
Hematology, HbA1c	x									x			x		x		x
Chemistry	x									x			x		x		x
Urinalysis	x									x			x		x		x
Hepatitis Serology	x																
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Lipoproteins, fasting insulin	x	x								x			x		x		x
Inflammation Panel		x						x					x				
Serum/Plasma Archive		x						x					x				
Pharmacogenomic	x	x			x												
Medical History/Demographics	x	x											x				x
ECG	x	x								x			x		x		x
EQ-5D-5L																	
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	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
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior / Con. Medication																	
Central Laboratory:																	
Drug Dispenser/Account.																	

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent	x																	
Randomization		x																
Inclusion / Exclusion		x			x													
MOCA																		

Table 1). Dipstick tests will be performed and results maintained at investigational sites.

7.1.4.5 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.

7.1.4.6 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 (

	Screen	Treatment																
Fasting Lipid profile	x										x			x		x		x
Hematology, HbA1c	x										x			x		x		x
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Urinalysis	x										x			x		x		x
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Biomarker Laboratory Tests																		
Informed Consent	x	x																
Lipoproteins, fasting insulin											x			x		x		x
Randomization		x						x						x				
Inflammation Panel		x																
Inclusion / Exclusion	x	x																
Serum/Plasma Archive		x						x						x				
Medical History/Demographics	x	x			x													
Pharmacogenomic		x																
MOCA	x	x												x				x
ECG		x																
EQ-5D-5L	x	x									x			x		x		x
Vital Signs	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
Physical Exam	x																	x
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Central Laboratory:																		
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1).

As defined in Section 6.10.1, 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

7.1.4.7 Pregnancy Test

All pre-menopausal women who are not surgically sterile will have a dipstick urine pregnancy test at Screening (Visit 1). Dipstick tests will be performed and results maintained at investigational sites.

7.1.5 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 7.1.5.1, 7.1.5.2, and 7.1.5.3) at visits indicated on the Schedule of Events (

	Screen	Treatment																
Fasting Lipid profile	x										x			x		x		x
Hematology, HbA1c	x										x			x		x		x
Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
hCG Safety Panel	x	x																
Biomarker Laboratory Tests	x																	
Lipoproteins, fasting insulin		x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive	x	x						x						x				
Pharmacogenomic	x	x			x													
MCCA	x	x												x				x
EQ-5D-5L	x	x									x			x		x		x
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Central laboratory:																		
Fasting Lipid profile	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

	Screen	Treatment																
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± Nue Day		x	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent	x																	
Randomization		x																
Inclusion / Exclusion	x	x																
Medical History/Demographics	x	x			x													
ECG	x	x												x				x
Vital Signs	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
Prior / Conc. Medication																		
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1).

7.1.5.1 Lipoproteins

Fasting bloodwork will also be collected from a selected subset of subjects for apoA-I and apoB at visits indicated on the Schedule of Events (

	Screen	Treatment																
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	-2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent	x																	
Randomization		x																
Inclusion / Exclusion	x	x			x													
MEDA	x	x												x				x
ECG	x	x																
EQ-5D-5l	x	x									x			x		x		x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	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
Prior/Conc. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam																		
Study Drug Dispensed/Account.																		
Fasting Lipid profile	x										x			x		x		x
Hematology, HbA1c	x										x			x		x		x
Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin	x	x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic		x			x													
Central Laboratory																		

Table 1).

7.1.5.2 Fasting Insulin

Fasting insulin will be measured in a selected subset of subjects at visits indicated on Schedule of Events
(

	Screen	Treatment																
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No./Day		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent	x																	
Randomization		x																
Inclusion / Exclusion	x	x												x				x
Medical History/Demographics	x	x									x			x		x		x
ECG	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	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	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin		x									x			x				x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic		x			x													
MOCA		x												x				x
EQ-5D-5L		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Central Laboratory:																		
Fasting Lipid profile	x										x			x		x		x
Hematology, HbA1c	x										x			x		x		x

Table 1).

7.1.5.3 Inflammation Panel

hsCRP, fibrinogen, and inflammatory cytokines will be measured in a selected subset of subjects at visits indicated on Schedule of Events (

	Screen	Treatment																
Chemistry	x									x			x		x		x	
Urinalysis	x									x			x		x		x	
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin		x	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7
Inflammation Panel		x						x						x				
Serum/Plasma Archive	x	x						x						x				
Pharmacogenomic		x			x													
Inclusion / Exclusion	x	x																
Medical History/Demographics	x	x									x			x		x		x
ECG	x																	
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	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
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.																		
Central Laboratory:																		
Fasting Lipid profile	x									x			x		x		x	
Hematology, HbA1c	x									x			x		x		x	
Chemistry	x									x			x		x		x	
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day																		
Informed Consent	x																	
Randomization		x																
Inclusion / Exclusion	x	x												x				x
MOCA		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1).

7.1.6 Serum and Plasma Archive Samples

Serum and plasma samples will be collected in subjects at visits indicated on the Schedule of Events (

Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin		x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic		x			x													
MOCA		x												x				x
EQ-5D-5L		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1). The serum and plasma samples will be stored for future exploratory biomarker analysis relevant to lipid and inflammatory pathways.

Details on the collection and shipment of samples and archiving will be provided to investigators in the laboratory manual.

7.1.7 Pharmacogenomic Testing (Optional)

Pharmacogenomics is the study of how drug response is affected by genetic variation. An individual's genotype may impact the pharmacokinetics, pharmacodynamics, and/or the clinical response to a medicine[2-5]. The objective of this research is to investigate a possible genetic relationship to the handling or response to RVX000222. If at any time during this clinical study or after a multiple studies with RVX000222 there appears to be variability in response to the investigational drug, the relationship between genetic variants and the pharmacokinetics, pharmacodynamics, safety, tolerability, and/or efficacy of RVX000222 may be investigated. Pharmacogenomic research generally relies on two approaches:

1) Analyzing specific sections of the DNA (i.e., candidate genes) known to encode the drug target and metabolic enzymes or analyzing areas of the genome known to be associated with adverse events and diabetes. Note: this could include genes relevant to disease or drug response identified in the future.
2) Evaluation of polymorphisms (e.g., single nucleotide polymorphisms) throughout the genome to identify markers that potentially correspond to response.

Subjects will be asked to provide additional whole blood samples for anonymized phamacogenomic analysis of both DNA and mRNA expression. Collection of these samples will be optional to the subjects and will require a separate informed consent. Subjects may opt not to provide these samples and still participate in the study.

The need for a pharmacogenomic analysis may not be identified until after the completion of this study. Therefore, samples will be stored securely for up to 15 years after the last subject has completed the study; however, the sponsor may destroy the samples sooner. The sponsor (or sponsor's designee) will use the samples only for the purpose stated in this protocol and the informed consent. Subjects can request that their samples be destroyed at any time prior to anonymization.

Where required, the IEC and applicable regulatory agency must approve the pharmacogenomic assessment before these can be conducted at a site. The written approval must clearly indicate approval of the pharmacogenomic assessment. When the pharmacogenomic assessments are not approved, the approval for the rest of the study must clearly indicate this and the pharmacogenomics portion will not be conducted at that site.

	Screen	Treatment																
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±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
Physical Exam	X																	X
Central Laboratory:																		
Fasting Lipid profile	X										X			X		X		X

Instructions for sampling, preparation, storage, dispatch and shipment of samples will be provided in the laboratory manual.

7.1.8 Montreal Cognitive Assessment (MOCA)

The MOCA[6] will be performed on subjects ≥70 years of age at randomization. It will be performed at the visits indicated on the Schedule of Events (

	Screen	Treatment																
Hematology, HbA1c	x										x			x		x		x
Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Lipoproteins, fasting insulin	x	x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic	x	x			x													
Medical History/Demographics	x	x												x				x
ECG	x	x									x			x		x		x
EQ-5D-5L	x	x									x			x		x		x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	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
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior / Con. Medication																		
Drug Dispense/Account.																		
Fasting Lipid profile	x										x			x		x		x
Hematology, HbA1c	x										x			x		x		x

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent	x																	
Randomization		x																
Inclusion / Exclusion		x			x													
MOCA		x												x				x
EQ-5D-5L		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1) to measure any cognitive changes from baseline.

7.1.9 EuroQOL Five Dimensions Questionnaire (EQ-5D-5L)

The EQ-5D-5L[7,8] will be used to measure Health Related Quality of Life (HRQOL) at the visits indicated on the Schedule of Events (

Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin		x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic		x			x													
MOCA		x												x				x
EQ-5D-5L		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1).

7.2 Study Assessments

For all study days, if a subject has any clinically significant, study-related abnormalities, additional evaluations may be performed at the discretion of the Investigator.

7.2.1 Screening/ Study Visit 1 (Week -2 to -1)

Before any study-specific procedures are performed, the subject must receive an explanation of all study procedures, have an opportunity to ask questions, and must sign and date an Institutional Ethics Committee (IEC) approved written informed consent form.

The following will be conducted at Screening:

- Assess inclusion/exclusion criteria
- Document in the subject's medical records the participation in this clinical trial, that informed consent has been obtained, and that a copy of the signed informed consent form has been given to the subject.
- Prepare subjects for the first treatment period participation by informing them of study restrictions and study procedures
- Record demographics
- Measure height and weight
- Review and record complete medical history (including CV history)
- Record prior and concomitant medications (including all CV medications), including detailed information related to the dose, starting and end dates for all medications. Prior medications taken during the 30 day period before Visit 1 will be collected
- Measure vital signs
- Perform a physical examination
- Perform a standard 12-lead ECG
- Collect clinical laboratory samples: fasting lipid profile, hematology, HbA1c, chemistry, urinalysis, liver safety panel
- Perform serology for hepatitis A, B, and C viruses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Subjects will continue or begin high intensity statin therapy as described in Section 6.6.

7.2.2 Study Visit 2/Randomization (Week 0)

- Review inclusion and exclusion criteria
- Record any AEs
- Record concomitant medications
- If subject satisfies all inclusion and exclusion criteria, randomization may occur
- Measure vital signs
- Collect clinical laboratory test samples: liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: lipoproteins, fasting insulin, and inflammation panel
- Collect serum/plasma archive samples
- Collect blood samples for phamacogenomic testing (DNA and RNA) if subject consent received
- Perform MOCA test for any subjects ≥ 70 years of age at randomization
- Administer EQ-5D-5L
- Dispense investigational drug
- Dispense high intensity statin

7.2.3 Study Visits 3-4 (Weeks 2-4)

- Collect clinical laboratory test samples: liver safety panel
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.4 Study Visits 5 (Week 6)

- Collect clinical laboratory test samples: liver safety panel
- Collect blood samples for phamacogenomic testing (RNA only) if subject consent received
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.5 Study Visits 6-7 (Weeks 8-10)

- Collect clinical laboratory test samples: liver safety panel
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.6 Study Visits 8 (Weeks 12)

- Collect clinical laboratory test samples: liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: inflammation panel
- Collect serum/plasma archive samples
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.7 Study Visits 9-10 (Weeks 16-20)

- Collect clinical laboratory test samples: liver safety panel
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.8 Study Visit 11 (Week 24)

- Measure vital signs
- Collect clinical laboratory test samples: fasting lipid profile, hematology, HbA1c, chemistry, urinalysis, liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: lipoproteins, fasting insulin
- Administer EQ-5D-5L
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.9 Study Visits 12-13 (Weeks 28, 40)

- Collect clinical laboratory test samples: liver safety panel
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.10 Study Visit 14 (Week 52)

- Measure vital signs
- Collect clinical laboratory test samples: fasting lipid profile, hematology, HbA1c, chemistry, urinalysis, liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: lipoproteins, fasting insulin, and inflammation panel
- Collect serum/plasma archive samples
- Perform MOCA test for any subjects ≥ 70 years of age at randomization
- Administer EQ-5D-5L
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.11 Study Visit 15 (Week 64)

- Collect clinical laboratory test samples: liver safety panel
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.12 Study Visit 16 (Week 76)

- Measure vital signs
- Collect clinical laboratory test samples: fasting lipid profile, hematology, HbA1c, chemistry, urinalysis, liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: lipoproteins, fasting insulin
- Administer EQ-5D-5L
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.13 Study Visit 17 (Week 88)

- Collect clinical laboratory test samples: liver safety panel
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.14 Study Visit 18 (Week 100)

- Measure vital signs
- Perform a physical examination
- Collect clinical laboratory test samples: fasting lipid profile, hematology, HbA1c, chemistry, urinalysis, liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: lipoproteins, fasting insulin
- Perform MOCA test for any subjects ≥ 70 years of age at randomization
- Administer EQ-5D-5L
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.15 Study Visit 19 (Week 112) and additional visits until end of study (at 12 week intervals)

- Collect clinical laboratory test samples: liver safety panel
- Record concomitant medications
- Monitor AEs
- Perform drug accountability; dispense investigational drug; dispense high intensity statin

7.2.16 Last Visit on Treatment (at end of study)

- Measure vital signs
- Perform a physical examination
- Collect clinical laboratory test samples: fasting lipid profile, hematology, HbA1c, chemistry, urinalysis, liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: lipoproteins, fasting insulin
- Perform MOCA test for any subjects ≥ 70 years of age at randomization
- Administer EQ-5D-5L
- Record concomitant medications
- Monitor AEs
- Perform final drug accountability for RVX000222; dispense high intensity statin

7.2.17 Follow-up Visit (4 weeks after Last Visit on Treatment) or Early Termination Visit

- Measure vital signs
- Perform a physical examination
- Collect clinical laboratory test samples: fasting lipid profile, hematology, HbA1c, chemistry, urinalysis, liver safety panel
- Collect biomarker laboratory test samples in a selected subset of subjects: lipoproteins, fasting insulin
- Record concomitant medications
- Monitor AEs
- Perform final drug accountability for high intensity statin
- Discharge from study

8.0 SAFETY MONITORING

8.1 Clinical Laboratory Tests

Clinical laboratory blood and urine samples will be collected as described in Section 7.1.4. The Investigator will monitor the laboratory test findings. If any laboratory test on or after first dose is abnormal, it will be followed at the discretion of the Investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AE eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study, then the subject must be followed until the abnormality resolves or until it is judged to be permanent.

8.2 Adverse Events

Adverse events that are reported, observed, or elicited by indirect questioning will be collected throughout the study beginning at the time of informed consent and continuing for the duration of the study. Ongoing AEs will be followed to resolution, whenever possible.

8.2.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject, which does not necessarily have a causal relationship with study treatment. It includes the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after informed consent even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the concomitant statin therapy that is given during any phase of the study.

8.2.2 Methods for Following and Documenting Adverse Events

All subjects are carefully monitored for the occurrence of any AE. The safety variables comprise physical examination findings, vital signs, ECGs, and clinical laboratory tests. Additional safety evaluations considered necessary might be performed at the discretion of the Investigator.

Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. Wherever possible, the underlying cause for signs or symptoms should be considered the AE and not the observed signs and symptoms (e.g., pneumonia is preferable to cough, fever, and chest pain). Laboratory values that precipitate dose interruption or discontinuation will be captured as AEs.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments. All reported AEs are to be recorded in the subject's medical record and in the eCRF. If no AE has occurred during the study period, this should also be indicated in the study documents. The severity and causal relationship to study treatment should be assessed.

Characteristics of the AE are to be recorded including:

- Nature (brief description)
- Time and date of onset
- Time and date of resolution
- Maximum intensity (mild, moderate, severe)
- Seriousness

- Treatment given
- Relationship (causality) to the investigational drug (scale: not related, possibly related, probably related, and related)
- Action taken (investigational drug)
- Relationship (causality) to the concomitant statin therapy
- Action taken (concomitant statin therapy)
- Outcome

8.2.2.1 Follow-up on Adverse Events

Adverse events, abnormal clinical laboratory test results, changes in physical examination findings, or changes in vital sign measurements or ECGs that the Investigator considers to be clinically significant will be followed until resolution or a until a stable condition has been established. Subjects withdrawn for safety reasons will be followed until the AE or abnormal laboratory test has been normalized, or until there is an adequate explanation for the AE or laboratory test that is unrelated to the study drug.

8.2.2.2 Rating Scale for Maximum Intensity

Maximum intensity of an AE is the accumulated degree of discomfort, or if the AE is life threatening. Intensity should be assessed according to the following definitions:

Mild: Awareness of signs or symptoms, but these are easily tolerated (acceptable)

Moderate: Discomfort enough to interfere with usual activity (disturbing)

Severe: Incapacity to work or to do usual activity (unacceptable)

8.2.2.3 Rating Scale for Causality

Assessment of causality of suspected AEs is based on associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and absence of alternative explanations. The Investigator will be asked to assess the causal relationship to the study drug according to the following classifications:

Not related: Time relationship with study drug administration is nonexistent or doubtful, or other factors, certain or probable, to have been causative.

Possible: Time relationship with study drug administration exists. Other possible causative factors may exist (e.g., concurrent disease or concomitant medication). Improvements on dechallenge or dose reduction (if performed) may or may not have been seen.

Probable: Time relationship with study drug administration exists. No other possible causative factors may exist (not reasonably explained by the subject's known clinical state or concomitant medication). Improvements on dechallenge or dose reduction (if performed) have occurred. Recurrence of symptoms on rechallenge (if performed) has occurred. A specific laboratory investigation (if performed) has confirmed the relationship.

Definite: Those events for which there is no shadow of doubt that they are a consequence of administration of the study drug. It is likely that such events will be widely documented and generally accepted as having association with the study drug or that they reoccurred after rechallenge (if performed).

8.2.2.4 Follow-up Period After an Adverse Event

If clinically significant findings are present at the study termination (Follow-Up Visit), a determination will be made about each persistent clinically significant finding. If not clinically important (i.e., does not pose a health risk to the subject), the findings will be labeled ongoing and follow-up will cease. If clinically important, follow-up will continue on a case-by-case basis until satisfactory resolution.

8.2.2.5 Coding of Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be performed after the eCRFs have been completed by the Investigative Sites.

8.2.3 Serious Adverse Events

8.2.3.1 Definition

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.

Medical judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.2.3.2 Hospitalization

Adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission to a healthcare facility meets these criteria.

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)

Hospitalizations or prolongation of hospitalization in the absence of precipitating clinical AE is not in itself an SAE. Examples include:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the subject's general condition

8.2.3.3 SAE Reporting to Sponsor

All SAEs must be reported, whether or not considered attributable to the study drug, on a separate SAE report form. As much information as possible should be supplied at the time of the initial report with at least the following information:

- Subject, treatment, and study identifiers;
- Investigator's name and address;
- Description of the event, action taken, and outcome;
- Date of onset and current status;
- Any suspect (study) drug, with its start date, dose, and form of administration;
- Reason the AE is regarded as serious;
- Current assessment or opinion of causality;
- Any other available diagnostic information that will contribute to the understanding of the event; and
- If applicable, whether the randomization code has been broken because of the SAE.

The Investigator must inform the Sponsor or Sponsor's designee within 24 hours of when the Investigator is aware of the occurrence of the SAE, whether or not the SAE is related to the study drug. A written report should be submitted, consisting of the SAE report form accompanied by the demographics, medical history, AE, and the concomitant medications pages from the study documents. All pertinent information must be followed by a full follow-up report to the Sponsor within 3 calendar days. As complete a report as possible, (e.g., results of any additional tests) should be forwarded within 8 additional calendar days to the Sponsor. Any significant new information on the SAE and final outcome must be supplied promptly to the Sponsor.

SAEs will be collected throughout the study beginning at Screening and continuing for the duration of the study. Ongoing SAEs will be followed to resolution, whenever possible.

8.2.3.4 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) which do not represent a protocol-defined MACE endpoint (see Section 8.2.3.5), and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs as applicable, in accordance with national regulations in the countries where the study is conducted.

Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial.

The Investigator should comply with the applicable regulatory requirements related to the reporting of SAEs to the local IEC.

8.2.3.5 MACE Adjudication

All potential primary and secondary MACE events will be reported as SAEs as noted in Section 8.2.3.3. The coronary revascularization cases collected in the eCRF will also be forwarded for adjudication.

An independent, treatment-blinded CEC will be appointed to adjudicate CV events. The Committee will confirm all primary and secondary MACE events as defined below:

Primary and Secondary MACE events will include:

- CV death
- Non-fatal MI
- Hospitalization for CVD events including:
  - Unstable angina
  - Congestive heart failure
  - Any revascularization procedure
- Stroke

All deaths will be adjudicated for CV deaths.

A Charter will be prepared to detail precise responsibilities and procedures applicable to this committee. Adjudications will be based on events as defined in the CEC charter and will be based on the CDISC standardized definitions for Cardiovascular and Stroke Endpoint Events[1].

8.2.4 Adverse Events of Special Interest

Adverse events of special interest (AESIs) in this study are AEs which could be associated with immunosuppression, including all opportunistic infections and any serious infections that occur during the AE reporting period. The study Medical Monitor will review AESIs on an ongoing basis in a blinded fashion, and the DSMB will periodically review unblinded AESIs at their regular meetings.

8.2.5 Pregnancies

Pregnancies during the study and within 4 weeks after end of treatment will be reported and tracked according to Safety monitoring documentation.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Considerations

A statistical analysis plan (SAP) will be prepared and finalized prior to the first unblinded interim analysis. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. This document may modify the analysis plans outlined in the protocol and supersede the statistical methods described in the protocol.

Blinded data review meetings will be conducted prior to unblinding. This blinded review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

Any change to the data analyses methods described in the protocol will require a protocol amendment only if it changes one or more of the principal features of the protocol. Any other change to the statistical analysis methods described in the protocol and the justification for making the change will be described in the clinical study report.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.2 Sample Size

Assuming a design with a provision for futility at 75% adjudicated events 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, 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)
- 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 2400 randomized subjects enrolled uniformly over 1.7 years with subjects followed until failure, drop out or end of study will provide the 250 events needed.

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

9.3 Analysis Sets

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 set. Subjects will be analyzed based on randomized treatment group.

Per-protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria, and have no other major protocol violations. The major protocol violation criteria will be finalized by the Clinical Science and Biostatistics teams as part of the treatment-blinded data review 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.

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.

9.4 Baseline and Demographic Data

Baseline and demographic information will be listed and summarized by group and overall Continuous demographic variables will be summarized using number of observations, mean and standard deviation, median and minimum and maximum values. Categorical values will be summarized using number of observations and percentages.

9.5 Subject Disposition

Subject disposition (analyses of randomized, treated, discontinued with primary reason for discontinuation) will be summarized using frequency and percentage by treatment group.

9.6 Efficacy Analysis

All efficacy analyses will use the FAS set. Key efficacy analyses will also be performed on the PPS as supportive evidence and to assess the robustness of the efficacy findings. Subjects will be analyzed according to randomized treatment group.

Time to event analyses for primary and secondary endpoints will use a Kaplan-Meier method to estimate the median onset 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.

Quantitative endpoints that are defined as a change from baseline will be analyzed using analysis of covariance (ANCOVA) models with strata and treatment group as factors and the baseline value as covariate. Mixed model repeated measurements (MMRM) will be used to analyse all assessments of continuous outcomes over time.

For continuous endpoints pertaining 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.

Efficacy results will be considered statistically significant after consideration of the control of multiplicity as specified in Section 9.6.1. All statistical tests will be conducted at alpha = 0.05 (2-sided) level, and a 2 sided *p*-values and CIs will be reported.

9.6.1 Multiplicity

Statistical tests for comparing RVX000222 arm with Placebo will be conducted for the primary endpoint and other efficacy endpoints as listed in Section 3.0.

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 $p = 0.05$.

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 3.0.

No multiplicity adjustment is planned to test the other secondary and exploratory endpoints as these endpoints are considered supportive.

Subjects will continue to be followed for both primary and secondary endpoints until 250 primary endpoint events have been observed. Other than the pre-specified sequential testing, no additional alpha adjustments for multiplicity will be made.

9.7 Safety Analysis

Drug administration, disposition data, medical history and prior medications will be summarized by treatment group using descriptive statistics. Safety data such as clinical laboratory results, vital signs, findings from physical examinations, and MOCAs will be listed and summarized by treatment group where appropriate. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, these summaries will include frequencies and corresponding percentages. 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 shift from Baseline in the clinical laboratory variables, and vital sign measurements. Baseline values for clinical laboratory variables, and vital sign measurements are defined as the last non-missing values obtained prior to dosing. Clinical laboratory variables outside reference ranges will be flagged in clinical laboratory listings.

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, non-serious treatment emergent AEs and serious treatment emergent AEs. Adverse events of special interest (opportunistic infections and all serious/severe infections) will be analyzed as a subset of the overall AEs. Treatment-emergent AEs will be defined as any AEs, regardless of relationship to study drug, that occur after the first dose of double-blind investigational drug and within 14 days after the last dose of double-blind investigational drug. Treatment-related AEs will be defined as any AEs that are considered by the investigator to be either possibly, probably, or definitely related to study drug. In addition, if relationship information is missing, the AE will be considered treatment-related. Listings for the subsets of SAEs and treatment-related SAEs will be provided.

9.8 Missing/Incomplete Subject Data

Missing values will not be imputed.

9.9 Interim Analysis

Prospective unblinded analyses for safety, futility, and sample size adjustment (SSA) if indicated will be conducted by an independent statistician as part of the study design as described in Section 10.8 (Data and Safety Monitoring Board). An interim analysis is planned to assess futility at 75% adjudication of primary endpoint events.

The statistical methodology for futility and SSA that preserves the overall Type I error will be described in greater detail in the DSMB interim futility / sample size adjustment plan.

10.0 REGULATORY AND PROCEDURAL REQUIREMENTS

It is the responsibility of the Investigator to assure that the study is conducted in accordance with current local and national regulations, International Conference on Harmonisation (ICH) and other applicable requirements governing the conduct of human clinical trials.

10.1 Institutional Ethics Committee

The study protocol, including final version of the subject information and informed consent form, must be approved by the IEC prior to enrolment of any subject. The approval of the IEC should be dated and

given in writing. A list of those present at the committee meeting (names and positions) should be attached whenever possible.

The Investigator is responsible for informing the IEC of any SAE or amendments to the protocol as specified in the local requirements. All correspondence with the IEC should be filed by the Investigator.

10.2 Ethical Conduct of the Study

The study will be performed in accordance with the principles stated in the Declaration of Helsinki and subsequent revisions, the ICH E6, FDA regulations, and applicable local regulations.

10.3 Informed Consent Document

At the Screening visit, and before any study-related procedures, the IEC-approved informed consent form will be provided to the subject. The Investigator, or a qualified designee, will fully inform the subject of all pertinent aspects of the study. Before informed consent is given, the Investigator or a designee should provide the subject ample time and opportunity to inquire about details of the study. All questions about the study should be answered to the subject's satisfaction.

Before participation in the study, the written informed consent form will be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Both the informed consent discussion and the written informed consent form will include clear explanations of the recommended elements of informed consent. No subject is to participate in study activities until informed consent has been obtained. Subjects will be given a copy of their signed informed consent form.

10.4 Responsibilities of the Investigator and IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IEC before study start. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to the Sponsor or Sponsor's designee before study initiation.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor or Sponsor's designee, IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

10.5 Monitoring the Study

Site visits and inspections will be conducted by the Sponsor or Sponsor's designee at regular intervals in accordance with the applicable health authority and ICH guidelines. The Investigator will permit representatives of the Sponsor's monitoring team and health authority auditors to inspect relevant facilities and records.

10.6 Protocol Adherence

The Investigator will not deviate from the protocol without prior written approval from Sponsor or its designee, except in medical emergencies. In the event of a medical emergency, the Medical Monitor must be notified as soon as possible. Any other change to the protocol must be implemented as an amendment to the protocol and must be approved by the IEC and Sponsor before implementation.

The governing IEC will be informed of all protocol changes by the Investigator in accordance with the IEC's established procedure. No deviations from the protocol of any type will be permitted without complying with established IEC procedures.

10.7 Clinical Steering Committee

An independent CSC will serve to oversee and guide the conduct of the study. The CSC will be blinded to the study data while the study is ongoing.

10.8 Data and Safety Monitoring Board

An independent DSMB will be appointed. The committee will not include any investigators involved with the study. The DSMB will monitor the un-blinded subject safety data on an ongoing basis at quarterly meetings during the course of the study. The ongoing DSMB safety review will also include review of adverse events of special interest, as defined in Section 8.2.4.

The DSMB charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding to those not part of the DSMB and the integrity of the study in the review of accumulating data and interactions with the CSC and protocol management team. The DSMB will also be involved in the monitoring unblinded efficacy data generated from interim analyses planned to assess futility at 75% adjudication of events. A DSMB futility / sample size adjustment analysis plan will contain more detail.

10.9 Changes in the Conduct of the Study or Planned Analyses

Only the Sponsor, on the recommendation of the CSC, may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the Investigator. The only exception is when the Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, the Investigator takes the appropriate action, documents the action taken, and informs the Sponsor and the IEC as soon as possible or within 5 working days after the emergency occurred. All amendments that have an impact on subject risk or the study objectives, or require revision of the informed consent form, must receive approval from the IEC before being implemented.

10.10 Participant Recruitment

If an Investigator chooses to advertise for subjects, whether in professional or consumer publications, radio, or television, Sponsor and the IEC must approve all advertising before it begins.

10.11 Compensation, Insurance and Indemnity

These elements will be covered in the contractual agreements between the Sponsor, the site and the Investigator.

11.0 DATA COLLECTION

11.1 Recording of Data

An electronic data capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are accurately entered into the eCRF as specified in the protocol and respond to any reported discrepancies rapidly.

	Screen	Treatment

The eCRFs allow data entry by authorized personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, Investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There is an internal quality review audit of the data and additional reviews by the Clinical Monitor.

The Investigator will sign the completed CRF. The Investigator's signature will be applied as specified in the Data Management Plan.

All suspected events included in the composite endpoint of CV death, non-fatal MI, stroke, or secondary CV endpoints will be recorded in the respective appropriate modules of the eCRF. Investigators are also required to provide the CEC copies of source documents (e.g., medical records, discharge summary, death certificate, autopsy report, etc.) Refer to the study manual for procedures regarding Events to be Adjudicated.

11.2 Recordkeeping and Retention

The Investigator must maintain adequate records for the study, including completed study documents, medical records, laboratory reports, signed informed consent documents, drug disposition records, AE reports, information regarding subjects who discontinued, all correspondence with the IEC and the Sponsor (or designee), and other pertinent data.

Source documents should be completed for each included subject. It is the Investigator's responsibility to ensure completion and to review and approve these source documents. Source documents must be signed/initialed by the investigator or by an authorized staff member. These signatures/initials serve to attest that the information contained on the source documents is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the source documents.

The Investigator will retain all records for a minimum of 2 years after the health authority approves the marketing application for the drug, or for a minimum of 2 years after the termination or withdrawal of the health regulatory agency exemption (e.g., Investigational New Drug [IND] or clinical trial application) under which the study was conducted. To avoid any possible errors, the Investigator must contact Sponsor or its designee before the destruction of any study records. The Investigator will also notify Sponsor or its designee of accidental loss or destruction of any study records.

11.3 Data Collection

Study data as indicated on the Schedule of Events (

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	- 2 to -1	0	2	4	6	8	10	12	16	20	24	28	40	52	64	76	88	100
± No. Day			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±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
Physical Exam	x																	x
Central Laboratory:																		
Fasting Lipid profile	x										x			x		x		x
Hematology, HbA1c	x										x			x		x		x
Chemistry	x										x			x		x		x
Urinalysis	x										x			x		x		x
Hepatitis Serology	x																	
Liver Safety Panel	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biomarker Laboratory Tests																		
Lipoproteins, fasting insulin		x									x			x		x		x
Inflammation Panel		x						x						x				
Serum/Plasma Archive		x						x						x				
Pharmacogenomic		x			x													
MOCA		x												x				x
EQ-5D-5L		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
Prior / Con. Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Dispense/Account.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1) will be collected at each study visit and recorded in the appropriate sections of the eCRF.

11.4 Efficacy

The primary and secondary CV efficacy variables will be adjudicated by the independent, treatment-blinded CEC. For documents to be sent to the CEC, refer to the study manual.

11.5 Disclosure of Data

A subject's medical information obtained as a result of this study is confidential. Disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by using subject identification code numbers to correspond to treatment data in the computer files. If results of this study are reported in medical journals or at meetings, the subject's identity will remain confidential.

Medical information may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by health authority auditors, the sponsor's monitors, and by the IEC. If the health authority or other regulatory agency should schedule an inspection, the medical monitor should be advised immediately.

11.6 Confidentiality and Communication of Results

All information concerning this study and Sponsor, including patent applications and manufacturing processes not previously published, is considered confidential and shall remain the sole property of

Sponsor. Confidential information may be published only in collaboration with participating personnel from the Sponsor.

12.0 REFERENCES

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13.0 APPENDICES

APPENDIX A: CHILD-PUGH CLASSIFICATION[9,10]

Child- Turcotte-Pugh (CTP) classification of the severity of cirrhosis

	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

CTP score is obtained by adding the score for each parameter
CTP class: A = 5-6 points
B = 7-9 points
C = 10-15 points