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CLINICAL STUDY REPORT

ASSURE I

ApoA-I Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation

Phase IIb multi-center, double-blind, randomized, parallel group, placebo-controlled clinical trial for the assessment of coronary plaque changes with RVX000222, as determined by intravascular ultrasound

Protocol No.: RVX222-CS-007
Phase: IIb
First Patient In: 30 Sep 2011
Last Patient Out: 16 May 2013

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This study was completed according to the guideline of Good Clinical Practice (GCP) and was conducted in full compliance with the accepted version of the World Medical Assembly Declaration of Helsinki.

2 SYNOPSIS

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Title of Study:

Phase IIb multi-center, double-blind, randomized, parallel group, placebo-controlled clinical trial for the assessment of coronary plaque changes with RVX000222, as determined by intravascular ultrasound.

Investigator(s) and Study Centers:

A total of 66 sites received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval to participate in this study; at least 1 patient was screened at 60 sites.

Publication(s): None

Study Period:	**Clinical Phase:**
30 Sep 2011 to 16 May 2013	IIb

Objective(s):

Primary Objective

- To evaluate the effect of RVX000222 on the change in burden of coronary atherosclerosis, as measured by percent atheroma volume (PAV), in patients with coronary artery disease and a low level of high density lipoprotein cholesterol (HDL-C) requiring angiography for a clinical indication.

Secondary Objectives

- To evaluate the effect of RVX000222 on the change in total atheroma volume (TAV), changes in the 10-mm most diseased artery sub-segment containing the most amount of disease and the percentage of patients who demonstrate regression of coronary atherosclerosis.
- To evaluate the effect of RVX000222 on biomarkers (HDL-C, apolipoprotein A-I [ApoA-I], high density lipoprotein [HDL] subclasses) at various time points.
- To evaluate the safety and tolerability of RVX000222.

Exploratory Objectives

- To determine the relationship between changes in lipid parameters and changes in measures of atheroma burden.
- To evaluate the effect of RVX000222 on plaque composition.
- To evaluate the pharmacokinetics (PK) of RVX000222.

Methodology:

This was a 26-week active treatment period, double-blind, placebo-controlled, 2-arm parallel-group (allocation ratio 3:1) study of RVX000222 at a daily dose of 200 mg or matching placebo administered to patients with a low HDL-C level who required coronary angiography for a clinical indication.

Period 1 Screening

Eligibility for study participation was to be assessed at Study Visit 1. Patients were identified for participation in the study based on the requirement that they were scheduled to undergo a clinically indicated coronary catheterization procedure. If suitable, and if the patient agreed to enter the study, they were asked to sign an informed consent prior to performing any study related procedures. Patients then entered a screening period of up to 4 weeks in order to allow adequate time for completion of all qualifying screening and eligibility evaluations. Consenting patients who fulfilled the inclusion and exclusion criteria underwent the screening cardiac catheterization. If the patient's angiographic criteria were met then the intravascular ultrasound (IVUS) procedure was done. The IVUS imaging was reviewed and confirmed by the IVUS Core Laboratory for eligibility.

In the majority of cases, the screening/clinically indicated baseline cardiac catheterization and the IVUS were performed during the same visit. However, if the initial screening catheterization resulted in an outcome that required percutaneous coronary intervention (PCI), the patient was discharged from the hospital and brought back at a later date to have the PCI performed. In such cases, the baseline IVUS was performed at the time of the second catheterization procedure. This second

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catheterization procedure was performed ≤14 days of the initial screening cardiac catheterization.

If the screening cardiac catheterization, IVUS procedure, and other qualifying evaluations fulfilled the protocol requirements and the site received confirmation from the IVUS Core Laboratory, the patient was randomized to study drug (Visit 2) no later than 7 days following confirmation.

Period 2 Active Treatment Period

At Visit 2 (no more than 7 days after the baseline IVUS confirmation), all eligible patients who fulfilled the inclusion/exclusion criteria were randomized, via the Interactive Voice Response System (IVRS), to either RVX000222 200 mg (100 mg twice a day [BID]) or matching placebo and had regularly scheduled clinic visits. Patients currently on atorvastatin (10 mg, 20 mg, or 40 mg) or rosuvastatin (5 mg, 10 mg, or 20 mg) at Visit 1 remained on this statin during the study. Those patients currently on other or no statin therapy were assigned to either atorvastatin or rosuvastatin treatment at Visit 1 and remained on statin treatment during the study. The double-blind randomized treatment phase lasted 26 weeks (Visit 2 through Visit 12). At Visit 12, patients underwent a cardiac catheterization and final IVUS procedure.

Period 3 Final Follow-up of Study Drug (30 Days after discontinuation of active treatment)

Visit 13 was a single follow-up visit occurring 30 days following Visit 12.

Number of Subjects:

A total of 323 men and women ≥18 years of age, with coronary artery disease and a low HDL-C level requiring a clinically indicated coronary angiography with an acceptable IVUS were randomized into this study.

Diagnosis and Key Criteria for Inclusion:

Inclusion criteria

1. Male and female patients ≥18 years of age that were scheduled to undergo coronary angiography for a clinical indication.
2. Women of child-bearing potential, that is, women not surgically sterilized and between menarche and 1 year post-menopause, were required to test negative for pregnancy at the time of enrollment based on a serum pregnancy test and agree to use a reliable method of birth control (for example, use of oral contraceptives or Norplant®; a reliable barrier method of birth control (diaphragms with contraceptive jelly; cervical caps with contraceptive jelly; condoms with contraceptive foam; intrauterine devices; partner with vasectomy; or abstinence) during the study and for 1 month following the last dose of study drug.
3. Current (local laboratory within 60 days prior to Visit 1)
   - HDL-C of ≤45 mg/dL (1.2 mmol/L) for females
   - HDL-C of ≤40 mg/dL (1.0 mmol/L) for males
4. In the opinion of the investigator, patients currently not on statin therapy were able to start either atorvastatin (10 mg, 20 mg, or 40 mg) or rosuvastatin (5 mg, 10 mg, or 20 mg) at Visit 1.
5. In the opinion of the investigator, patients currently on statin therapy other than atorvastatin (10 mg, 20 mg, or 40 mg) or rosuvastatin (5 mg, 10 mg or 20 mg) could be switched to rosuvastatin (5 mg, 10 mg, or 20 mg) at Visit 1.
6. Patients were required to meet all of the following criteria at the qualifying coronary catheterization procedure:

   A. **Entire Coronary Circulation**:
   - Angiographic evidence of coronary heart disease as defined by at least 1 lesion in any of the three major native coronary arteries that had >20% reduction in lumen diameter by angiographic visual estimation or prior history of PCI.
   - This vessel was not required to be the target coronary artery for IVUS.
   - Any vessel with previous PCI could not be used as the target coronary artery.

   B. **Left Main Coronary Artery**:
   - Must not have had a >50% reduction in lumen diameter by visual angiographic estimation.

   C**. Target Coronary Artery for IVUS**:

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- Must have been accessible to the IVUS catheter.
- Must have had a <50% reduction in lumen diameter by angiographic visual estimation throughout a segment of at least 40 mm in length (the "target segment"). A lesion of up to 60% stenosis was permitted, distal to the target segment. A single branch of the "target vessel" may have had a narrowing up to <70% by visual estimation, as long as the target segment contained no lesion >50%, provided that the branch in question was not a target for PCI or coronary artery bypass graft (CABG) surgery.
- Had not undergone prior PCI or CABG.
- The target vessel was not currently a candidate for intervention or a likely candidate for intervention over the next 6 months.
- The target vessel was not a bypass graft.
- The target vessel was not a bypassed vessel.
- The target vessel was not the culprit vessel for a previous myocardial infarction (MI).

7. Have given signed informed consent to participate in this study.

Exclusion Criteria

1. Clinically significant heart disease which required coronary bypass, PCI, cardiac transplantation, surgical repair and/or replacement during the course of the study.
2. Any elective surgical procedure that would require general anesthesia during the course of the study.
3. CABG procedure within the past 90 days.
4. Previous or current diagnosis of severe heart failure (New York Heart Association Class III-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 patient without a previous or current diagnosis of heart failure did not prohibit entry into the study.
5. Patients 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 four weeks prior to Visit 1.
6. Evidence of renal impairment as determined by any of the following:
   - serum creatinine >1.5 mg/dL (>133 mcmol/L) by central laboratory at Visit 1,
   - a calculated creatinine clearance <60 mL/min at Visit 1,
   - a history of dialysis,
   - a history of nephrotic syndrome.
7. Had hypertension that was uncontrolled defined as 2 consecutive measurements of sitting blood pressure of systolic >160 mmHg or diastolic >95 mmHg at Visit 1.
8. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive ß-human chronic gonadotropin laboratory test (≥5 mIU/mL).
9. Current or recent (within 12 months prior to Visit 1) treatment with immunosuppressants (e.g. cyclosporine).
10. Use of fibrates at any dose or niacin/nicotinic acid 250 mg or more within 90 days prior to Visit 1.
11. Atorvastatin >40 mg daily at Visit 1.
12. Rosuvastatin >20 mg daily at Visit 1.
13. Triglycerides >400 mg/dL at Visit 1.
14. Any medical or surgical condition which might significantly have altered the absorption, distribution, metabolism, or excretion of medication including, but not limited to any of the following: cholecystitis, Crohn's disease, ulcerative colitis, or any gastric bypass alteration.
15. Evidence of hepatic disease as determined by any one of the following:

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- a history of hepatic encephalopathy,
- history of Hepatitis B, C or E,
- history of esophageal varices,
- history of porta-caval shunt,
- Any one of the following liver enzymes that is greater than upper limit of normal (>ULN) by central laboratory at Visit 1:
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Gamma-glutamyltransferase (GGT)

16. A total bilirubin that was >ULN by central laboratory at Visit 1.
17. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
18. History or evidence of drug or alcohol abuse within the last 12 months.
19. Any surgical or medical condition, which in the opinion of the investigator, might have placed the patient at higher risk from his/her participation in the study, or was likely to prevent the patient from complying with the requirements of the study or completing the study.
20. Use of other investigational drugs and devices at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer.
21. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
22. Any condition that in the opinion of the investigator would confound the evaluation and interpretation of efficacy and/or safety data.
23. Persons directly involved in the execution of this protocol.

Test Product, Dose, Mode of Administration, Batch No(s):

RVX000222, 200 mg (100 mg BID), oral

11JM-122, 11JM-125, and 11JM-128 (dosage formulation is 50 mg capsules)

Duration of Treatment:

26 weeks

Reference Therapy, Dose, Mode of Administration, Batch No(s):

Placebo, 0 mg BID, oral

11JM-122

Criteria for Evaluation:

This study used three analysis sets, referred to as populations, to carry out the planned analyses: Modified Intent-to-Treat (mITT), Full Analysis Set (FAS) and Per Protocol (PP) Population.

The Safety Population was used for all safety analyses; mITT, FAS, and PP Populations were used for the efficacy analyses.

Modified Intent-to-Treat

A mITT population was used for both primary and secondary endpoint analyses. This consisted of all randomized patients who had received at least 1 dose of study drug. A patient was considered randomized as soon as a treatment number was assigned by the interactive voice response system. Patients were analyzed according to the treatment to which they were randomized regardless of whether or not the study drug was prematurely discontinued or dose lowered due to an adverse event (AE). The mITT Population was the primary efficacy analysis population.

Full Analysis Set

The FAS population was used for the primary and secondary endpoint analyses. The FAS consisted of all randomized patients who have received at least 1 dose of study drug and completed both the baseline (Visit 1) and Week 26 (Visit 12)

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intravascular ultrasound (IVUS).

Per Protocol Population

All patients who completed all protocol-specified dosing days (active or control), and who had completed both a baseline and follow-up IVUS procedure between Week 17 and Week 30, had a study drug compliance rate of 80%, and had no major protocol violations were included in the PP Population.

The PP Population was defined after a review of the blinded data and protocol deviations prior to unblinding the data.

The PP Population was used to assess the effect of treatment in completers who had no substantial protocol deviations.

Safety Population

All patients who received at least 1 dose of study drug (active or control) were included in the Safety Population and were analyzed based on the actual treatment received. The Safety Population was used for all safety summaries.

Efficacy:

Primary Efficacy Endpoint

- Nominal change in PAV from baseline to 26 weeks post-randomization, as determined by IVUS within the RVX000222 treated group.

Secondary Efficacy Endpoints

- Nominal change in TAV from baseline to 26 weeks post-randomization, as determined by IVUS within the RVX000222 treated group as well as compared to placebo.
- Nominal change in TAV for the 10-mm sub-segment with the greatest disease burden at baseline, within the RVX000222 treated group as well as compared to placebo.
- Proportion of patients with regression of coronary atherosclerosis, defined as a change in PAV from baseline to 26 weeks of less than zero (e.g. any reduction in PAV).
- Percent change from baseline in HDL-C, ApoA-I, HDL-subclasses, and high sensitivity C-reactive protein (hs-CRP) at various time points within the RVX000222 treated group and compared to placebo.

Exploratory Efficacy Endpoints

- Correlations between changes in atheroma burden (PAV and TAV) and change in lipid biomarkers (HDL-C, ApoA-I, HDL-subclasses).
- Change in spectral features of plaque composition by radiofrequency analysis (RFA) within the RVX000222 treated group and to placebo on a subset of patients.
- Evaluation of PK trough values (C_{min}) at various time points.
- Correlation between C_{min} and change in PAV.

Safety:

Incidence of AEs by treatment group, including major adverse cardiac events (MACE) (death, MI, stroke, coronary revascularization, hospitalization for acute coronary syndrome [ACS] or heart failure) was measured.

Statistical Methods:

Categorical variables were summarized using counts and percentages. Percentages were based on the number of patients in the analysis set for whom there were non-missing data, unless otherwise specified. Continuous variables, including change from baseline, were summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, maximum, and 95% confidence intervals (CIs).

Baseline was defined as the last non-missing measurement prior to randomization.

Unless otherwise stated, all summaries were presented by treatment group (RXV000222 or placebo) when appropriate. Patient data listings included all patients and were sorted by treatment group, site, patient number, and date (if applicable).

Statistical analyses were carried out using SAS statistical analysis software version 9.2 or higher (SAS Institute, Inc., Cary,

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North Carolina, USA).

Any additional safety data collected during the 30 day follow-up period, when patients were no longer taking study drug, were summarized separately.

For all additional/secondary and exploratory analyses, the mITT Population, FAS, and PP Population were used.

Efficacy:

Primary Efficacy Endpoint

The primary efficacy analysis was performed on the mITT Population. A paired t-test was performed to determine if there was a significant difference in the change from baseline to end-of-treatment in PAV for the RVX000222 dose group. The Shapiro-Wilk test was used to test for normality. If the test for normality was rejected (i.e., p-value < 0.05), the Wilcoxon signed-rank test was performed. In addition, the 95% CIs were presented for PAV change from baseline for the RVX000222 dose group.

In addition, descriptive statistics were presented for the observed PAV and change in PAV from baseline (Visit 1) to Week 26 (Visit 12).

Supplementary Analysis

As a supplementary analysis, the primary endpoint analysis was repeated for the placebo dose group.

Sensitivity Analysis

To investigate influences on the outcome of the primary endpoint, the primary efficacy analysis was repeated for the FAS and PP Population.

Secondary Efficacy Endpoint

The following secondary efficacy endpoints were analyzed, as described below:

- Nominal change in PAV from baseline to Week 26 (Visit 12), comparing the RVX000222-treated group to placebo, was presented for the mITT, FAS, and PP Population.
- Nominal change in TAV as determined by IVUS from baseline to Week 26 (Visit 12) within the RVX000222-treated group as well as compared to placebo was presented for the mITT, FAS, and PP Population.
- Nominal change from baseline to Week 26 (Visit 12) in TAV for the 10-mm sub-segment with the greatest disease burden at baseline within the RVX000222-treated group as well as compared to placebo was presented for the mITT, FAS, and PP Population.
- Percent change in HDL-C, ApoA-I, HDL-subclasses, and hs-CRP from baseline were presented for the mITT, FAS, and PP Population. The Week 26 (Visit 12) value for each parameter was derived using the last observation carried forward (LOCF) methodology. The LOCF analyses used the last non-missing assessment after Visit 1 (baseline) as an estimate for all subsequent missing values.

Paired t-tests were used to evaluate the change from baseline to Week 26 for each endpoint within each treatment group. The Shapiro-Wilk test was used to test for normality. If the test for normality was rejected (i.e., p-value < 0.05) the Wilcoxon signed-rank test was performed. In addition, the parametric or nonparametric 95% CIs, consistent with the statistical test was presented for each endpoint for both the RVX000222 and placebo dose groups.

To assess differences between treatment groups in the change from baseline to Week 26, an analysis of covariance (ANCOVA) model was used. The ANCOVA model included the baseline value as a covariate, and treatment group as a factor. For modeling results, least squares (LS) means, 95% CIs of the LS mean and standard errors (SE) were presented.

The following additional secondary endpoints were analyzed as follows:

- The proportion of patients with regression of coronary atherosclerosis from baseline (Visit 1) to Week 26 (Visit 12) was summarized by treatment group for the mITT, FAS, and PP Population, and was compared using an unadjusted chi-square test.
- Incidence of AEs by treatment group, including MACEs (death, MI, stroke, coronary revascularization, hospitalization for ACS or heart failure) were evaluated using descriptive statistics with counts, percentages and

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95% CIs. Incidence of AEs was presented for the Safety Population.

The primary endpoint, change in PAV within the active RVX000222 treatment group, was analyzed for the following subgroups for the FAS and PP Population:

- Baseline PAV (at or above or below the overall median)
- Baseline HDL-C (at or above or below the overall median)
- History of diabetes mellitus (yes or no)
- Gender (male or female)
- Age (≥65 or <65)
- Statin Use (atorvastatin or rosuvastatin)
- Baseline Apo-A1 (at or above or below the overall median)
- Baseline large HDL (nuclear magnetic resonance) (at or above or below the overall median)
- Baseline hs-CRP (at or above or below the overall median)

Paired t-tests were used to evaluate the change from baseline to Week 26 for each endpoint within the RVX000222 dose group for each subgroup. The Shapiro-Wilk test was used to test for normality. If the test for normality was rejected (i.e., p-value < 0.05) the Wilcoxon signed rank test was performed. In addition, the parametric or nonparametric 95% CIs, consistent with the statistical test was presented for each endpoint for the RVX000222.

As supplementary analyses, the subgroup analyses were repeated for the placebo dose group.

Exploratory Efficacy Endpoints

Correlations between changes in atheroma burden (PAV and TAV) and percent change in lipid biomarkers (HDL-C, ApoA-I, HDL-subclasses which includes HDL total particles, HDL size, large HDL, and small HDL) were presented. Correlations were presented for the FAS and PP Population.

The percent changes in lipids at Week 26 (Visit 12) were correlated with the changes in measures of atheroma volume in the RVX000222 treated group using the Pearson correlation coefficient. If both variables were non-normal based on the Shapiro-Wilk test, the Spearman rank correlation coefficient was used.

- Change in spectral features of plaque composition by radio frequency analysis (fibrous, fibro-fatty, necrotic core, and dense calcium) within the RVX000222-treated group and placebo group was conducted on a subset of patients.
- Spectral features of plaque composition were described by treatment group using descriptive statistics, for the mITT, FAS, and PP Population.
- Evaluation of PK trough values (C_{min}).

  Individual and mean PK trough concentration values were plotted against time points.
- Correlation between PK trough values and change in PAV.

  The relationship between C_{min} was correlated with the change in PAV at Week 26 (Visit 12) for the RVX000222 treated group using the Pearson correlation coefficient. If both variables were non-normal based on the Shapiro-Wilk test, the Spearman rank correlation coefficient was used. Correlations were presented for the FAS and PP Population.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. Coding included system organ class (SOC) and preferred term (PT). All verbatim and coded terms were listed for all AEs. The frequency and percentage of patients with AEs were summarized by SOC and PT. Adverse events were recorded at the maximum intensity of the event, assuming that the verbatim term did not change. All AE summaries were based on the Safety Population.

Tabular summaries included all AEs, AEs by severity (mild, moderate, severe), AEs by relationship to treatment (related,

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not related), serious AEs, and AEs leading to withdrawal of study drug and discontinuation. Any deaths while on study were presented in a listing that included the AE leading to death, details of study treatment, and relationship to study drug of the AE leading to death.

Laboratory data were presented for the Safety Population. All laboratory data (fasting lipid profile, chemistry, hematology, and urinalysis) were flagged with regards to the investigator reference ranges (provided by a designated central laboratory). Abnormal values were flagged with H when the value was higher than the upper limit of the reference ranges and with L when the value was lower than the lower limit of the reference ranges. All laboratory results were reported in conventional units as reported by the central laboratory.

A summary of patients with elevated transaminase levels (ALT/AST) during the treatment period was presented. Patients with elevated transaminase levels (ALT and AST) were categorized as follows:

- >1x ULN but ≤ 3x ULN
- >3x ULN but ≤ 5x ULN
- >5x ULN but ≤ 8x ULN
- >8x ULN

The following were categorized for patients with elevated ALT/AST >3x ULN during the treatment period:

- first occurrence of ALT >3x ULN before or at Week 11 (Visit 7)
- first occurrence of ALT >3x ULN after Week 11 (Visit 7)

In addition, patients with elevated ALT were categorized as follows:

- >5x ULN
- >8x ULN

The following vital signs were collected at each visit and were summarized by treatment group for the Safety Population:

- oral body temperature (°C),
- systolic and diastolic blood pressure (mmHg) (seated),
- pulse (beats/min) and
- respiration rate (breaths/min).

A standard 12-lead electrocardiogram (ECG) was performed for each patient at Screening (Visit 1), Week 14 (Visit 8) and at Week 26 (Visit 12). The results were listed for each patient, including the overall ECG impression and any abnormalities.

A complete physical examination was performed at Screening (Visit 1), Week 14 (Visit 8) and Week 26 (Visit 12). Results of the examinations were listed by patient and body system for the Safety Population.

Pharmacokinetics:

Plasma concentration of RVX000222 was measured in trough samples collected at Study Visits 2, 4, 8 and 12 using a validated analytical method. Individual plasma RVX000222 concentrations at each study visit were listed. Summary statistics (n, arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum) by treatment group were also generated for the steady-state trough plasma concentration of RVX000222 in each patient over the course of the study (the mean of Study Visits 2,4, 8, and 12).

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SUMMARY OF RESULTS

Efficacy:

- A decrease in PAV from baseline to 26 weeks was observed in the mITT population; however the difference was not statistically significant (median -0.4, p=0.08), and therefore the study did not meet the primary efficacy endpoint. The study did meet the secondary efficacy endpoints in that significant reductions from baseline to Week 26 in TAV and TAV for the 10 mm sub segment with the greatest disease burden at baseline were observed within the RVX000222 treatment group (p<0.001, for both). However, there were no significant differences between the RVX000222 treatment group and placebo for TAV or TAV for the 10 mm sub segment with the greatest disease burden.
- No significant differences were observed for change from baseline to Week 26 in PAV (p=0.534), TAV (p=0.888), and TAV for the 10 mm sub segment with the greatest disease burden (p=0.782) in the RVX000222 group compared to placebo. However, the study was not powered to detect these differences.
- Additional secondary efficacy analyses showed a significant percent change from baseline to Week 26 in HDL-C, ApoA-I, hs-CRP, and large HDL particles in the RVX000222 200 mg group (p<0.001) across all analysis populations. Similarly, significant changes from baseline were observed in the placebo group across all parameters with the exception of hs-CRP (p=0.065).
- Other parameters were also analyzed including HDL size, HDL particles (total), small HDL, and medium HDL. Percent change from baseline to Week 26 was significant for all of these parameters in the RVX000222 group (p<0.001).
- The RVX000222 and placebo groups had the same percentage of patients demonstrating any regression in coronary atherosclerosis (p=0.990) (RVX000222=56.3%; placebo=56.2%).
- Exploratory analyses found no significant correlation between the change from baseline to Week 26 in PAV or TAV and percent changes in lipids (HDL-C, ApoA-I, HDL subclasses which included HDL total particles, HDL size, large HDL (HDL-L), and small HDL (HDL-S) in the RVX000222-treated group.
- The necrotic core to dense calcium ratio (NC/DC) ratio in RVX000222-treated patients was significantly lower (p<0.03) versus baseline while those given placebo had a non-significant reduction (p=0.47) versus baseline. The initial VH-IVUS findings show that the actions of RVX000222 improved the NC/DC ratio pointing to less vulnerability of the atherosclerotic plaque for rupture.
- Correlation analysis did not indicate a significant relationship between C_{min} and the change in PAV at Week 26 (Visit 12) for the RVX000222-treated group.
- Subgroup analyses of the primary endpoint demonstrated significant reductions in PAV at Week 26 in RVX000222-treated patients who had PAV above the baseline median, in patients without a history of diabetes mellitus, and in patients with large HDL and HDL-C that were below the baseline median.
- Analysis showed a trend for reduction in MACEs by RVX000222 treatment compared to control (p=0.09) and post-hoc analysis showed a statistically significant MACE reduction by active treatment compared to placebo in the subpopulation with hs-CRP >2 mg/L (p<0.016).
- Post-hoc subgroup analyses demonstrated a significant reduction in hs-CRP, PAV, TAV, TAV for the 10 mm sub-segment with the greatest disease burden at baseline, and MACE in RVX000222-treated patients who had baseline serum hs-CRP >2.0 mg/dL. Percent atheroma volume, TAV, and TAV for the 10 mm sub-segment with the greatest disease burden at baseline were also significantly decreased in the subgroup of patients with below median HDL (<39.0 mg/dL) at baseline who were taking rosuvastatin with RVX000222.

Safety:

- The proportion of patients reporting at least 1 treatment-emergent adverse event (TEAE) was similar in the RVX000222 and placebo groups (53.9% and 58.8%, respectively).
- At least 1 MACE occurred in 8.7% of patients. Major adverse cardiac events occurred more frequently in the

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placebo group than in the RVX000222 200 mg group (p=0.083, 13.8% vs. 7.0%, respectively).

- The most frequently occurring TEAE in both the study drug and placebo groups was angina pectoris (8.6% and 10.0% in the RVX000222 and placebo groups, respectively).
- Overall, the majority of TEAEs were mild or moderate in severity. A similar pattern of results was observed for both RVX00022 and placebo groups.
- The frequency of treatment-related AEs was higher in the RVX000222 group (13.6%) compared to the placebo group (8.8%). The most common treatment-related AEs reported in the study drug group were hepatic enzyme increase (5 patients [2.1%]) and ALT increase (4 patients [1.6%]).
- Serious TEAEs were reported for 13.6% of RVX000222-treated patients and 22.5% of placebo patients; of these, only 2 were related to treatment (0.8% of patients in the RVX000222 group and none in the placebo group). The related events were ALT elevation and rhabdomyolysis. However, upon further review by the Sponsor the event rhabdomyolysis was deemed related to rosuvastatin use, not to RVX000222.
- Overall, 4.3% of patients discontinued study drug due to a TEAE, 4.9% and 2.5% in the treatment and placebo groups, respectively.
- One patient in the placebo group died due to a TEAE; no patients in the RVX000222 group died due to a TEAE.
- There were no clinically significant observations in laboratory results, with the exception of ALT/AST elevations, which occurred more frequently in the RVX000222 group compared with placebo (42.0% vs. 22.5%, p=0.002). In the RVX000222 group, 7.0% (17/243) had ALT elevations >3x ULN; among patients with any ALT elevation, 9.3% (9/97) had elevations >5x ULN. In the RVX000222 group, 4.1% (10/243) had AST elevations >3x ULN; among patients with any AST elevation, 7.0% (5/71) had elevations >5x ULN.
- No clinically significant observations were made by the Sponsor with regard to vital signs, physical examinations, or ECG results.

CONCLUSIONS:

- Though the primary endpoint of this study was not met, a reduction in PAV was observed and there was a trend toward decreased PAV for change from baseline to Week 26 with RVX000222 (p=0.08). However, there were no significant differences between the RVX000222 treatment group and placebo for TAV or TAV for the 10 mm sub segment with the greatest disease burden.
- The study met the secondary endpoints in that significant reductions from baseline to Week 26 in TAV and TAV for the 10 mm sub-segment with the greatest disease burden at baseline were observed within the RVX000222 treatment group (p<0.001, for both).
- Additional secondary efficacy analyses showed a significant percent change from baseline to Week 26 in HDL-C, ApoA-I, hs-CRP, and large HDL particles in the RVX000222 group (p<0.001).
- RVX000222 was well tolerated, with a similar proportion of patients reporting TEAEs and a smaller proportion of patients reporting SAEs in the RVX000222 group as compared to the placebo group.
- Major adverse cardiac events occurred more frequently in the placebo group than in the RVX000222 group, though the difference was not statistically significant (p=0.083).
- ALT/AST increases were more common in the RVX000222 group, observed mainly between Weeks 4 and 11; however, levels returned to normal after suspension of the study drug.

Date of the Report: 12 Mar 2015

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IN-TEXT TABLES

IN-TEXT FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
ACS	acute coronary syndrome
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoA-I	apolipoprotein A-I
ApoB	apolipoprotein B
AST	aspartate aminotransferase
BID	twice a day
CABG	coronary artery bypass graft
CI	confidence intervals
CK	creatinine kinase
C_{min}	trough values
ECG	electrocardiogram
eCRF	electronic case report form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HbA1c	glycosylated hemoglobin
HDL	high density lipoproteins
HDL-C	high density lipoprotein cholesterol
hs-CRP	high sensitivity C-reactive protein
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IVUS	intravascular ultrasound
LDH	lactate dehydrogenase

LDL	low density lipoprotein
LDL-C	low density lipoprotein-cholesterol
LOCF	last observation carried forward
LS	least squares
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infraction
mITT	modified intent to treat
mmHg	millimeters of Mercury
NC/DC ratio	necrotic core to dense calcium ratio
NMR	nuclear magnetic resonance
PAV	percent atheroma volume
PCI	percutaneous coronary intervention
PK	pharmacokinetics
PP	Per Protocol
PT	preferred term
RBC	red blood cell count
RFA	radiofrequency analysis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard errors
SOC	system organ class
TAV	total atheroma volume
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

5 ETHICS AND ADMINISTRATION

5.1 Independent Ethics Committee or Institutional Review Board

The clinical study protocol, informed consent document(s), and any other appropriate study-related documents were reviewed and approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB). Appendix 16.1.3 contains a list of all IECs/IRBs consulted.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations, and in compliance with Good Clinical Practice (GCP) guidelines.

5.3 Patient Information and Consent

Prior to each patient entering the study, the investigator (or designee) explained the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. Prospective patients were given written information about the study, and before any study procedures were performed each patient voluntarily signed and dated the Informed Consent Form (ICF).

If the patient was unable to read, oral presentation and explanation of the written ICF and information was supplied to patients in the presence of an impartial witness. The patient and the witness signed and dated the consent document.

Appendix 16.1.3 contains a sample informed consent document. Site-specific versions are archived in the study master file and are available on request.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigators

A total of 66 sites received IRB/IEC approval to participate in this study; at least 1 patient was screened at 60 sites. The names and addresses of the Investigators, their affiliations, and their curricula vitae are provided in Appendix 16.1.4.

6.2 Study Personnel

The names and addresses of the organizations and/or individuals involved in the coordination of the study or in analysis of and reporting of results are listed in Table 6.1 below.

Table 6.1: Individuals and Organizations Responsible for Study Coordination

Sponsor: Resverlogix Corp 44 Montgomery Street Suite 2150 San Francisco, CA 94104 Phone: +1-415-470-5600	Study Monitors: Karina Castellano Sr CRA, LA PharmaNet SRL –Argentina Av. Leandro N. Alem 855 piso 23, Buenos Aires, C1001AAD Argentina Twan van Exsel Sr CRA, EU PharmaNet Storkstraat 18-20 II PO Box 285 3830 AG Leusden, Netherlands Julia Vasileva Sr CRA, Russia,OOO PharmaNet 6/2, Turchaninov pereulok, Moscow, 119034, Russia
Data Management: Jennifer Horan Director, Data Management inVentiv Health Clinical 1787 Sentry Parkway West Building 16, Suite 300 Blue Bell, PA 19422	Medical Monitors: William Garland, MD Executive Medical Director, inVentiv Health Clinical 4225 Executive Square Ste 800 La Jolla, CA 92037 Simonetta Alvino, MD Sr. Medical Director Pharmanet Services GmbH via Maurizio Gonzaga 7 Milan, 20123 Italy

Statistician: Shushma Patel Senior Statistician inVentiv Health Clinical, LLC 1000 Winstead Drive Suite 200 Cary, NC 27513 USA	Medical Writer: Bryan Greene, PhD Senior Medical Writer inVentiv Health Clinical, 504 Carnegie Center Princeton, NJ 08540 USA
Central Clinical Laboratory: Mike Totedo Sr Project Manager ACM Global Central Laboratory 160 Elmgrove Park Rochester, NY 14624 USA	Clinical Supply Packaging: Jean Paul Velasquez Clinical Supply Chain Consultant Pacific Pharmaceutical Services, LLC 257 Lands End Court Vallejo, CA 94591

7 INTRODUCTION AND STUDY RATIONALE

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in the Western world. While randomized controlled trials have demonstrated that therapies that target established risk factors such as low density lipoprotein cholesterol (LDL-C) and blood pressure reduce cardiovascular event rates, substantial residual risk remains. As a result, there is an important need to develop new therapeutic strategies that complement current therapies in order to achieve more effective reduction in cardiovascular risk. High-density lipoproteins (HDL) have received considerable attention as a potential target for the development of new preventive therapies. Population studies have consistently demonstrated an inverse relationship between systemic levels of HDL cholesterol (HDL-C) and the prospective risk of coronary heart disease. Promoting the biological activity of HDL has a beneficial impact on the extent and composition of lesions in animal models of atherosclerosis. The beneficial effect of HDL on the artery wall is likely to result from a combination of functional properties including promotion of cholesterol efflux and reverse cholesterol transport, increasing the bioavailability of nitric oxide and inhibiting inflammatory, oxidative, apoptotic and thrombotic pathways. Consistent with these observations, it has been reported that modestly raising levels of HDL-C is an independent predictor of the clinical benefit of currently prescribed therapies, including statins, fibrates and nicotinic acid.

Arterial wall imaging has been increasingly incorporated into clinical development programs of agents that promote the biological activity of HDL. Early clinical studies demonstrated that raising HDL-C with niacin, when used in combination with statin therapy, had a

beneficial impact on progression of carotid intimal medial thickness and obstructive disease on coronary angiography. The development of intravascular ultrasound (IVUS) permits imaging within the coronary arteries with high frequency ultrasound transducers. This generates high-resolution images of the entire thickness of the artery wall, allowing visualization of the full extent of atherosclerosis. As a result, IVUS permits precise quantitation of the burden of atherosclerotic plaque and therefore provides an opportunity to evaluate the impact of medical therapies on disease progression.

Clinical studies that have employed IVUS have demonstrated the beneficial impact of therapies promoting HDL function on the burden of coronary atherosclerosis. In an early study of patients following an acute coronary syndrome (ACS), five weekly intravenous infusions of reconstituted HDL containing recombinant human apolipoprotein (Apo) A-I$_{Milano}$ promoted rapid regression of coronary atherosclerosis. A similar finding was observed when patients received infusions of reconstituted HDL containing wild-type ApoA-I. This suggested that the benefit was not specific to the protein involved, but was more likely to be due to the administration of lipid-depleted forms of HDL. This is consistent with reports that lipid-depleted HDL, or preβ-HDL are efficient in mediating cholesterol efflux from macrophages and supported by the more recent report that infusion of delipidated HDL also promotes rapid disease regression. The benefit of raising levels of HDL-C has been demonstrated in IVUS studies that have evaluated the effect of oral therapies. In a pooled analysis of four clinical studies of 1455 patients, modestly raising HDL-C levels independently predicted the beneficial impact of statins on plaque progression. Changing the ratio of apolipoprotein B (ApoB)/ApoA-I, an index of the balance between atherogenic and protective lipid particles, was the greatest predictor of statins on disease progression. The greatest degree of regression was observed in patients who achieved very low levels of LDL-C, in combination with HDL-C rising. More recently, it has been demonstrated that while the cholesteryl ester transfer protein inhibitor torcetrapib did not slow disease progression, regression was observed in those who achieved the highest levels of HDL-C. This suggested that the lack of efficacy of torcetrapib was more likely to result from off-target toxicity and provided further impetus for the concept that novel therapies that promote HDL function may provide clinical benefit in humans. Therapeutic strategies that increase endogenous synthesis of ApoA-I remain a cornerstone of interest in the development of new

therapies to promote HDL function, RVX000222 is a member of a novel class of small molecules that increase ApoA-I levels by transcriptional up-regulation of ApoA-I.

Accordingly, the objective of the ApoA1 Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation (ASSURE) study was to determine the 26-week impact of the ApoA-I inducer, RVX000222, on the burden of coronary atherosclerosis in patients with coronary disease and low HDL cholesterol levels.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To evaluate the effect of RVX000222 on the change in burden of coronary atherosclerosis, as measured by percent atheroma volume (PAV), in patients with coronary artery disease and a low level of HDL-C requiring angiography for a clinical indication.

8.2 Secondary Objectives

- To evaluate the effect of RVX000222 on the change in total atheroma volume (TAV), changes in the 10-mm most diseased artery sub-segment containing the most amount of disease and the percentage of patients who demonstrate regression of coronary atherosclerosis.
- To evaluate the effect of RVX000222 on biomarkers (HDL-C, ApoA-I, HDL-subclasses) at various time points.
- To evaluate the safety and tolerability of RVX000222.

8.3 Exploratory Objectives

- To determine the relationship between changes in lipid parameters and changes in measures of atheroma burden.
- To evaluate the effect of RVX000222 on plaque composition.
- To evaluate the pharmacokinetics (PK) of RVX000222.

9 INVESTIGATIONAL PLAN

For full details of the investigational plan, see the relevant sections of the clinical study protocol in Appendix 16.1.1.

9.1 Overall Study Design and Plan

This was a 26-week active treatment period, double-blind, placebo-controlled, 2-arm parallel-group (allocation ratio 3:1) study of RVX000222 at a daily dose of 200 mg or matching placebo administered to patients with a low HDL-C level who required coronary angiography for a clinical indication. The study designed is schematically summarized in Figure 1.

Period 1 Screening

Eligibility for study participation was to be assessed at Study Visit 1. Patients were identified for participation in the study based on the requirement that they were scheduled to undergo a clinically indicated coronary catheterization procedure. If suitable, and if the patient agreed to enter the study, they were asked to sign an informed consent prior to performing any study related procedures. Patients then entered a screening period of up to 4 weeks in order to allow adequate time for completion of all qualifying screening and eligibility evaluations. Consenting patients who fulfilled the inclusion and exclusion criteria underwent the screening cardiac catheterization. If the patient's angiographic criteria were met then the IVUS procedure was done. The IVUS imaging was reviewed and confirmed by the IVUS Core Laboratory for eligibility.

In the majority of cases, the screening/clinically indicated baseline cardiac catheterization and the IVUS were performed during the same visit. However, if the initial screening catheterization resulted in an outcome that required percutaneous coronary intervention (PCI), the patient was discharged from the hospital and brought back at a later date to have the PCI performed. In such cases, the baseline IVUS was performed at the time of the second catheterization procedure. This second catheterization procedure was performed ≤14 days of the initial screening cardiac catheterization.

If the screening cardiac catheterization, IVUS procedure, and other qualifying evaluations fulfilled the protocol requirements and the site received confirmation from the IVUS Core Laboratory, the patient was randomized to study drug (Visit 2) no later than 7 days following confirmation.

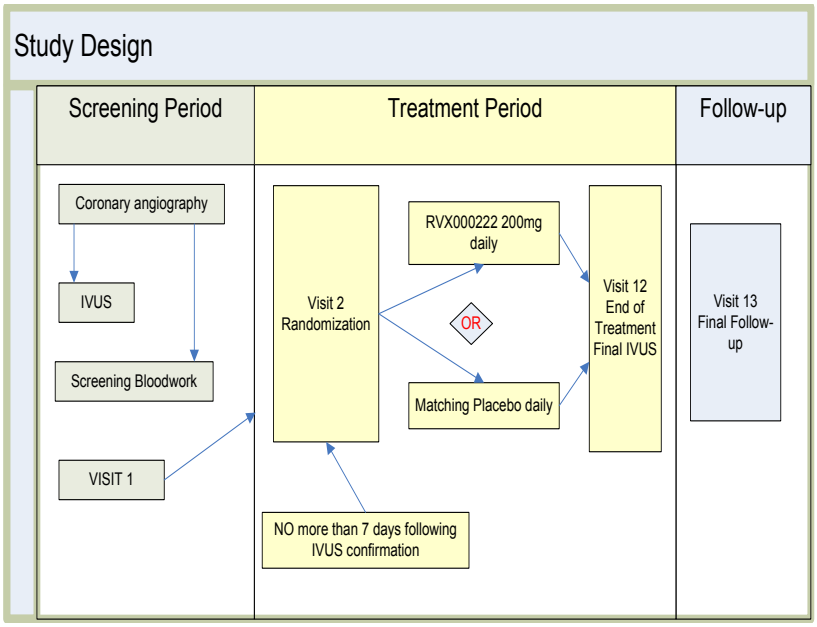
Period 2 Active Treatment Period

At Visit 2 (no more than 7 days after the baseline IVUS confirmation), all eligible patients who fulfilled the inclusion/exclusion criteria were randomized, via the Interactive Voice Response System (IVRS), to either RVX000222 200 mg (100 mg twice a day [BID]) or matching placebo and had regularly scheduled clinic visits. Statin treatment was determined prior to the time of randomization and remained unchanged throughout the study. The double-blind randomized treatment phase lasted 26 weeks (Visit 2 through Visit 12). At Visit 12, patients underwent a cardiac catheterization and final IVUS procedure.

Period 3 Final Follow-up of Study Medication (30 Days after Discontinuation of Active Treatment)

Visit 13 was a single follow-up visit occurring 30 days following Visit 12.

Figure 1: Study Design



9.2 Selection of Study Population

A total of 323 men and women ≥18 years of age, with coronary artery disease and a low HDL-C level requiring a clinically indicated coronary angiography with an acceptable IVUS were randomized into this study at 60 sites worldwide.

9.2.1 Inclusion Criteria

Patients meeting all of the following criteria were considered for enrollment into the study:

1. Male and female patients ≥18 years of age that were scheduled to undergo coronary angiography for a clinical indication.
2. Women of child-bearing potential, that is, women not surgically sterilized and between menarche and 1 year post-menopause, were required to test negative for pregnancy at the time of enrollment based on a serum pregnancy test and agree to use a reliable method of birth control (for example, use of oral contraceptives or Norplant®; a reliable barrier method of birth control (diaphragms with contraceptive jelly; cervical caps with contraceptive jelly; condoms with contraceptive foam; intrauterine devices; partner with vasectomy; or abstinence) during the study and for 1 month following the last dose of study drug.
3. Current (local laboratory within 60 days prior to Visit 1)
    - HDL-C of ≤45 mg/dL (1.2 mmol/L) for females
    - HDL-C of ≤40 mg/dL (1.0 mmol/L) for males
4. In the opinion of the investigator, patients currently not on statin therapy were able to start either atorvastatin (10 mg, 20 mg, or 40 mg) or rosuvastatin (5 mg, 10 mg, or 20 mg) at Visit 1.
5. In the opinion of the investigator, patients currently on statin therapy other than atorvastatin (10 mg, 20 mg, or 40 mg) or rosuvastatin (5 mg, 10 mg or 20 mg) could be switched to rosuvastatin (5 mg, 10 mg, or 20 mg) at Visit 1.
6. Patients were required to meet all of the following criteria at the qualifying coronary catheterization procedure:

A. **Entire Coronary Circulation**:

- Angiographic evidence of coronary heart disease as defined by at least 1 lesion in any of the three major native coronary arteries that had >20% reduction in lumen diameter by angiographic visual estimation or prior history of PCI.
- This vessel was not required to be the target coronary artery for IVUS.
- Any vessel with previous PCI could not be used as the target coronary artery.

B. **Left Main Coronary Artery**:

- Must not have had a >50% reduction in lumen diameter by visual angiographic estimation.

C**. Target Coronary Artery for IVUS**:

- Must have been accessible to the IVUS catheter.
- Must have had a <50% reduction in lumen diameter by angiographic visual estimation throughout a segment of at least 40 mm in length (the "target segment"). A lesion of up to 60% stenosis was permitted, distal to the target segment. A single branch of the "target vessel" may have had a narrowing up to <70% by visual estimation, as long as the target segment contained no lesion >50%, provided that the branch in question was not a target for PCI or coronary artery bypass graft (CABG) surgery.
- Had not undergone prior PCI or CABG.
- The target vessel was not currently a candidate for intervention or a likely candidate for intervention over the next 6 months.
- The target vessel was not a bypass graft.
- The target vessel was not a bypassed vessel.
- The target vessel was not the culprit vessel for a previous MI.

7. Had given signed informed consent to participate in this study.

9.2.2 Exclusion Criteria

1. Clinically significant heart disease which required coronary bypass, PCI, cardiac transplantation, surgical repair and/or replacement during the course of the study.
2. Any elective surgical procedure that would require general anesthesia during the course of the study.
3. CABG procedure within the past 90 days.
4. Previous or current diagnosis of severe heart failure (New York Heart Association Class III-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 patient without a previous or current diagnosis of heart failure does not prohibit entry into the study.
5. Patients 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.
6. Evidence of renal impairment as determined by any of the following:
    - serum creatinine >1.5 mg/dL (>133 mcmol/L) by central laboratory at Visit 1,
    - a calculated creatinine clearance <60 mL/min at Visit 1,
    - a history of dialysis,
    - a history of nephrotic syndrome.
7. Had hypertension that was uncontrolled defined as 2 consecutive measurements of sitting blood pressure of systolic >160 mmHg or diastolic >95 mmHg at Visit 1.
8. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive ß-human chronic gonadotropin laboratory test (≥5 mIU/mL).
9. Current or recent (within 12 months prior to Visit 1) treatment with immunosuppressants (e.g. cyclosporine).

10. Use of fibrates at any dose or niacin/nicotinic acid 250 mg or more within 90 days prior to Visit 1.
11. Atorvastatin >40 mg daily at Visit 1.
12. Rosuvastatin >20 mg daily at Visit 1.
13. Triglycerides >400 mg/dL at Visit 1.
14. Any medical or surgical condition which might significantly have altered the absorption, distribution, metabolism, or excretion of medication including, but not limited to any of the following: cholecystitis, Crohn's disease, ulcerative colitis, or any gastric bypass alteration.
15. Evidence of hepatic disease as determined by any one of the following:
    - a history of hepatic encephalopathy
    - history of Hepatitis B, C or E
    - history of esophageal varices
    - history of porta-caval shunt
    - Any one of the following liver enzymes that was greater than the upper limit of normal (>ULN) by central laboratory at Visit 1:
        - Alanine aminotransferase (ALT)
        - Aspartate aminotransferase (AST)
        - Gamma-glutamyltransferase (GGT)
16. A total bilirubin that was >ULN by central laboratory at Visit 1.
17. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
18. History or evidence of drug or alcohol abuse within the last 12 months.
19. Any surgical or medical condition, which in the opinion of the investigator, might have placed the patient at higher risk from his/her participation in the study, or was

likely to prevent the patient from complying with the requirements of the study or completing the study.

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

9.2.3 Withdrawal, Removal, and Replacement of Patients

Patients who discontinued from the study after signing the informed consent, but prior to randomization, were considered screening failures. The investigator advised all patients who discontinued from the study regarding alternative treatment(s) whether discontinuation occurred during the screening period, or after randomization.

The following circumstances required withdrawal from study participation and study drug discontinuation:

- Withdrawal of informed consent.
- Lost to follow-up.
- Pregnancy.
- Adverse events (AEs) – Patients who experienced an AE which in the opinion of the investigator required termination from the study. The investigator was required to follow the patient clinically until the event resolved or became stable.
- Investigator discretion for safety, behavioral or administrative reasons.
- Study termination by the sponsor or regulatory body.

Patients were permitted to voluntarily withdraw from the study for any reason at any time. They were considered withdrawn if they stated an intention to withdraw, or failed to return for visits, or became lost-to-follow-up for any other reason.

For patients who were lost-to-follow-up (i.e., those patients whose status was unclear because they failed to appear for study visits without stating an intention to withdraw), the investigator was asked to show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients were expected to remain in the study until the end even if they permanently withdrew from treatment. Patients who prematurely withdrew from the study were not replaced by an equal number of newly enrolled patients.

Reasonable attempts were made to perform all Visit 12 assessments at the time of study withdrawal. Drug discontinuation criteria and dose interruption/re-challenge criteria are outlined in Section 7.10 and 7.11 of the protocol, respectively (Appendix 16.1.1)

9.3 Study Treatments

9.3.1 Treatments Administered

RVX000222 or matching placebo was administered orally with meals in the morning and in the evening, 10 to 12 hours apart. Except when PK testing was done at Visits 2, 4, 8, and 12, study drug was taken with food at 8 pm ±1 hour on the evening before the visit.

The patient's background therapy for coronary artery disease and any coexisting conditions such as dyslipidemia, hypertension, and diabetes, adhered to acceptable standards of care, and remained unaltered during the 26-week treatment period, unless clinically indicated.

9.3.2 Identity of Investigational Product(s)

The formulation, lot number, and expiration date, and treatment code for study materials used in this study are provided in Table 9.1.

Table 9.1: Identity of Study Drugs

Treatment Code	Investigational Material	Lot Number	Expiration Date
Treatment A	RVX000222 - 200 mg/day	11JM-125 and 11JM-128	April 2013
Treatment A	RVX000222 -100 mg/day	11JM-122 and 11JM-125	April 2013
Treatment B	Placebo	11JM-122	April 2013

Note: The drug interruption/re-challenge rules allowed for a 100 mg/day dose under certain circumstances.

9.3.3 Method of Assigning Patients to Treatment Groups

The study drug was administered only to patients included in this study as per the procedures described in the clinical study protocol.

Double-blind study drug was supplied in identically appearing capsules in blister packs. Placebo capsules were equally matched in size, shape, and color to RVX000222.

At Visit 2, all qualified patients were randomized in a ratio of 3:1 to 1 of the following 2 treatment arms: RVX000222 200 mg or matching placebo daily. The method of assignment to treatment is summarized in Table 9.2.

Table 9.2: Method of Assignment to Treatment

Treatment Arm	Daily Dose (mg)	Dose Administration BID (mg)	AM Dose (mg)	PM Dose (mg)	No. Capsules per Day
A (RVX000222)	200	100	50 + 50	50 + 50	4
B (Placebo)	0	0	0 + 0	0 + 0	4

9.3.4 Selection of Doses in the Study

Based on the existing safety data, including data from the RVX222-CS-003 and RVX222-CS-005 clinical trials, the dose of 200 mg of RVX000222 daily was chosen for the ASSURE study.

In the Phase I study (RVX222-CS-003), favorable efficacy and safety were observed in patients receiving 2 mg/kg/day on BID dose regimen for 28 days. At total daily doses below 400 mg, no elevations in liver-related biomarkers were observed above 3xULN for ALT and AST. This observation in addition to efficacy was used to select the dose interval in the ASSERT study (RVX222-CS-005) of 100 to 300 mg daily.

In the ASSERT study (RVX222-CS-005), the biomarkers associated with lipid transport were evaluated to assess the efficacy of RVX000222. Following 12 weeks of treatment patients treated with RVX000222 demonstrated elevations in ApoA-I, HDL-C, and the concentration of large HDL particles, measured by nuclear magnetic resonance (NMR) and alpha1-HDL sub-particles, measured by two dimensional polyacrylamide gel electrophoresis.

A greater effect on HDL-related biomarkers was observed in patients treated with either 200 or 300 mg RVX000222 daily. There were no unfavorable effects on atherogenic lipid markers including LDL-C, ApoB,, and triglycerides, on any dose of RVX000222.

ASSERT had a total of 18 patients with elevations in ALT or AST >3xULN, of these 2 were not related to study drug. Of the remaining 16 patients, no patients had a concomitant elevation of total bilirubin (>2xULN) and ALT or AST. The highest ALT or AST elevation was >19xULN (904 IU/L) and that occurred in the 100 mg dose arm. The mean values for ALT or AST among the patients without aminotransferase >3xULN were about 30% lower in the patients treated with 200 mg as compared to those treated with 300 mg daily. Furthermore, only 2 patients had ALT or AST >3xULN with the statins chosen for this study, i.e. rosuvastatin or atorvastatin below 40 and 80 mg respectively.

More prominent changes in HDL-related biomarkers were observed in the 200 and 300 mg daily treatment groups in ASSERT. While elevations in ALT or AST were observed at these doses, no significant elevation in total bilirubin was demonstrated. Otherwise, RVX000222 was well tolerated at all doses. Accordingly, 200 mg daily was selected as the only dose in the ASSURE trial with the possibility of down-titrating to 100 mg daily.

9.3.5 Selection and Timing of Dose for Each Patient

RVX000222 or matching placebo was administered orally with meals in the morning and in the evening, 10 to 12 hours apart. Except when PK testing was done at Visits 2, 4, 8, and 12, the evening before the visit, study drug was taken with food at 8 pm ± 1 hour.

9.3.6 Blinding, Packaging, and Labeling

Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization. No unblinding occurred due to patient emergencies.

Study drugs were received by a designated person at the study site and were stored safely and properly (per instructions on the drug labels) in a secured location to which only the investigator and designated assistants had access.

Investigators maintained an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Patients returned all unused study drug and packaging at each visit, the end of the study or at the time of study drug discontinuation.

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

Emergency unblinding would have been permitted only when it was essential for effective treatment of the patient. In the event of such a circumstance, unblinding was allowed to be performed as instructed in the study reference manual. The investigator was required to notify the inVentiv Medical Monitor as soon as possible for unblinding authorization of any patient. There was no emergency unblinding during the study.

9.3.7 Prior and Concomitant Illnesses and Treatments

9.3.7.1 Prior and Concomitant Illnesses

It was required that the patient's background therapy for coronary artery disease and any coexisting conditions, such as dyslipidemia, hypertension, and diabetes, adhere to acceptable standards of care (in the investigator's opinion) and preferably remain unaltered during the 26-week treatment period unless clinically indicated.

9.3.7.2 Prior and Concomitant Treatments

Prior medications were defined as non-study medications with an end date prior to the first dose of study drug. Concomitant medications were defined as non-study medications with a start or end date on the first dose of study drug through the patient's last visit in the study. Medications with partial onset dates that indicated usage from the first study drug dose date (or study drug treatment period) without stop dates, and medications with completely missing stop dates were classified as concomitant. Statin medication was presented independently from other concomitant medications. Patients currently on atorvastatin (10 mg, 20 mg, or 40 mg) or rosuvastatin (5 mg, 10 mg, or 20 mg) at Visit 1 remained on this statin during the study. Those patients currently on other or no statin therapy were assigned to either atorvastatin or rosuvastatin treatment at Visit 1 and remained on statin treatment during the study.

Prior, concomitant and statin medications were summarized using descriptive statistics by treatment group for the Safety Population. Medications were coded using the World Health Organization (WHO) Drug Dictionary, March 2010. Levels of summarization included WHO Anatomic Therapeutic Chemical Level 4 drug class. At each level of summarization, a patient was counted once for each prior or concomitant medication he/she had within that level. The percentage of patients having at least 1 medication at each level was calculated.

The use of the following treatments was not allowed beginning at Visit 1 until the end of the study, as these medications may have interfered with the evaluation of safety, tolerability and/or efficacy. Patients who might have required any of the following medication(s) during the course of the study were excluded:

- Cyclosporine. The initiation of cyclosporine therapy during the study constituted a mandatory reason for permanent discontinuation of study drug.
- Fibrates at any dose.
- Niacin/nicotinic acid ≥ 250 mg per day.

The investigator instructed the patients to notify the study site about any new medications he/she took after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient started treatment with study drug were listed on the concomitant medications/significant non-drug therapies section of the electronic case report form (eCRF).

9.3.8 Treatment Compliance

Compliance was assessed by the investigator and/or study personnel at each clinic visit and phone contact using pill counts and information provided by the patient or caregiver. This information was captured in the source document at each visit. The administration of all medication (including the study drug) was recorded in the appropriate section of the eCRF. Patient compliance was expected to be at least 80% during the double-blind treatment period. The investigator and/or study personnel were asked to counsel the patient if compliance was below 80% at any visit.

Patients were instructed to bring their study drug to every visit. Compliance was assessed by counting the number of capsules dispensed and the number of capsules returned. The information was documented in the source document.

9.4 Efficacy and Safety Variables

9.4.1 Efficacy and Safety Measurements Assessed and Flow Chart

The schedule of procedures and assessments is presented in Table 9.3. A complete description of the planned evaluations during screening, study days, end-of-study and follow-up is given in the protocol (see Appendix 16.1.1).

Table 9.3: Schedule of Procedures and Assessments

	Screening	Active Treatment											Follow-up
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**11**	**14**	**17**	**20**	**23**	**26**	**30**
± No. day		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+14**	**±3**
Informed Consent	X												
Randomization (≤7 days following IVUS confirmation)		X											
Coronary Angiogram[a]	X											X	
Intravascular ultrasound	X											X	
Inclusion/Exclusion Criteria	X	X											
Medical History and Demography	X												
Electrocardiogram	X							X				X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (including height and weight)	X							X				X	
CENTRAL LABORATORY													
Fasting Lipid Profile[b]	X							X				X	
Hematology[c]	X							X				X	
Chemistry[d]	X							X				X	
Urinalysis[e]	X							X				X	
Safety Labs[f]		X	X	X	X	X	X		X	X	X		X
Pharmacokinetic Sample		X		X				X				X	
Archived Biomarkers		X										X	
Anomymized Pharmacogenomic[g]		X											
Pregnancy Test	X												
Adverse Events	X[h]	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication		X		X		X	X	X	X	X	X		
Dispense Appropriate Statin Medication	X	X					X				X		
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	

a: Coronary angiogram to guide the repeat intravascular ultrasound study, quantitative coronary angiography will not be performed.
b: Lipid profile included: total cholesterol, low density lipoprotein cholesterol , high density lipoprotein cholesterol, triglycerides, apolipoprotein B, apolipoprotein A-I, low density and high density subclasses, non-high density lipoprotein, lipid nuclear magnetic resonance.
c: Hematology included: platelet count, hemoglobin, hematocrit, RBC, WBC with differential, HbA1c.
d: Chemistry included: albumin blood urea nitrogen, CK, serum creatinine, fasting glucose, LDH, alkaline phosphatase, calcium, chloride, phosphate, potassium, sodium, hs-CRP, and total protein.

e: Urinalysis sample was to consist of visual description, a dipstick test (specific gravity, pH, protein [qualitative], glucose, ketones, bilirubin, and blood), and microscopy (RBC, WBC, bacteria, casts, and crystals).
f: Safety labs included: ALT (SGPT), AST (SGOT), GGT, bilirubin (direct and total), if indicated international normalized ratio.
g: Optional per IRB regulatory approval and patient's consent for genotyping; may be performed any time during study participation at or after randomization.
h: SAEs only.

9.4.2 Appropriateness of Measurements

The efficacy and safety assessments were conducted according to standard medical practices generally accepted as reliable, accurate, and relevant. The study data were analyzed using standard methods widely accepted by the Food and Drug Administration (FDA) and other regulatory agencies.

9.4.3 Methods

9.4.3.1 Efficacy Data

9.4.3.1.1 Primary Endpoint

The primary endpoint was the nominal change in PAV from baseline to 26 weeks post-randomization, as determined by IVUS within the RVX000222 treated group.

9.4.3.1.2 Secondary Endpoints

- Nominal change in PAV, from baseline to 26 weeks post-randomization, as determined by IVUS compared to placebo.
- Nominal change in TAV from baseline to 26 weeks post-randomization, as determined by IVUS within the RVX000222-treated group as well as compared to placebo.
- Nominal change in TAV for the 10-mm sub-segment with the greatest disease burden at baseline, within the RVX000222-treated group as well as compared to placebo.
- Proportion of patients with regression of coronary atherosclerosis, defined as a change in PAV from baseline to 26 weeks of less than zero (e.g. any reduction in PAV).
- Percent change from baseline in HDL-C, ApoA-I, and HDL-subclasses at various time points within the RVX000222-treated group and compared to placebo were measured.

9.4.3.2 Safety Endpoints

The incidence of AEs by treatment group, including major adverse cardiac events (MACE) (death, myocardial infraction [MI], stroke, coronary revascularization, hospitalization for ACS, or heart failure) was measured.

9.4.3.2.1 Adverse Events

The investigator observed patients for AEs (local or systemic) and instructed patients to report any events that occurred during the study. For the purpose of the study, the period of observation for each individual patient extended from the time the patient gave informed consent until Visit 13. To ensure patient safety, every serious adverse event (SAE) regardless of suspected causality, occurring after the patient had provided informed consent and until 30 days after the patient had stopped study participation (defined as time of last dose of study drug taken) or had completed Visit 13 (Follow-up) was collected. Any SAEs experienced after this 30-day period were only reported to Resverlogix Corp. if the investigator suspected a causal relationship to the study drug.

The definitions used in the study for the terms AE and SAE are given below.

The term AE was defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event was not considered to be related to 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..

Worsening of a sign or symptom of the condition under treatment was normally measured by efficacy parameters. However, if the outcome fulfilled the definition of SAE, it was recorded as such (see definition below).

No causal relationship with the study drug or with the clinical study itself was implied by the use of the term AE.

Adverse events have been reported by the investigator as serious or non-serious. An SAE was defined as any untoward medical occurrence at any dose that:

- was fatal or life-threatening
- resulted in persistent or significant disability/incapacity
- constituted a congenital anomaly/birth defect
- required inpatient hospitalization or prolongation of existing hospitalization
- was an important medical event that may have jeopardized the patient or may have required medical intervention to prevent one of the outcomes listed above.

Adverse events were documented by the investigator as follows:

- All AEs (whether serious or non-serious, or considered as an alert term) were documented on the "Adverse Event" page of the CRF; and
- If the AE was serious, the investigator also had to complete a "Serious Adverse Event/Expedited Report from a Clinical Study" form and send it immediately to the Sponsor.

When a "significant overdose" of the study drug occurred without an AE or in other situations where the Sponsor required an expedited report without an AE, the investigator only completed a "Serious Adverse Event/Expedited Report from a Clinical Study" form.

9.4.3.2.2 Laboratory Safety Data

Details on the collections, shipment of samples and reporting of results by the central laboratory were provided to investigators in the laboratory manual. All laboratory results (excluding biomarker and PK laboratory results) were communicated to the investigators.

If the laboratory abnormality induced clinical signs or symptoms, or required therapeutic intervention, then the diagnosis or medical condition was entered on the AE eCRF. If the laboratory abnormality was the primary reason for an unforeseen hospitalization or otherwise fulfilled the seriousness category of an AE, then the procedure for rapid notification of SAEs was followed. Likewise, if the laboratory abnormality led to discontinuation from the study, then the patient was followed until the abnormality resolved or until it was judged to be permanent. All tests were carried out according to standard laboratory procedures at ACM Global Central Laboratory, which defined the normal reference range for each analyte; see Appendix 16.1.10.

Hematology

Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count and glycosylated hemoglobin (HbA1c) were measured at Study Visits 1, 8, and 12.

Clinical Chemistry

A complete chemistry panel including fasting blood urea, creatinine, glucose, bilirubin (direct and total), ALT, AST, GGT, lactate dehydrogenase (LDH), high sensitivity C-reactive protein

(hs-CRP), alkaline phosphatase, creatinine kinase (CK), calcium, phosphorous, total protein, albumin, electrolytes (sodium, potassium and chloride), were obtained from patients at Study Visits 1, 8, and 12. Safety laboratories for ALT, AST, GGT and bilirubin (direct and total) were also collected at Visits 2, 3, 4, 5,6, 7, 9, 10, 11, and 13.

The lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C, non-HDL-C, ApoB, ApoA-I, LDL and HDL sub-classes) was measured at Visits 1, 8, and 12. Lipid NMR was measured at Visits 1, 8, and 12.

Biomarkers

Serum samples were collected from patients at Study Visits 2 and 12 for the measurement of biomarkers relevant to lipid and inflammatory pathways. Details on the collection and shipment of samples and archiving were provided to investigators in the laboratory manual. A central laboratory was used for analysis of all laboratory specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory were provided to investigators in the laboratory manual.

Pharmacokinetics

Blood samples for analysis of RVX000222 and its metabolites (RVX000404 and RVX000288) plasma levels were collected in dipotassium ethylenediaminetetraacetic acid (K_2EDTA) tubes according to the Schedule of Events (Table 9.3). The samples were collected at baseline (Visit 2) and at Visits 4, 8, and 12.

When PK sampling times coincided with other interventions, such as vital sign measurements, the highest priority was the PK followed by the electrocardiogram (ECG), vital signs and clinical laboratory samples. Other scheduled interventions were performed either prior to or after the stipulated time. Pharmacokinetic sample collection, processing, assay, and shipping information are described in the laboratory manual.

Urinalysis

Analysis of the urinalysis sample consisted of visual description, a dipstick test (specific gravity, pH, protein [qualitative], glucose, ketones, bilirubin, and blood), and microscopy (RBC, WBC, bacteria, casts and crystals). Urinalysis was done at Visits 1, 8, and 12.

Pregnancy and Assessments of Fertility

All pre-menopausal women who were not surgically sterile had a serum pregnancy test at Visit 1.

9.4.3.2.3 Other Safety Data

Physical Examination

A physical examination was performed by the investigator at Study Visit 1 in order to confirm the patient's initial eligibility. A physical examination was also performed at Visit 8 and 12. It included but was not limited to the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological.

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

Vital Signs

Heart rate, blood pressure, respirations and temperature were recorded at each clinic visit. All measurements were recorded in the patient's source documents and eCRF.

Height and Weight

Height in centimeters (cm) was measured at Visit 1.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) was measured at Visits 1, 8, and 12.

Electrocardiogram

A standard 12-lead ECG was performed at baseline (Visit 1), Visit 8, and Visit 12 (end of treatment or premature withdrawal from study visit). Interpretation of the tracing was made by a qualified physician and documented on the ECG section of the eCRF. Each ECG tracing was labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Only clinically significant abnormalities were reported on this page.

Clinically significant abnormalities were also recorded on the relevant medical history/current medical conditions eCRF page.

9.5 Data Quality Assurance and Quality Control

9.5.1 Data Quality Assurance

InVentiv Health clinical (formerly known as PharmaNet/i3, (company name change applicable in US only) implemented and maintained quality control procedures to insure that the study was conducted, and that the data were generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory documents. The eCRF was created to limit and control data recorded. This included but not limited to defining data points to capture exact required data numeric verse character data, minimal text, data validation checks during data entry for missing data and data out of range.

Resverlogix Corp. and/or its designee informed the investigator/institution as to when these documents no longer need to be retained. Patient identification codes were to be retained according to ICH GCP guidelines or for at least 15 years after the completion or discontinuation of the study, whichever was the longest period of time.

The investigator was instructed to retain study records at the site for 2 years after the study drug's New Drug Application was approved or Investigational New Drug was withdrawn. The investigator was asked to take measures to prevent accidental or premature destruction of these documents.

9.5.2 Standardization Procedures

All samples collected at each site were sent to the Central laboratory for determination of safety and efficacy parameters. The reference ranges were included in the laboratory manual and on lab reports sent to all sites. These ranges were also available to all team members through the lab manual.

9.5.3 Monitoring and Auditing

This study was monitored at all stages of its development by designated study monitoring personnel. Monitoring included on-site visits and telephone communication to assure that the investigation was conducted according to the study protocol and in order to comply with

guidelines of GCP. On-site review of eCRFs included a review of forms for completeness and clarity, and consistency with source documents available for each patient. A variety of original documents, data, and records were considered as source documents in this trial. The site ensured the reliability, quality, integrity, and traceability of electronic source data and source records maintained for monitor and potential FDA inspection. Any electronic source data processes was required to be clearly validated in order to ensure accurate, legible, original, attributable (e.g., user name and password), and contemporaneously entered and was expected to meet the regulatory requirements for recordkeeping and record retention. The eCRF itself was not used as a source document without a recorded exception and written approval from Resverlogix Corp. and/or its designee.

The study may have been subjected to audit by Resverlogix Corp. and/or its designee or by regulatory authorities. If such an audit had occurred, the investigator was expected to agree to allow access to required patient records. By signing the protocol, the investigator granted permission to personnel from Resverlogix Corp. and/or its designee, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

9.6 Statistical and Analytical Procedures

The statistical analyses performed in this study were initially specified in the clinical study protocol (see Appendix 16.1.1). Further details of the planned statistical analysis are provided in the Statistical Analysis Plan (SAP) (see Appendix 16.1.9) that was finalized prior to unblinding of treatment assignments. Statistical analyses were performed by the Biostatistics Department at inVentiv Health Clinical.

9.6.1 Analysis Variables

Demographic and baseline characteristics were listed and summarized by treatment group for the Safety, modified intent to treat (mITT), Full Analysis Set (FAS), and PP Protocol Populations.

9.6.2 Efficacy Variables

9.6.2.1 Primary Efficacy Endpoint

The primary efficacy analysis was performed on the mITT Population. A paired t-test was performed to determine if there was a significant difference in the change from baseline to end-of-treatment in PAV for the RVX000222 dose group. The Shapiro-Wilk test was used to test for normality. If the test for normality has been rejected (i.e., p-value <0.05), the Wilcoxon signed-rank test was to be performed. In addition, the 95% confidence intervals (CIs) were presented for PAV change from baseline for the RVX000222 dose group.

In addition, descriptive statistics were presented for the observed PAV and change in PAV from baseline (Visit 1) to Week 26 (Visit 12).

Supplementary Analysis

As a supplementary analysis, the primary endpoint analysis was repeated for the placebo dose group.

Sensitivity Analysis

To investigate influences on the outcome of the primary endpoint, the primary efficacy analysis was repeated for the FAS and Per Protocol (PP) Population.

9.6.2.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints were analyzed, as described below:

- Nominal change in PAV from baseline to Week 26 (Visit 12), comparing RVX000222 treated group to placebo, was presented for the mITT, FAS, and PP Population.
- Nominal change in TAV as determined by IVUS from baseline to Week 26 (Visit 12) within the RVX000222 treated group as well as compared to placebo was presented for the mITT, FAS, and PP Population.
- Nominal change from baseline to Week 26 (Visit 12) in TAV for the 10-mm sub-segment with the greatest disease burden at baseline within the RVX000222 treated group as well as compared to placebo was presented for the mITT, FAS, and PP Population.

- Percent change in HDL-C, ApoA-I, and HDL-subclasses from baseline were presented for the mITT, FAS, and PP Population. The Week 26 (Visit 12) value for each parameter was derived using the last observation carried forward (LOCF) methodology. The LOCF analyses used the last non-missing assessment after Visit 1 (baseline) as an estimate for all subsequent missing values.

The nominal change from baseline to Week 26 was presented using descriptive statistics (N, mean, standard deviation [SD], median, minimum, and maximum).

Paired t-tests were used to evaluate the change from baseline to Week 26 for each endpoint within each treatment group. The Shapiro-Wilk test was used to test for normality. If the test for normality was rejected (i.e., p-value < 0.05) the Wilcoxon signed-rank test was performed. In addition, parametric or nonparametric 95% CIs, consistent with the statistical test, were presented for each endpoint for both the RVX000222 and placebo dose groups.

To assess differences between treatment groups in the change from baseline to Week 26 an analysis of covariance (ANCOVA) model was used. The ANCOVA model included the baseline value as a covariate, and treatment group as a factor. For modeling results, least squares (LS) means, 95% CIs of the LS mean and standard errors (SE) were presented.

The following underlying model assumptions were tested for the ANCOVA model. If either assumption was rejected an ANCOVA model with rank transformed data on the dependent variable and covariate was used to evaluate the change from baseline between treatment groups:

- Homogeneity of slope – To assess the interaction between the covariate and treatment group an ANCOVA model with treatment group, baseline value, and treatment by baseline value was used. If there was evidence of treatment by baseline value interaction (p-value ≤ 0.05) at Week 26 the assumption was rejected.
- Homogeneity of variance – The Levene's Test of Equality was used to assess equality of variance of the dependent variable between treatment groups. The assumption of equal variance was rejected if the p-value ≤ 0.05.

The following additional secondary endpoints were analyzed as follows:

- The proportion of patients with regression of coronary atherosclerosis from baseline (Visit 1) to Week 26 (Visit 12) was summarized by treatment group for the mITT, FAS, and PP Population, and was compared using an unadjusted chi-square test.
- Incidence of AEs by treatment group, including MACE (death, MI, stroke, coronary revascularization, hospitalization for ACS or heart failure) were evaluated using descriptive statistics with counts, percentages and 95% CIs. The incidence of AEs was presented for the Safety Population.

The primary endpoint, change in PAV within the active RVX000222 treatment group, was analyzed for the following subgroups for the FAS and PP Population:

- Baseline PAV (at or above or below the overall median)
- Baseline HDL-C (at or above or below the overall median)
- History of diabetes mellitus (yes or no)
- Gender (male or female)
- Age (≥65 or <65)
- Statin use (atorvastatin or rosuvastatin)
- Baseline Apo-A1 (at or above or below the overall median)
- Baseline large HDL (NMR) (at or above or below the overall median)
- Baseline hs-CRP (at or above or below the overall median)

The nominal change from baseline to Week 26 was presented using descriptive statistics (N, mean, SD, median, minimum, and maximum).

Paired t-tests were used to evaluate the change from baseline to Week 26 for each endpoint within the RVX000222 dose group for each subgroup. The Shapiro-Wilk test was used to test for normality. If the test for normality was rejected (i.e., p-value < 0.05) the Wilcoxon signed-rank test was performed. In addition, the parametric or nonparametric 95% CIs, consistent with the statistical test, was presented for each endpoint for the RVX000222.

As supplementary analyses, the subgroup analyses were repeated for the placebo dose group.

9.6.2.3 Exploratory Efficacy Endpoints

Correlations between changes in atheroma burden (PAV and TAV) and percent change in lipid biomarkers (HDL-C, ApoA-I, HDL-subclasses which included HDL total particles, HDL size, large HDL, and small HDL) were presented. Correlations were presented for the FAS and PP Population.

The relationship between percent changes in lipids at Week 26 (Visit 12) were correlated with the changes in measures of atheroma volume in the RVX000222 treated group using the Pearson correlation coefficient. If both variables were non-normal based on the Shapiro-Wilk test the Spearman rank correlation coefficient was used.

Change in spectral features of plaque composition by radiofrequency analysis (RFA) (fibrous, fibro-fatty, necrotic core, and dense calcium) within the RVX000222-treated group and placebo group was evaluated on a subset of patients.

Spectral features of plaque composition were described by treatment group using descriptive statistics, for the mITT, FAS, and PP Population.

Individual and mean PK trough concentration values were plotted against time points.

The relationship between PK trough values (C_{min}) was correlated with the change in PAV at Week 26 (Visit 12) for the RVX000222 treated group using the Pearson correlation coefficient. If both variables were non-normal based on the Shapiro-Wilk test, the Spearman rank correlation coefficient was used. Correlations were presented for the FAS and PP Population.

9.6.3 Safety Variables

Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. Coding included system organ class (SOC) and preferred term (PT). All verbatim and coded terms were listed for all AEs. Adverse events were recorded at the maximum intensity of the event, assuming that the verbatim term did not change. All AE summaries were based on the Safety Population.

Pre-treatment Adverse Events

Pre-treatment AEs were defined as any AE that started prior to the first dose of study drug. Pre-treatment AEs were included in data listings and summarized by treatment group using counts and percentages.

Treatment-emergent Adverse Events

The following AEs were defined as treatment-emergent adverse events (TEAEs):

- AEs starting after the first study drug administration;
- AEs with partial onset dates if the stop date is after the first study drug administration;
- AEs with completely missing onset dates.

All AEs were listed by patient and date/time of onset, and TEAEs were flagged in all listings.

The frequency and percentage of patients with AEs were summarized by SOC and PT. At each summary level, a patient was counted only once if he/she experiences 1 or more AEs. The percentage of patients having had at least 1 AE at each level was calculated.

In instances where a patient might have multiple AEs with differing levels of severity or relatedness, the most severe or most related event, respectively, was reported for the severity and relatedness tables. Adverse events with relatedness of definite, probable, possible or missing were considered related. Adverse events with missing severity were presented as severe in the tables but were listed as missing.

Tabular summaries included all AEs, AEs by severity (mild, moderate, severe), AEs by relationship to treatment (related, not related), serious AEs, and AEs leading to withdrawal of study drug and discontinuation. Deaths were presented in a listing that included the AE leading to death, details of study treatment, and relationship to study drug of the AE leading to death.

All AEs (including non-treatment-emergent events) recorded in the CRF were listed.

All deaths and SAEs were identified in the listing of all AEs. The number of SAEs was summarized by SOC and preferred term similar to all AEs described above.

Laboratory data were presented for the Safety Population. All laboratory data (fasting lipid profile, chemistry, hematology, and urinalysis) were flagged with regards to the investigator

reference ranges (provided by a designated central laboratory). Abnormal values were flagged with H when the value was higher than the upper limit of the reference ranges and with L when the value was lower than the lower limit of the reference ranges. All laboratory results were reported in conventional units as reported by the central laboratory.

Descriptive statistics for all numeric laboratory values and change from baseline values were summarized by treatment group for each visit collected. Shift tables of abnormal laboratory values were presented for all laboratories at baseline, Week 14 (Visit 8), and Week 26 (Visit 12). Baseline was defined as the last non-missing laboratory value up to and including Visit 2 for each lab test. If appropriate, relevant non-parametric test results were included.

A summary of patients with elevated transaminase levels (ALT/AST) during the treatment period was presented. Patients with elevated transaminase levels (ALT and AST) were categorized as follows:

- >1x ULN but ≤3x ULN
- >3x ULN but ≤5x ULN
- >5x ULN but ≤8x ULN
- >8x ULN

The following were categorized for patients with elevated ALT/AST >3x ULN during the treatment period:

- >3x ULN in patients who without study drug discontinuation returned to normal transaminase levels (i.e., who had all subsequent values < ULN)
- >3x ULN in patients who without study drug interruption returned to normal transaminase levels (i.e., who had all subsequent values < ULN)
- first occurrence of ALT >3x ULN before or at Week 11 (Visit 7)
- first occurrence of ALT >3x ULN after Week 11 (Visit 7)

In addition, patients with elevated ALT were categorized as follows:

- >5x ULN
- >8x ULN

The following vital signs were collected at each visit and were summarized by treatment group for the Safety Population:

- oral body temperature (°C),

- systolic and diastolic blood pressure (mmHg) (seated),
- pulse (beats/min) and
- respiration rate (breaths/min).

Summary statistics (n, mean, SD, median, minimum, and maximum) were reported for each visit as well as change from baseline (Visit 2) at each visit. A listing of all patient vital signs data was reported by treatment group, patient, and visit.

A standard 12-lead ECG was performed for each patient at Screening (Visit 1), Week 14 (Visit 8) and at Week 26 (Visit 12). The results were listed for each patient, including the overall ECG impression and any abnormalities (including whether the abnormalities were clinically significant).

Electrocardiogram parameters were summarized descriptively for each of the treatment groups, and the number and proportion of patients with shifts in results were presented (shift tables). Electrocardiogram results were presented for the Safety Population.

A complete physical examination was performed at Screening (Visit 1), Week 14 (Visit 8) and Week 26 (Visit 12). Results of the examinations were listed by patient and body system for the Safety Population.

Plasma concentration of RVX000222 was measured in trough samples collected at Study Visits 2, 4, 8 and 12 using a validated analytical method. Individual plasma RVX000222 concentrations at each study visit were listed. Summary statistics (n, arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum) by treatment group were also generated for the steady-state trough plasma concentration of RVX000222 over the course of the study (the mean of Study Visits 2, 4, 8, and 12).

9.6.4 Study Populations

This study used three analysis sets, referred to as populations, to carry out the planned analyses: mITT, Full FAS, and PP Population.

The Safety Population was used for all safety analyses; the mITT, FAS, and PP Populations were used for the efficacy analyses.

Modified Intent-to-Treat

A mITT population was used for both primary and secondary endpoint analyses. This consisted of all randomized patients who received at least 1 dose of study drug. A patient was considered randomized as soon as a treatment number was assigned by IVRS. Patients were analyzed according to the treatment to which they were randomized regardless of whether or not the study drug was prematurely discontinued or dose lowered due to an AE. The mITT Population was the primary efficacy analysis population.

Full Analysis Set

FAS was used for the primary and secondary endpoint analyses. The FAS consisted of all randomized patients who received at least 1 dose of study drug and completed both the baseline (Visit 1) and Week 26 (Visit 12) IVUS.

Per Protocol Population

All patients who completed all protocol-specified dosing days (active or control), and who had completed both a baseline and follow-up IVUS procedure between Week 17 and Week 30, had a study drug compliance rate of 80%, and had no major protocol violations were included in the PP Population.

The PP Population was defined after a review of the blinded data and protocol deviations prior to unblinding the data.

The PP Population was used to assess the effect of treatment in completers who had no substantial protocol deviations.

Safety Population

All patients who received at least 1 dose of study drug (active or control) were included in the Safety Population and were analyzed based on the actual treatment received. The Safety Population was used for all safety summaries.

9.7 Statistical Methods

Categorical variables were summarized using counts and percentages. Percentages were based on the number of patients in the analysis set for whom there were non-missing data, unless

otherwise specified. Continuous variables, including change from baseline, were summarized using descriptive statistics (n, mean, SD, minimum, maximum, and 95% CIs).

Baseline was defined as the last non-missing measurement prior to randomization.

Unless otherwise stated, all summaries were presented by treatment group (RXV00022 or placebo) when appropriate. Patient data listings included all patients and were sorted by treatment group, site, patient number, and date (if applicable).

Statistical analyses were carried out using SAS statistical analysis software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

Any additional safety data collected during the 30-day follow-up period, when patients were no longer taking study drug, were summarized separately.

For all additional/secondary and exploratory analyses, the mITT, FAS, and PP Populations were used.

A copy of the final SAP for this study is provided in Appendix 16.1.9.

9.8 Sample Size Justification

The sample size estimation was based on the primary efficacy endpoint, nominal change from baseline in PAV, in the RVX000222 treatment arm. Assuming a SD around the change in PAV of 2.7%, a total of 186 patients in the RVX000222 treatment arm would provide 85% power to detect regression in PAV of -0.6% or greater with a 2-sided alpha of 0.05. An additional 62 patients would be randomized into a placebo arm, for a total of 248 patients. Given an expected non-completion rate of approximately 20% (defined as patients who did not have a final IVUS evaluation) a total of 310 patients were planned to be enrolled in the study. Although this study was not adequately powered to compare the active treatment group to placebo, this relationship was explored as a secondary objective. The power of the between-group test was about 33%, assuming the placebo group had the same SD of 2.7% and 0 change from baseline, both groups were normally distributed, and a 2-sample t-test was used.

9.9 Changes in the Conduct of the Study or Planned Analyses

9.9.1 Changes in the Conduct of the Study

The protocol was amended three times. The details of changes in each amendment are provided below.

Amendment 1: Protocol amendment 1 included the following changes:

Amendment 1, dated 01 November 2010 extended the study sites to outside of USA. However, the study was never conducted under this amendment.

Amendment 2: Protocol amendment 2 included the following changes:

Amendment 2, dated 22 March 2011, stipulated that the study would be conducted outside of USA only.

Amendment 3: Protocol amendment 3 included the following changes:

The protocol amendment 3, dated 08 July 2011, came into effect on 11 July 2011. The amendment 3 became necessary to incorporate Central Ethics Committee recommendations, to provide administrative clarifications and to make necessary corrections to amendment 2.

1. The number of study sites was changed from 50 to approximately 60 sites worldwide in the synopsis.
2. The exploratory objective "To evaluate the pharmacokinetics of RVX000222" was added to the objectives section of the synopsis.
3. Inclusion criterion #3 was modified to indicate that current laboratory results may have been taken with 60 days prior to Visit 1 rather than 30 days prior to Visit 1 in the synopsis.
4. The exploratory endpoint "Evaluation of Pharmacokinetics trough values (C_{min}) at various time points" was added to the objectives section of the synopsis.
5. Exclusion criterion #6 in the synopsis was modified to include additional exclusion parameter "a calculated creatinine clearance less than 60 ml/min at Visit 1".
6. Exclusion criterion #11 in the synopsis was modified to change the excluded values of atorvastatin from 80 mg daily at visit 1 to >40 mg daily at Visit 1.

7. Exclusion criterion #12 in the synopsis was modified to change the excluded values of rosuvastatin from 40 mg daily at visit 1 to >20 mg daily at Visit 1.
8. Exclusion criterion #15 in the synopsis was modified to clarify the criterion related to liver enzymes. The criterion was changed from "ALT, AST, GGT that is >ULN" to "Any one of the following liver enzymes that is >ULN by central laboratory at Visit 1: ALT, AST, GGT".
9. The exploratory objective "To evaluate the pharmacokinetics of RVX000222" was added to Section 3.3.
10. The exploratory endpoint "Evaluation of Pharmacokinetics trough values (C_{min}) at various time points" was added to Section 4.3.
11. The following phrase was deleted from Section 5, Study Design, Period 2 Active Treatment Period: "and one phone follow-up at Visit 3".
12. The number of study sites was changed from 50 to approximately 60 sites worldwide in Section 6, Study Population.
13. Inclusion criterion #3 in Section 6.1 was modified to indicate that current laboratory results may have been taken with 60 days prior to Visit 1 rather than 30 days prior to Visit 1.
14. Exclusion criterion #6 in Section 6.2 was modified to include additional exclusion parameter "a calculated creatinine clearance less than 60 ml/min at Visit 1".
15. Exclusion criterion #11 in Section 6.2 was modified to change the excluded values of atorvastatin from 80 mg daily at Visit 1 to >40 mg daily at Visit 1.
16. Exclusion criterion #12 in Section 6.2 was modified to change the excluded values of rosuvastatin from 40 mg daily at Visit 1 to >20 mg daily at Visit 1.
17. Exclusion criterion #15 in Section 6.2 was modified to clarify the criterion related to liver enzymes. The criterion was changed from "ALT, AST, GGT that is >ULN by central lab at Visit 1" was changed to "Any one of the following liver enzymes that is >ULN by central laboratory at Visit 1: ALT, AST, GGT".
18. The following sentence was added to Section 7.14, Study Completion and Post-study Treatment: "Any abnormal liver function tests should be monitored until a return to either ULN or baseline or for at least 30 days after dose interruption or discontinuation."

19. The phrase "each scheduled fasting" was deleted from Section 8, Visit Schedule and Assessments in order to indicate that patients should be instructed to fast prior to each laboratory evaluation.
20. Bullet point #10 of Visit, 1 Screening Visit part of Section 8.1 (Study visits) was revised to indicate that patients currently on statins other than atorvastatin or rosuvastatin would be switched to an appropriate dose of rosuvastatin; the text previously indicated they would be switched to either rosuvastatin or atorvastatin. This section was also revised to indicate that patients not on a statin agent would be started on either rosuvastatin or atorvastatin; the text previously indicated that these patients would be started on rosuvastatin only.
21. Section 8.1 was modified to delete the phrase "phone follow up" from Visit 3. In addition, the following bullet points were added to Visit 3.
    - "Vital signs."
    - "Central lab blood for safety lab (ALT (SGPT), AST (SGOT), GGT, bilirubin (direct and total)."
22. Section 8.4.4, Laboratory Evaluations, was modified to add "and PK" to the following sentence: "All laboratory results (excluding biomarker and PK laboratory results) will be communicated to the investigators."
23. Section 8.4.4, Laboratory Evaluations, was modified to add "and HbA1c" to the following sentence: **"**Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count, and HbA1c will be measured at Study Visits 1, 8 and 12."
24. The Biomarkers sub-section of the Laboratory Evaluations, Section 8.4.4 was modified to indicate that serum samples were collected rather than plasma samples, and that the samples would be collected for measurement of biomarkers relevant to lipid and inflammatory pathways rather than "this pathophysiology."
25. Section 9.6, Serious Adverse Event Reporting, was modified to indicate that SAEs would be collected up until 30 days after the patient had stopped study medication or until the patient had completed Visit 13. The text previously indicated that SAEs would be

collected up until 30 days after the patient had stopped study medication or until the last visit, whichever was later.

26. The following sentence was deleted from Section 10.1, Site Monitoring: "Medical advisors and study monitoring personnel may request to witness patient evaluations occurring as part of this protocol."
27. The exploratory endpoint "evaluation of pharmacokinetics trough values (C_{min}) at various time points" was added to the Section 11.3.
28. The following statement was added to Section 12.4, Analysis of the Primary Endpoint: "The PROC MI multiple imputation procedure in SAS will be implemented to impute the primary endpoint."
29. The following bullet point was added to Section 12.6, Analysis of Exploratory Endpoints:
    - "Evaluation of standard Pharmacokinetics parameters at various time points. Further details of the analysis will be described in the statistical analysis plan (SAP.)"

9.9.2 Changes in the Planned Analysis

Changes to the planned analyses specified in the SAP are described below:

1. For Tables 14.1.3.1 – 14.1.3.3 (Demographic and Baseline Characteristics), the age groups evaluated were changed from <50, 50-65, and >65 to <65 and ≥65 for consistency with the categories used in the subgroup analyses.
2. The PP Population was originally defined as "all patients who complete all protocol-specified dosing days (active or control)." However, since diary data were not collected it was not possible to determine if patients took all doses on specified days. Therefore, this criterion was not imposed.
3. The footnote for the efficacy tables was changed from "P-value comparing within group change using the paired t-test" to "P-value comparing within group change using a paired t-test or the Wilcoxon signed-rank test, if the assumption for normality was rejected" so that the footnote did not need to be changed based on the assumption being rejected/accepted.
4. The categories used in Table 14.3.4 were changed to be consistent with the previous Resverlogix studies.

In addition, several post-hoc analyses were performed. These analyses are described below:

1. Additional analyses on the VH data were performed.
2. Additional PK analyses including trough PK levels of rosuvastatin at baseline and Visit 12 for a subgroup of patients were performed.
3. Additional subgroup analyses on below median HDL-C and rosuvastatin.
4. Additional subgroup analysis on patients with baseline hs-CRP >2.

10 STUDY POPULATION

10.1 Disposition of Patients

Overall, 324 patients were randomized to the study; of these, 323 received RVX000222 or placebo: 243 of them were randomized to receive 200 mg RVX000222 and 80 patients were randomized to receive placebo. One patient was randomized in the IVRS in error and was never dosed. Except for this 1 patient, all randomized patients received at least 1 dose of RVX000222 or placebo.

Overall, 87.0% of the randomized patients received at least 1 dose of study drug and completed both baseline and Week 26 IVUS (FAS population). Among the treatment groups, 85.6% of the patients in the RVX000222 200 mg group and 91.3% of patients in the placebo group were included in the FAS population.

The proportion of patients who completed the active treatments (Visit 2 through 12) in the RVX000222 200 mg and placebo groups was 87.2% and 92.5%, respectively. Overall, 92.6% of the study population completed the study (visits 2 through 13). Less than 10% of the study population prematurely discontinued from the study. More patients in the RVX000222 200 mg group discontinued (8.2%, 20/243) from the study than in the placebo group (5%, 4/80). Withdrawal of consent was the most common reason for patients discontinuing from the study (14/243, 5.8% and 2/80, 2.5%) in the RVX000222 200 mg and placebo groups, respectively. There was 1 death in the placebo group during the study.

A summary of the overall patient disposition for both treatment groups is provided in Table 10.1. Details of analysis population and patient disposition by treatment group for all randomized patients are provided in the End-of-Text Table 14.1.1.

Randomization and informed consent dates and disposition data for all patients are presented in Listings 16.2.1.1 and 16.2.1.3, respectively.

Table 10.1: Patient Disposition Overall and by Treatment Group - All Randomized Patients

	RVX000222 200 mg n (%)	Placebo n (%)	Overall n (%)
Patients randomized	243	80	323[e]
Safety Population[a]	243 (100.0)	80 (100.0)	323 (100.0)
Modified Intent-to-Treat (mITT) Population[b]	243 (100.0)	80 (100.0)	323 (100.0)
Full Analysis Set (FAS)[c]	208 (85.6)	73 (91.3)	281 (87.0)
Per Protocol (PP) Population[d]	191 (78.6)	70 (87.5)	261 (80.8)
Completed active treatment (Visit 2 through 12)	212 (87.2)	74 (92.5)	286 (88.5)
Completed study (Visit 2 through 13)	223 (91.8)	76 (95.0)	299 (92.6)
Discontinued prematurely from study	20 (8.2)	4 (5.0)	24 (7.4)
Reason for discontinuation from study:			
Adverse event(s)	1 (0.4)	1 (1.3)	2 (0.6)
Protocol violation(s)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew consent	14 (5.8)	2 (2.5)	16 (5.0)
Lost to follow-up	2 (0.8)	0 (0.0)	2 (0.6)
Sponsor's request	0 (0.0)	0 (0.0)	0 (0.0)
Principal investigator decision	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	1 (1.3)	1 (0.3)
Other	2 (0.8)	0 (0.0)	2 (0.6)
Missing	1 (0.4)	0 (0.0)	1 (0.3)

FAS = full analysis set; mITT = modified intent-to-treat; PP = per protocol
a: The Safety Population included all patients who received at least 1 dose of study drug (active or control). The actual treatment taken was used to summarize the Safety Population.
b: The mITT population included all randomized patients who received at least 1 dose of study drug. The randomized treatment assignment was used to summarize the mITT Population.
c: The FAS consisted of all randomized patients who received at least 1 dose of study drug and completed both baseline (Visit 1) and Week 26 (Visit 12) IVUS.
d: The PP Population included all patients who completed both a baseline and follow-up IVUS procedure with no major protocol violations and had a study drug compliance rate of at least 80%.
e: A total of 324 patients were randomized; however, only 323 received study drug or placebo. One patient was randomized in the IVRS in error and was never dosed.
Source Data: Table 14.1.1

10.2 Protocol Deviations

By-patient protocol deviations are presented in Listing 16.2.3. A listing of individual patient indicating whether each patient met the inclusion/exclusion criteria is presented in Listing 16.2.2. By-patient listings of screen failures and patients unblinded are presented in Listings 16.2.1.2 and 16.2.13, respectively. Criteria for exclusion from the PP Population is shown in End-of-text Table 14.1.2.

11 EFFICACY EVALUATION

11.1 Data Sets Analyzed

The efficacy analyses were performed for the FAS, mITT, and PP Populations. Patient populations are defined in Section 9.6.4.

There were 243 and 80 patients in the mITT population in the RVX000222 200 mg and placebo groups, respectively, 208 and 73 patients in the FAS population in the RVX000222 200 mg and placebo groups, respectively, and 191 and 70 patients in the PP Population in the RVX000222 200 mg and placebo groups, respectively. Patients included in each analysis population are presented in Listing 16.2.4.

11.2 Demographic and Other Baseline Characteristics

11.2.1 Demographics

Demographic data for the mITT population are summarized in Table 11.1. Overall, the majority of patients were male (76.2%, 246/323) and Caucasian (98.5%, 318/323). The proportion of male and female patients in the RVX000222 200 mg and placebo groups is similar to what is noted in the overall population. The mean age of patients was approximately 58.1 years and ranged from 33 to 77 years. No clinically meaningful demographic or baseline differences were noted among the treatment groups.

Demographic and baseline characteristics for the Safety, mITT, FAS, and PP Populations were similar and are summarized in the End-of-Text Tables 14.1.3.1, 14.1.3.2, 14.1.3.3, and 14.1.3.4, respectively.

By-patient demographics are presented in Listing 16.2.5.

Table 11.1: Demographic and Baseline Characteristics – mITT Population

	RVX000222 200 mg (N=243)	Placebo (N=80)	Overall (N=323)
Gender, n (%)			
Male	189 (77.8)	57 (71.3)	246 (76.2)
Female	54 (22.2)	23 (28.8)	77 (23.8)
Race, n (%)			
Caucasian	238 (97.9)	80 (100.0)	318 (98.5)
Asian	1 (0.4)	0 (0.0)	1 (0.3)
Black/African American	3 (1.2)	0 (0.0)	3 (0.9)
American Indian/Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian/Pacific Islander	1 (0.4)	0 (0.0)	1 (0.3)
Ethnicity, n (%)			
Hispanic	45 (18.5)	12 (15.0)	57 (17.6)
Not Hispanic	198 (81.5)	68 (85.0)	266 (82.4)
Age (years)			
N	243	80	323
Mean (SD)	58.3 (8.49)	57.6 (9.60)	58.1 (8.77)
Median	59.0	58.0	59.0
Min, Max	34, 77	33, 77	33, 77
Age group (years), n (%)			
<65	184 (75.7)	67 (83.8)	251 (77.7)
≥65	59 (24.3)	13 (16.3)	72 (22.3)
Height (cm)			
N	243	80	323
Mean (SD)	171.2 (8.91)	170.4 (10.31)	171.0 (9.27)
Median	170.0	171.5	171.0
Min, Max	140, 193	149, 194	140, 194
Weight (kg)			
N	243	80	323
Mean (SD)	88.2 (15.75)	88.3 (16.69)	88.2 (15.96)
Median	87.0	84.5	86.0
Min, Max	50, 160	62, 140	50, 160
Tobacco usage history, n (%)			
Never consumed tobacco	73 (30.0)	28 (35.0)	101 (31.3)
Previously consumed tobacco	103 (42.4)	27 (33.8)	130 (40.2)
Currently consume tobacco	67 (27.6)	25 (31.3)	92 (28.5)

cm = centimeter; kg = kilogram; Max = maximum; Min = minimum; SD = standard deviation.
Source Data: Table 14.1.3.2

11.2.2 Medical History

Overall, 40.2% of patients had a history of MI, 39.3% had PCI, 81.1% had hypertension, and 14.2% of patients reported a history of congestive heart failure (28.3% Class 1 and 71.7% Class 2). The majority of patients had angina (77.7%). Of those reporting angina, 76.1% were stable and 21.1% were unstable per Canadian Cardiovascular Society grading. History of angina that required hospitalization was reported in 65.7% of those reporting angina.

Metabolic syndrome was reported in 10.5% of the patients while dyslipidemia, diabetes (type 1 and 2) and peripheral vascular disease were reported in 83.6%, 30.7%, and 10.8% of the patients respectively. The medical history is similar for patients in the RVX000222 200 mg and placebo groups.

Significant cardiovascular medical history for the Safety, mITT, and FAS populations is presented in End-of-Text Tables 14.1.4.1.1, 14.1.4.1.2, and 14.1.4.1.3, respectively. Other significant medical history for the Safety Population is presented in End-of-Text Table 14.1.4.2.

Baseline characteristics, significant cardiovascular medical history, other significant medical history, and physical examination findings for all patients are provided in Listings 16.2.6, 16.2.7.1, 16.2.7.2 and 16.2.8, respectively.

11.2.3 Prior and Concomitant Medications

All patients reported taking at least 1 concomitant medication; of which 100% were taking concomitant statin medication. The most commonly used statins overall were rosuvastatin 61.6% (rosuvastatin 44.9% and rosuvastatin calcium 16.7%), atorvastatin 45.2% (atorvastatin 35.9% and atorvastatin calcium 9.3%), and simvastatin (2.8%). Concomitant statin use was similar in the RVX000222 and placebo groups (rosuvastatin, 62.1% vs 60%; atorvastatin, 44.9% vs 46.3%; simvastatin, 2.9% vs 2.5%) (End-of-Text Table 14.1.6.3).

Summaries and listings of prior medications, concomitant medications, and concomitant statin medications for the Safety Population are presented in End-of-Text Tables 14.1.6.1, 14.1.6.2, and 14.1.6.3, and in Listings 16.2.9.1, 16.2.9.2, and 16.2.9.3, respectively.

11.3 Measurements of Treatment Compliance

Percent compliance, calculated as 100 x [(capsules dispensed–capsules returned)/(4 x [last dose date - first dose date+1])], was high (100.8% overall; 101.7% in the RVX000222 200 mg group, and 98.2% in the placebo group).

A summary of compliance for all patients is provided in End-of-Text Table 14.1.5; a by-patient listing of study drug accountability is provided in Listing 16.2.10.1.

11.4 Analysis of Efficacy

11.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint was nominal change PAV from baseline to 26 weeks post-randomization, as determined by IVUS within the RVX000222-treated group. The primary efficacy analysis was performed on the mITT population.

A decrease in PAV from baseline to 26 weeks was observed; however the difference was not statistically significant (median -0.4, p=0.08), and therefore the study did not meet the primary efficacy endpoint (Table 11.2).

Even though the study was not designed nor powered to show effects in the placebo group, an analysis of the primary endpoint was presented for the placebo group. A significant change in PAV was not observed from baseline to Week 26 (median -0.3, p=0. 228).

Analysis of the FAS and PP analysis populations were confirmatory of the results in the mITT Population.

Summaries of the primary endpoint analysis in the mITT, FAS, and PP Populations are presented in End-of-Text Tables 14.2.1.1, 14.2.1.2, and 14.2.1.3, respectively; by-patient IVUS coronary angiography and IVUS results are available in Listings 16.2.11.1 and 16.2.11.2, respectively.

Table 11.2: Primary Efficacy Endpoint - Percent Atheroma Volume (PAV) Change from Baseline to Week 26 in the RVX000222 Treatment Group - mITT Population

	RVX000222 200 mg (N=243)		
	Baseline (Visit 1)	**Week 26 (Visit 12)**	**Week 26 change from baseline**
N	243	208	208
Mean (SD)	38.42 (8.545)	38.16 (8.440)	-0.20 (2.419)
Median	38.16	37.83	-0.40
Min, Max	17.9, 60.5	17.4, 65.9	-7.2, 8.3
95% CI			(-0.53, 0.13)
P-value[a]			0.080

CI = confidence intervals; SD = standard deviation; Min = minimum; Max = maximum
a: P-value comparing within group change using the Wilcoxon signed-rank test.
Source Data: Table 14.2.1.1

11.4.2 Secondary Efficacy Endpoints

Secondary efficacy variables included nominal change from baseline to Week 26 post-randomization in 1) PAV in the RVX000222 group compared to placebo, and in 2) TAV and TAV for the 10-mm sub-segment with the greatest disease burden at baseline within the RVX000222 treated group as well as compared to placebo. The proportion of patients with regression of coronary atherosclerosis (e.g. change in PAV <0) from baseline to 26 weeks post-randomization was also analyzed.

As shown in Table 11.3, no significant difference was observed for change from baseline to Week 26 in PAV in the RVX000222 group compared to placebo (p=0.534). Significant reductions from baseline to Week 26 in TAV (mean decrease of 4.18) and TAV for the 10-mm sub-segment with the greatest disease burden at baseline (median decrease of 2.20) were observed within the RVX000222 treatment group (p<0.001 for both). Significant reductions were also observed for these parameters in the placebo group (TAV mean decrease of 3.78, p=0.013 and TAV for the 10-mm sub-segment with the greatest disease burden median decrease of 1.30, p=0.014). No significant differences were observed for change from baseline to Week 26 in TAV or TAV for the 10 mm sub segment with the greatest disease burden in the RVX000222 group compared to placebo. Analysis of the FAS and PP Populations were confirmatory of the results in the mITT population.

Regression of coronary atherosclerosis in the FAS occurred in the same proportion of patients in each group (RVX00022=56.3%; placebo=56.2%). Similar results were seen in the PP Population.

A summary of PAV results is presented for the mITT Population in End-of-Text Table 14.2.1.1. Summaries of TAV and TAV for the 10-mm sub-segment with the greatest disease burden at baseline are presented in End-of-Text Tables 14.2.2.1 and 14.2.3.1 for the mITT Population, Tables 14.2.2.2 and 14.2.3.2 for the FAS, and Tables 14.2.2.3 and 14.2.3.3, for the PP Population, respectively. A summary of regression of coronary atherosclerosis for the FAS and PP Population are provided in End-of-Text Tables 14.2.7.1 and 14.2.7.2, respectively.

Table 11.3: Secondary Efficacy Endpoints - Change in PAV and TAV from Baseline to Week 26 - mITT Population

	RVX000222	Placebo
PAV		
Baseline (Visit 1)		
N	243	80
Mean (SD)	38.42 (8.545)	37.50 (9.616)
Median	38.16	36.44
Min, Max	17.9, 60.5	20.4, 64.4
Week 26 (Visit 12)		
N	208	73
Mean (SD)	38.16 (8.440)	36.49 (9.184)
Median	37.83	36.11
Min, Max	17.4, 65.9	19.4, 62.7
Week 26 change from baseline		
N	208	73
Mean (SD)	-0.20 (2.419)	-0.34 (2.275)
Median	-0.40	-0.30
Min, Max	-7.2, 8.3	-8.2, 5.5
95% CI	(-0.53, 0.13)	(-0.87, 0.19)
P-value[a]	0.080	0.228
ANCOVA		
LS Mean (SE)	-0.18 (0.164)	-0.38 (0.277)
95% CI of LS Mean	(-0.50, 0.14)	(-0.93, 0.16)
P-value[b]	0.534	
TAV		
Baseline (Visit 1)		

	RVX000222	Placebo
N	243	80
Mean (SD)	209.86 (85.663)	187.09 (87.606)
Median	198.29	172.03
Min, Max	37.6, 517.2	69.0, 457.2
Week 26 (Visit 12)		
N	208	73
Mean (SD)	206.24 (83.738)	169.82 (69.683)
Median	198.60	156.59
Min, Max	37.8, 504.9	67.3, 346.8
Week 26 change from baseline		
N	208	73
Mean (SD)	-4.18 (17.228)	-3.78 (12.622)
Median	-3.20	-3.77
Min, Max	-58.9, 44.2	-38.6, 28.8
95% CI	(-6.54, -1.83)	(-6.72, -0.83)
P-value[c]	<0.001	0.013
ANCOVA		
LS Mean (SE)	-3.91 (1.117)	-4.56 (1.903)
95% CI of LS Mean	(-6.10, -1.71)	(-8.31, -0.81)
P-value[b]	0.888	
TAV, 10-mm Sub-segment with the Greatest Disease Burden at Baseline		
Baseline (Visit 1)		
N	209	72
Mean (SD)	64.85 (30.434)	59.65 (31.619)
Median	62.45	58.07
Min, Max	10.4, 176.0	8.4, 142.5
Week 26 (Visit 12)		
N	174	65
Mean (SD)	61.39 (27.374)	52.90 (25.546)
Median	59.12	51.71
Min, Max	8.1, 154.7	8.8, 103.9
Week 26 change from baseline		
N	174	65
Mean (SD)	-2.14 (8.177)	-1.72 (5.256)
Median	-2.20	-1.30
Min, Max	-44.2, 27.1	-12.7, 10.1
95% CI	(-3.36, -0.92)	(-3.03, -0.42)
P-value[a]	<0.001	0.014
ANCOVA		

	RVX000222	Placebo
LS Mean (SE)	-1.95 (0.545)	-2.24 (0.896)
95% CI of LS Mean	(-3.02, -0.87)	(-4.00, -0.47)
P-value[b]	0.782	
Regression in Coronary Atherosclerosis - FAS (Change in PAV <0)		
N	208	73
Yes	117 (56.3)	41 (56.2)
No	91 (43.8)	32 (43.8)
P-value[d]	0.990	

CI = confidence interval; FAS = full analysis set; LS = least squares; Max = maximum; Min = minimum; PAV = percent atheroma volume; SD = standard deviation; SE = standard error; TAV = total atheroma volume
a: P-value comparing within group change using the Wilcoxon signed-rank test.
b: P-value from an ANCOVA with baseline variable as a covariate and treatment group as a factor.
c: P-value comparing within group change using the paired t-test.
d: P-value based on the chi-square test.
Source Data: Tables 14.2.1.1, 14.2.2.1, 14.2.3.1, and 14.2.7.1

Additional secondary efficacy analyses including the percent change in HDL-C, ApoA-I, hs-CRP, and large HDL particles from baseline to Week 26 post-randomization are presented in Table 11.4. Percent change from baseline to Week 26 was significant for all parameters in the RVX000222 group ($p<0.001$). Similarly, significant changes from baseline were observed in the placebo group across all parameters with the exception of hs-CRP ($p=0.065$).

Other parameters were also analyzed including HDL size, HDL particles (total), small HDL, and medium HDL. Percent change from baseline to Week 26 was significant for all of these parameters in the RVX000222 group ($p<0.001$). Similarly, significant changes from baseline were observed in the placebo group across all parameters with the exception of medium HDL ($p=0.127$).

Although consistently greater changes were seen in the RVX000222 group than the placebo group with respect to the secondary parameters assessed, none were statistically significant.

Analysis of the FAS and PP analysis populations were confirmatory of the results in the mITT population.

Summaries for the mITT, FAS, and PP Populations are presented in the following End-of-Text Tables: HDL-C, Tables 14.2.4.1.1, 14.2.4.1.2, and 14.2.4.1.3, respectively; ApoA-I, Tables 14.2.4.2.1, 14.2.4.2.2, and 14.2.4.2.3, respectively; hs-CRP, Tables 14.2.4.3.1, 14.2.4.3.2, and

14.2.4.3.3, respectively; large HDL particles, Tables 14.2.4.4.1, 14.2.4.4.2, and 14.2.4.4.3, respectively; HDL size, Tables 14.2.4.5.1, 14.2.4.5.2, and 14.2.4.5.3, respectively; HDL particles (total), Tables 14.2.4.6.1, 14.2.4.6.2, and 14.2.4.6.3, respectively; small HDL particles, Tables 14.2.4.7.1, 14.2.4.7.2, and 14.2.4.7.3, respectively; and medium HDL particles, Tables 14.2.4.8.1, 14.2.4.8.2, and 14.2.4.8.3, respectively. Individual patient lipid profiles are available in Listing 16.2.14.5.

Table 11.4: Secondary Efficacy Endpoints – Percentage Change in HDL-C, ApoA-I, hs-CRP, and Large HDL Particles from Baseline to Week 26 - mITT Population

	RVX000222	Placebo
HDL-C		
Baseline (Visit 1)		
N	243	80
Mean (SD)	38.02 (7.477)	38.24 (6.967)
Median	39.00	39.00
Min, Max	12.0, 58.0	23.0, 58.0
Week 26 (Visit 12 - LOCF)		
N	232	77
Mean (SD)	41.72 (9.383)	40.86 (7.375)
Median	41.00	39.00
Min, Max	19.0, 81.0	23.0, 62.0
Week 26 % change from baseline		
N	232	77
Mean (SD)	11.92 (24.856)	8.59 (19.146)
Median	10.27	7.69
Min, Max	-46.6, 135.3	-26.2, 59.0
95% CI	(8.70, 15.14)	(4.24, 12.93)
P-value[a]	<0.001	<0.001
ANCOVA		
LS Mean (SE)	11.83 (1.420)	8.86 (2.465)
95% CI of LS Mean	(9.04, 14.62)	(4.01, 13.71)
P-value[b]	0.298	
ApoA-I		
Baseline (Visit 1)		
N	236	80
Mean (SD)	117.21 (18.737)	116.59 (18.349)
Median	118.30	115.30
Min, Max	32.1, 177.7	76.1, 172.8

	RVX000222	Placebo
Week 26 (Visit 12)		
N	231	77
Mean (SD)	132.26 (19.594)	128.72 (16.726)
Median	133.70	129.70
Min, Max	67.8, 200.9	93.0, 168.3
Week 26 % change from baseline		
N	226	77
Mean (SD)	13.85 (18.013)	11.65 (14.306)
Median	12.77	10.58
Min, Max	-47.2, 88.2	-14.4, 56.3
95% CI	(11.49, 16.21)	(8.41, 14.90)
P-value[a]	<0.001	<0.001
ANCOVA		
LS Mean (SE)	13.94 (0.960)	11.37 (1.644)
95% CI of LS Mean	(12.06, 15.83)	(8.14, 14.61)
P-value[b]	0.178	
hs-CRP		
Baseline (Visit 1)		
N	243	80
Mean (SD)	5.37 (9.156)	5.05 (7.041)
Median	2.28	3.14
Min, Max	0.1, 76.2	0.2, 53.7
Week 26 (Visit 12)		
N	223	74
Mean (SD)	2.98 (4.219)	3.08 (3.432)
Median	1.39	1.84
Min, Max	0.1, 23.7	0.2, 17.8
Week 26 % change from baseline		
N	223	74
Mean (SD)	35.43 (288.162)	11.02 (146.639)
Median	-32.14	-36.26
Min, Max	-98.7, 2729.4	-97.4, 876.1
95% CI	(-2.60, 73.46)	(-22.95, 44.99)
P-value[a]	<0.001	0.065
ANCOVA		
LS Mean (SE)	35.87 (17.232)	9.69 (29.916)
95% CI of LS Mean	(1.96, 69.78)	(-49.18, 68.57)
P-value[b]	0.449	
Large HDL Particles		

	RVX000222	Placebo
Baseline (Visit 1)		
N	236	79
Mean (SD)	2.46 (1.297)	2.54 (1.460)
Median	2.35	2.10
Min, Max	0.2, 8.4	0.2, 7.0
Week 26 (Visit 12)		
N	229	77
Mean (SD)	3.48 (1.920)	3.38 (1.616)
Median	3.10	3.00
Min, Max	0.1, 9.8	0.7, 7.9
Week 26 change from baseline		
N	223	76
Mean (SD)	74.76 (156.348)	76.36 (155.190)
Median	37.50	37.98
Min, Max	-93.8, 1350.0	-51.4, 900.0
95% CI	(54.13, 95.40)	(40.90, 111.82)
P-value[a]	<0.001	<0.001
ANCOVA		
LS Mean (SE)	73.99 (9.403)	78.63 (16.109)
95% CI of LS Mean	(55.48, 92.49)	(46.93, 110.33)
P-value[b]	0.804	

CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; Min = minimum; SD = standard deviation; SE = standard error.
a: P-value comparing within group change using the Wilcoxon signed-rank test (non-parametric analysis).
b: P-value from an ANCOVA (non-parametric) with baseline value as covariate and treatment group as a factor.
Source Data: Tables 14.2.4.1.1, 14.2.4.2.1, 14.2.4.3.1, 14.2.4.4.1

11.4.3 Exploratory Efficacy Analyses

11.4.3.1 Relationship between Lipids and Atheroma Volume

The relationship between percent changes in lipids (HDL-C, ApoA-I, HDL-subclasses which includes HDL total particles, HDL size, large HDL, and small HDL) at Week 26 (Visit 12) were correlated with the changes in measures of atheroma volume (PAV and TAV) in the RVX000222 treated group. There was no significant correlation between the change from baseline to Week 26 in PAV or TAV in any of the lipid parameters evaluated (Table 11.5). A summary of the results in the FAS and PP Populations are provided in End-of-Text Tables 14.2.6.1 and 14.2.6.2, respectively.

Table 11.5: Correlation between Changes in Atheroma Burden and Changes in Lipid Biomarkers - FAS

	Change from Baseline at Week 26			
	HDL-C (N=281)	**ApoA-I (N=276)**	**HDL-S (N=272)**	**HDL-L (N=272)**
Change from baseline at Week 26 of PAV				
Correlation[a]	-0.006	0.006	0.036	-0.016
p-value[b]	0.914	0.915	0.555	0.790
Change from baseline at Week 26 of TAV				
Correlation[a]	0.025	-0.041	-0.055	0.034
p-value[b]	0.680	0.498	0.367	0.582

HDL-S = high density lipoprotein small; HDL-L = high density lipoprotein large
a: Correlation based on Pearson correlation coefficient or Spearman rank correlation coefficient, if the assumption for normality was rejected.
b: P-value from the t-test for zero correlation.
Source Data: Table 14.2.6.1

11.4.3.2 Plaque Composition

A subset of patients (n=83) underwent IVUS treatment using the Volcano Revolution catheter to assess plaque histology. Virtual histology (VH) provides data to assess plaque stability and vulnerability as a measure of future cardiovascular risk. This information was used to reflect plaque vulnerability by calculating the ratio of necrotic core to dense calcium (NC/DC) as established by Missel et al[1]. The NC/DC ratio in RVX000222-treated patients (n=61) was significantly lower by -7.5% ($p<0.03$) versus baseline while those given placebo (n=24) had a non-significant reduction of -3.8% ($p=0.47$) versus baseline. The initial VH-IVUS findings show that the actions of RVX000222 improved the NC/DC ratio pointing to less vulnerability of the atherosclerotic plaque for rupture.

Change from baseline at Week 26 in spectral features of plaque composition by RFA (fibrous, fibro-fatty, necrotic core, and dense calcium) within the RVX000222-treated group and placebo group is presented in Table 11.6.

Summaries of change from baseline at Week 26 by treatment group are presented for the mITT, FAS, and PP Populations in End-of-Text Tables 14.2.8.1, 14.2.8.2, and 14.2.8.3, respectively.

Table 11.6: Change from Baseline at Week 26 in Virtual Histology Parameters

	RVX00222 (N=61)	Placebo (N=26)	P-Value[a]	Total (N=87)
Change in Fibrous Percent Based on Volume				
Median	1.727	-1.532	0.051	0.530
P-value (μ=0)	0.043	0.345		0.318
Change in Fibro Fatty Percent Based on Volume				
Median	-2.911	-0.192	0.034	-2.792
P-value (μ=0)	<0.001	0.785		0.007
Change in Necrotic Core Percent Based on Volume				
Median	1.247	1.523	0.255	1.247
P-value (μ=0)	0.002	0.639		0.007
Change in Dense Calcium Percent Based on Volume				
Median	0.307	0.312	0.588[a]	0.307
P-value (μ=0)	0.001[a]	0.380		<0.001[a]
Change in Ratio of Necrotic Core to Dense Calcium				
Median	-0.396	-0.073	0.473[a]	-0.239
P-value (μ=0)	0.044[a]	0.469[a]		0.033[a]

a: P-value calculated using Wilcoxon signed-rank test.
Source Data: Appendix 16.4

11.4.3.3 Pharmacokinetics

A summary of PK trough plasma concentration of RVX000222 in the FAS is presented in Table 11.7 and End-of-Text Table 14.3.7.1; results for the PP Population are provided in End-of-Text Table 14.3.7.2. A by-patient listing of the PK sample record is presented in Listing 16.2.15.1. Five patients had PK samples collected before study drug administration and are not included in Table 11.7.

Table 11.7: Summary of Pharmacokinetic Trough Plasma Concentration of RVX000222 – FAS

	RVX000222 (N=208)
Week 4	
N	201
Mean (SD)	225.91 (206.741)
Coefficient of Variation	0.92
Geometric Mean	133.07
Median	175.00
Min, Max	2.1, 1180.0
Week 14	
n	190
Mean (SD)	200.99 (178.815)
Coefficient of Variation	0.89
Geometric Mean	111.13
Median	178.50
Min, Max	2.2, 1080.0
Week 26	
n	172
Mean (SD)	194.06 (195.114)
Coefficient of Variation	1.01
Geometric Mean	89.20
Median	150.50
Min, Max	1.0, 1080.0
Steady State Trough Concentration [a]	
n	204
Mean (SD)	207.68 (166.045)
Coefficient of Variation	0.80
Geometric Mean	134.13
Median	178.83
Min, Max	3.3, 819.0

SD = standard deviation
a Trough for each patient is calculated as the mean of Visit 4, Visit 8, and Visit 12
Source Data: Table 14.3.7.1

A PK model was developed to provide some clarity around the diverse trough concentrations observed in this trial. In the ASSERT trial (Protocol No. RVX222-CS-005), median trough value was 161 ng/mL where patients were dosed 100 mg BID RVX000222 with co-administered statins. This trough value is in agreement with, and even somewhat higher than, that predicted

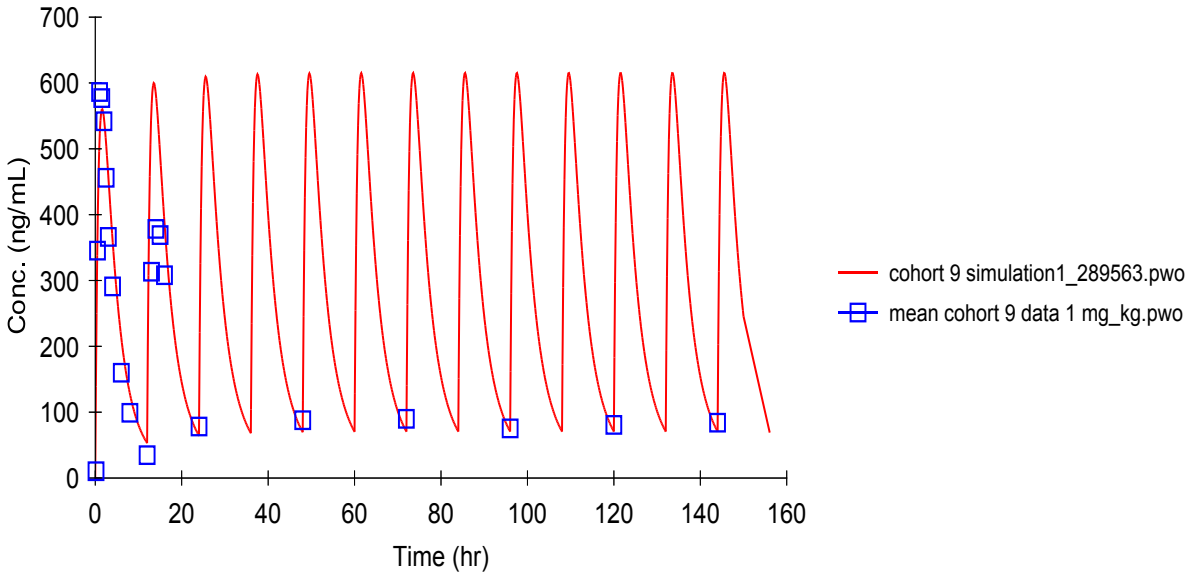
from the PK model. Taken together, the PK model and ASSERT trough levels clearly indicate that the BLOQ data from the present study is not likely due to PK variability in the patient population. Trough levels below the 75 ng/mL threshold observed in this trial are deemed questionable in terms of patient compliance of RVX000222 administration, which could have affected the pharmacodynamic outcomes.

Model Development and Simulation Results

Cohort 9, 1 mg/kg BID dose oral data from RVX222-CS-002 study was used for modeling since this data and doses were close to the dose used in the current study. To develop the PK model, it was assumed that dose formulations were equivalent in the present study and RVX222-CS-002. Day 7 complete profile was used for modeling purposes. The model selected was a 2-compartment 1st Order, micro-constants, no lag time, 1st order elimination. The model fit the data well, as shown in simulation Figure 2. There was a good fit of the actual data from 7 subjects for this selected model. To generate the simulation, a 200 mg daily dose (100 mg BID) was used, assuming a body weight of 80 kg and dose equivalence to about 1.25 mg/kg BID (or 2.5 mg/kg daily).

A steady state trough concentration of ~88 ng/mL was determined. A steady-state peak concentration of ~770 ng/mL was determined. Given that the assay sensitivity (LLOQ) was 1 ng/mL, the steady state trough concentration should be about 88-fold higher than the LLOQ. We concluded that for patients with measured plasma levels below LLOQ (i.e. <1 ng/mL), the compliance for regular dosing is questionable. The model reliably predicts a trough level of 88 ng/mL for a 100 mg BID dose in healthy volunteers.

Figure 2: Simulation Result (Red Line) vs. Actual Data (Blue Square) in Cohort 9 (1 mg/kg BID)



Correlation analysis did not indicate a significant relationship between C_{min} and the change in PAV at Week 26 (Visit 12) for the RVX000222 treated group (correlation = -0.048, p-value = 0.494). A summary of the correlation analysis for the FAS and PP Populations are provided in End-of-Text Tables 14.2.9.1 and 14.2.9.2, respectively.

11.4.4 Statistical/Analytical Issues (if applicable)

Statistical analysis and any related issues are described in Section 9.7. Detailed documentation of statistical methods is found in Appendix 16.1.9.

11.4.4.1 Adjustments for Covariates

Baseline values were used to adjust for the secondary efficacy endpoints which used the ANCOVA model as the method for analyses.

11.4.4.2 Handling of Dropouts or Missing Data

For primary and secondary efficacy analyses, no values were imputed for missing data unless otherwise stated. Observed data were presented in tables and listing without imputation of missing values, unless otherwise stated.

Medication, except study drug, with missing stop dates was considered in concurrent use during the study period and counted in the table of concomitant medications. Adverse events with missing onset dates were considered treatment-emergent if the stop date is after the first exposure to study drug. Adverse events with missing stop dates were considered treatment-emergent. If only the year was present for stop dates, then December 31 was used as the month and day, respectively. If only the day was missing, the first of the month was used for all start dates and the last day of the month was used for all end dates. Missing AE relationship was presented as 'related' in the tables and missing in the listings. Missing AE intensity was considered 'severe' in the tables but was reported as missing in the listings.

11.4.4.3 Interim Analyses and Data Monitoring

No interim analysis was planned or performed for this study.

11.4.4.4 Multicenter Studies

Data from all centers were pooled for summaries.

11.4.4.5 Multiple Comparisons/Multiplicity

There were no adjustments made for multiplicity of endpoints.

11.4.4.6 Use of an "Efficacy Subset" of Patients

The primary efficacy analyses were performed on the mITT population. The supportive analyses were conducted with FAS and PP Population. The definitions of these populations are provided in Section 9.6.4.

11.4.4.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.4.8 Examination of Subgroups

The primary endpoint, change in PAV within the active RVX000222 treatment group, was analyzed among several subgroups in the FAS and PP Population. As supplementary analyses, the subgroup analyses were repeated for the placebo dose group. A summary of the analyses is presented in **Table 11.8**.

Significant reductions in PAV from baseline to Week 26 were observed in RVX000222-treated patients who had PAV above the baseline median (p=0.031), in patients without a history of diabetes mellitus (p=0.023), in patients with large HDL (p=0.006) and HDL-C (p=0.033) that were below the baseline median.

In the placebo group, a significant reduction in PAV from baseline to Week 26 was also observed in patients who had PAV above the baseline median (p=0.007) and with HDL-C that was below the baseline median (p=0.031).

Summaries of all subgroup analyses are provided in End-of-Text Tables 14.2.5.1.1 through 14.2.5.9.2 for the FAS and PP Population.

Table 11.8: PAV Change from Baseline to Week 26 (Visit 12) Subgroup Analyses - FAS

	RVX000222	Placebo	RVX000222	Placebo
Subgroup	**Below Baseline PAV Median**		**Above Baseline PAV Median**	
Week 26 change from baseline				
N	94	46	114	27
Mean (SD)	0.09 (2.245)	0.20 (2.011)	-0.44 (2.538)	-1.27 (2.433)
Median	-0.20	0.60	-0.54	-0.90
Min, Max	-4.7, 8.2	-4.1, 5.5	-7.2, 8.3	-8.2, 3.7
95% CI	(-0.37, 0.55)	(-0.39, 0.80)	(-0.91, 0.03)	(-2.23, -0.30)
P-value[a]	0.830	0.579	0.031	0.007
Subgroup	**Below Baseline HDL-C Median**		**Above Baseline HDL-C Median**	
Week 26 change from baseline				
N	91	30	117	43
Mean (SD)	-0.38 (2.612)	-0.82 (2.052)	-0.05 (2.258)	-0.01 (2.385)
Median	-0.61	-0.79	-0.08	0.07
Min, Max	-5.1, 8.3	-5.6, 3.7	-7.2, 5.5	-8.2, 5.5
95% CI	(-0.93, 0.16)	(-1.58, -0.05)	(-0.46, 0.36)	(-0.74, 0.73)
P-value[a]	0.033	0.031	0.763	0.868
Subgroup	**With History of Diabetes Mellitus**		**Without History of Diabetes Mellitus**	
Week 26 change from baseline				
N	64	19	144	54
Mean (SD)	0.17 (2.360)	-0.23 (2.062)	-0.36 (2.436)	-0.38 (2.363)
Median	-0.03	-0.30	-0.50	-0.32
Min, Max	-3.8, 6.4	-3.8, 4.1	-7.2, 8.3	-8.2, 5.5
95% CI	(-0.42, 0.76)	(-1.23, 0.76)	(-0.76, 0.04)	(-1.02, 0.27)
P-value[a]	0.817	0.595	0.023	0.300
Subgroup	**Male**		**Female**	
Week 26 change from baseline				
N	162	51	46	22
Mean (SD)	-0.22 (2.449)	-0.25 (2.476)	-0.10 (2.336)	-0.56 (1.756)
Median	-0.49	-0.30	-0.13	-0.38
Min, Max	-7.2, 8.3	-8.2, 5.5	-3.8, 5.5	-4.1, 2.4
95% CI	(-0.60, 0.16)	(-0.94, 0.45)	(-0.79, 0.59)	(-1.34, 0.22)
P-value[a]	0.092	0.493	0.587	0.219
Subgroup	**Age <65**		**Age ≥65**	
Week 26 change from baseline				
N	156	62	52	11
Mean (SD)	-0.23 (2.540)	-0.25 (2.136)	-0.08 (2.032)	-0.86 (3.015)
Median	-0.48	-0.28	0.04	-0.67

	RVX000222	Placebo	RVX000222	Placebo
Min, Max	-7.2, 8.3	-5.6, 5.5	-3.8, 4.5	-8.2, 4.1
95% CI	(-0.64, 0.17)	(-0.79, 0.29)	(-0.65, 0.48)	(-2.88, 1.17)
P-value[a]	0.072	0.372	0.740	0.206
Subgroup	**With Statin Use[b]**		**Without Statin Use**	
Week 26 change from baseline				
N	203	67	5	6
Mean (SD)	-0.18 (2.430)	-0.33 (2.289)	-1.05 (1.934)	-0.48 (2.314)
Median	-0.46	-0.29	-0.10	-1.59
Min, Max	-7.2, 8.3	-8.2, 5.5	-3.6, 0.6	-2.1, 3.7
95% CI	(-0.51, 0.16)	(-0.89, 0.23)	(-3.45, 1.35)	(-2.91, 1.95)
P-value[a]	0.107	0.330	0.625	0.563
Subgroup	**Below Baseline ApoA-I Median**		**Above Baseline ApoA-I Median**	
Week 26 change from baseline				
N	97	41	106	32
Mean (SD)	-0.19 (2.543)	-0.25 (2.142)	-0.13 (2.317)	-0.45 (2.465)
Median	-0.55	-0.29	0.06	-0.57
Min, Max	-5.1, 8.3	-5.6, 5.5	-7.2, 5.5	-8.2, 4.1
95% CI	(-0.70, 0.32)	(-0.93, 0.43)	(-0.57, 0.32)	(-1.34, 0.43)
P-value[a]	0.063	0.440	0.729	0.388
Subgroup	**Below Baseline Large HDL (NMR) Median**		**Above Baseline Large HDL (NMR) Median**	
Week 26 change from baseline				
N	91	40	111	32
Mean (SD)	-0.57 (2.152)	-0.41 (2.429)	0.18 (2.592)	-0.36 (2.052)
Median	-0.60	-0.36	0.07	-0.32
Min, Max	-5.1, 8.3	-8.2, 4.1	-7.2, 8.2	-4.1, 5.5
95% CI	(-1.02, -0.13)	(-1.19, 0.36)	(-0.31, 0.67)	(-1.10, 0.38)
P-value[a]	0.006	0.412	0.735	0.237
Subgroup	**Below Baseline hs-CRP Median**		**Above Baseline hs-CRP Median**	
Week 26 change from baseline				
N	108	31	100	42
Mean (SD)	-0.20 (2.122)	0.17 (2.348)	-0.19 (2.715)	-0.71 (2.172)
Median	-0.14	0.60	-0.55	-0.46
Min, Max	-6.7, 5.5	-5.6, 5.5	-7.2, 8.3	-8.2, 3.7
95% CI	(-0.60, 0.21)	(-0.70, 1.03)	(-0.73, 0.34)	(-1.39, -0.04)
P-value[a]	0.341	0.848	0.135	0.064

CI = confidence interval; Max = maximum; Min = minimum; SD = standard deviation;
a: P-value comparing within group change using the Wilcoxon signed-rank test.
b: Statin use was defined as a patient using any statin prior to the first visit.
Source data: Tables 14.2.5.1.1, 14.2.5.2.1, 14.2.5.3.1, 14.2.5.4.1, 14.2.5.5.1, 14.2.5.6.1, 14.2.5.7.1, 14.2.5.8.1,and 14.2.5.9.1

11.4.4.9 Post-hoc Subgroup Analyses

A post-hoc analysis was performed on the subgroups of patients with baseline hs-CRP >2 mg/dL at baseline and those with below median HDL-C who were treated with rosuvastatin or atorvastatin in addition to the study drug. Summaries of these analyses are available in Appendix 16.5.

Serum levels of hs-CRP, when >2.0 mg/dL, reflect a heightened state of inflammation that is a well-known and major component of cardiovascular disease risk. A total of 184 patients with hs-CRP >2.0 mg/dL at time of entry were enrolled into this trial, of which 54 received placebo and 130 received RVX000222. In the RVX000222-treated patients, there was a 60% reduction in hs-CRP vs. baseline ($p<0.0001$). Furthermore, atheroma regression was observed in patients treated with RVX000222 as measured by PAV, TAV, and the worst 10 mm TAV segment by -0.75% ($p<0.03$), -6.3 mm^3 ($p<0.001$) and -2.63 mm^3 ($p<0.001$), respectively, vs. baseline. In RVX000222-treated patients with hs-CRP >2.0 mg/dL, the incidence of MACE was lower by 63% versus placebo ($p=0.023$).

An additional subgroup analysis of patients with below median HDL (<39 mg/dL) at baseline (n=92) who were taking either rosuvastatin or atorvastatin together with RVX000222 found a statistically significant PAV plaque regression of -1.43% ($p<0.002$) among the subgroup of patients taking rosuvastatin. This PAV regression exceeded the trial's pre-specified PAV endpoint (-0.6%) by more than two-fold. However, those patients taking atorvastatin together with RVX000222 had a PAV plaque progression of +0.19% (non-significant).

The responder population (i.e. patients with HDL <39 mg/dL taking rosuvastatin and RVX000222) also surpassed secondary endpoints (TAV regression versus baseline of -12.3 mm^3 [$p< 0.0001$], and TAV regression for the 10-mm sub-segment with the greatest disease burden at baseline of -4.3 mm^3 [$p<0.0001$]), reflecting regression in coronary atherosclerosis. Other secondary endpoints assessed in this population were biomarkers of reverse cholesterol transport (RCT), including: HDL-C, ApoA-I, and large HDL particles which increased by 18.2% ($p<0.0001$), 16.4% ($p<0.0001$), and 74.7% ($p<0.0001$), respectively, versus baseline.

11.4.5 Tabulation of Individual Response Data

By-patient efficacy results are available in End-of-Text Tables located in Section 14 and listings located in Section 16.2.

11.4.6 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

11.4.7 Drug-Drug and Drug-Disease Interactions (if applicable)

Not applicable.

11.4.8 By-Patient Displays

No by patient displays (other than data listings) were constructed during the study.

11.5 Efficacy Conclusions

- A decrease in PAV from baseline to 26 weeks was observed in the mITT population; however the difference was not statistically significant (median -0.4, p=0.08), and therefore the study did not meet the primary efficacy endpoint. The study did meet the secondary efficacy endpoints in that significant reductions from baseline to Week 26 in TAV and TAV for the 10-mm sub-segment with the greatest disease burden at baseline were observed within the RVX000222 treatment group ($p<0.001$, for both). However, there were no significant differences between the RVX000222 treatment group and placebo for TAV or TAV for the 10 mm sub segment with the greatest disease burden.

- No significant differences were observed for change from baseline to Week 26 in PAV (p=0.534), TAV (p=0.888), and TAV for the 10 mm sub segment with the greatest disease burden (p=0.782) in the RVX000222 group compared to placebo. However, the study was not powered to detect these differences.

- Additional secondary efficacy analyses showed a significant percent change from baseline to Week 26 in HDL-C, ApoA-I, hs-CRP, and large HDL particles in the RVX000222 200 mg group ($p<0.001$) across all analysis populations. Similarly, significant changes from baseline were observed in the placebo group across all parameters with the exception of hs-CRP (p=0.065).

- Other parameters were also analyzed including HDL size, HDL particles (total), small HDL, and medium HDL. Percent change from baseline to Week 26 was significant for all of these parameters in the RVX000222 group ($p<0.001$).
- The RVX000222 and placebo groups had the same percentage of patients demonstrating any regression in coronary atherosclerosis ($p=0.990$) (RVX000222=56.3%; placebo=56.2%).
- Exploratory analyses found no significant correlation between the change from baseline to Week 26 in PAV or TAV and percent changes in lipids (HDL-C, ApoA-I, HDL subclasses which included HDL total particles, HDL size, large HDL, and small HDL) in the RVX000222-treated group.
- The NC/DC ratio in RVX000222-treated patients was significantly lower ($p<0.03$) versus baseline while those given placebo had a non-significant reduction ($p=0.47$) versus baseline. The initial VH-IVUS findings show that the actions of RVX000222 improved the NC/DC ratio pointing to less vulnerability of the atherosclerotic plaque for rupture.
- Correlation analysis did not indicate a significant relationship between C_{min} and the change in PAV at Week 26 (Visit 12) for the RVX000222-treated group.
- Subgroup analyses of the primary endpoint demonstrated significant reductions in PAV at Week 26 in RVX000222-treated patients who had PAV above the baseline median, in patients without a history of diabetes mellitus, and in patients with large HDL and HDL-C that were below the baseline median.
- Analysis showed a trend for reduction in MACEs by RVX000222 treatment compared to control ($p=0.09$) and post-hoc analysis showed a statistically significant MACE reduction by active treatment compared to placebo in the subpopulation with hs-CRP >2 mg/L ($p<0.016$).
- Post-hoc subgroup analyses demonstrated a significant reduction in hs-CRP, PAV, TAV, TAV for the 10 mm sub-segment with the greatest disease burden at baseline, and MACE in RVX000222-treated patients who had baseline serum hs-CRP >2.0 mg/dL. Percent

atheroma volume, TAV, and TAV for the 10 mm sub-segment with the greatest disease burden at baseline were also significantly decreased in the subgroup of patients with below median HDL (<39 mg/dL) at baseline who were taking rosuvastatin with RVX000222.

12 SAFETY EVALUATION

The Safety Population was comprised of all patients who received at least 1 dose of study drug (active or control). Each patient was analyzed based on the actual treatment received.

12.1 Extent of Exposure

Overall, the mean number of days on treatment was 174.7, and was similar in the RVX000222 200 mg and placebo groups (173.4 and 178.7, respectively). In the overall population, study duration was 207.3 days; duration was 206.8 and 208.8 days in the RVX000222 200 mg and placebo groups, respectively.

A summary of study drug exposure and compliance for the Safety Population is provided in End-of-Text Table 14.1.5; a by-patient listing is provided in Listing 16.2.10.2.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

Overall, 178 patients reported a total of 427 TEAEs (131 patients reported 327 TEAEs in the RVX000222 group, and 47 patients reported 100 TEAEs in the placebo group) (End-of-Text Table 14.3.1.4). Of the 427 TEAEs reported, the majority were mild (255, 59.7%) or moderate (152, 35.6%) in severity. In the RVX000222 group, the majority of TEAEs reported were mild (187/327, 57.2%) or moderate (129/327, 39.4%). Similar findings were observed in the placebo group, with 68.0% (68/100) of TEAEs reported as mild and 23.0% (23/100) as moderate in intensity (End-of-Text Table 14.3.1.5).

Table 12.1 provides an overall summary of AEs. Approximately half (55.1%) of the patients in the overall population experienced at least 1 TEAE. The proportion of patients reporting at least 1 TEAE was similar in the RVX000222 and placebo groups (53.9% and 58.8%, respectively). Overall, 22.9% of patients reported mild TEAEs while 26.6% of patients reported moderate TEAEs. A similar pattern of results was observed for the both treatment and placebo groups. Serious TEAEs were reported for 13.6% of RVX000222-treated patients and 22.5% of patients receiving placebo; of these, few patients experienced serious treatment-related TEAEs (0.8% in the RVX000222 200 mg group and none in the placebo group). Overall, 4.3% of patients

discontinued study drug due to a TEAE, 4.9% and 2.5% in the RVX000222 200 mg and placebo groups, respectively. One patient in the placebo group died due to a TEAE.

An overview of AEs for the Safety Population is provided in End-of-Text Table 14.3.1.2. By-patient listings of pre-treatment AEs, TEAEs, and serious TEAEs are provided in Listings 16.2.12.1, 16.2.12.2, and 16.2.12.3, respectively.

Table 12.1: Overview of Adverse Events - Safety Population

	RVX000222 200 mg (N=243)	Placebo (N=80)	Overall (N=323)
At least one pre-treatment AE[a]	13 (5.3)	3 (3.8)	16 (5.0)
At least one TEAE[b]	131 (53.9)	47 (58.8)	178 (55.1)
TEAE by severity[c]			
Mild	52 (21.4)	22 (27.5)	74 (22.9)
Moderate	69 (28.4)	17 (21.3)	86 (26.6)
Severe	10 (4.1)	8 (10.0)	18 (5.6)
At least one serious TEAE	33 (13.6)	18 (22.5)	51 (15.8)
At least one related TEAE[d]	33 (13.6)	7 (8.8)	40 (12.4)
At least one related serious TEAE	2 (0.8)	0 (0.0)	2 (0.6)
At least one TEAE leading to study drug withdrawal	12 (4.9)	2 (2.5)	14 (4.3)
Death due to TEAE	0 (0.0)	1 (1.3)	1 (0.3)

AE = adverse event; TEAE = treatment-emergent adverse events
a: A pre-treatment AE was defined as any AE that started prior to the first dose of study drug.
b: A treatment-emergent adverse event was defined as any AE with an onset date on or after the first dose of study drug.
c: A patient was counted only once in the most severe category when multiple TEAEs were reported.
d: A treatment-related AE was defined as a relationship of possibly, probably or definitely related to study drug.
Source Data: Table 14.3.1.2

A summary of MACE is provided in Table 12.2. Overall, at least 1 MACE occurred in 8.7% of patients. Major adverse cardiac events occurred more frequently in the placebo group than in the RVX000222 200 mg group, though the difference was not statistically significant (p=0.083, 13.8% vs. 7.0%, respectively). No significant differences were observed between the two groups in any of the components of MACE.

A summary of MACE for the Safety Population is provided in End-of-Text Table 14.3.1.1.1.

Table 12.2: Major Adverse Cardiac Events – Safety Population

	RVX000222 200 mg (N=243)		Placebo (N=80)			Overall (N=323)
	n (%)	95% CI	n (%)	95% CI	p-value	n (%)
At least one MACE	17 (7.0)	(4.3, 9.7)	11 (13.8)	(7.4, 20.1)	0.083	28 (8.7)
Myocardial infarction	4 (1.6)	(0.3, 3.0)	1 (1.3)	(0.0, 3.3)	0.798	5 (1.5)
Stroke	0 (0.0)	NE	0 (0.0)	NE	NE	0 (0.0)
Coronary revascularization	10 (4.1)	(2.0, 6.2)	7 (8.8)	(3.6, 13.9)	0.134	17 (5.3)
Hospitalization for ACS or heart failure	5 (2.1)	(0.6, 3.6)	3 (3.8)	(0.3, 7.2)	0.423	8 (2.5)
Death	0 (0.0)	NE	1 (1.3)	(0.0, 3.3)	0.081	1 (0.3)

ACS = acute coronary syndrome; CI = confidence interval; MACE = major adverse cardiac event; NE = non-estimable
a: p-value from the log-rank test comparing the time-to-first major cardiac event after double-blind study drug administration, censored at 30 days after the last dose of study drug.
Source Data: Table 14.3.1.1.1

12.2.2 Display of Adverse Events

Overall, pre-treatment AEs occurred in 5.0% of patients (End-of-Text Table 14.3.1.3). A summary of the TEAEs that occurred in at least 2% of patients in any treatment group is presented by MedDRA preferred term in Table 12.3 below. The number and percent of patients reporting at least 1 TEAE was 131 (53.9%) and 47 (58.8%), in the RVX000222 200 mg and placebo groups, respectively. The most frequently occurring TEAE experienced by patients in both treatment groups was angina pectoris (8.6% and 10.0% in the RVX000222 200 mg and placebo groups, respectively).

A summary of treatment-related AEs that occurred in at least 1% of patients in any treatment group is presented in Table 12.4. The frequency of treatment-related AEs was higher in the RVX000222 group (33 patients [13.6%]) compared to the placebo group (7 patients [8.8%]). The most common treatment-related AEs reported in the RVX000222 200 mg group were hepatic enzyme increase (5 patients [2.1%]) and ALT increase (4 patients [1.6%]). In the placebo group, no treatment-related AE occurred in more than 1 patient.

Summaries of the incidence of TEAEs by MedDRA system organ class, TEAEs by severity, and TEAEs by relationship to treatment are provided in End-of-Text Tables 14.3.1.4, 14.3.1.5, and 14.3.1.6, respectively. A by-patient listing of AEs is provided in Listing 16.2.12.2.

Table 12.3: Incidence of Treatment-Emergent Adverse Events Reported for ≥ 2% of Patients in Any Treatment Group, by Body System/Organ Class and Preferred Term – Safety Population

Body System/Organ Class Preferred Term	RVX000222 200 mg (N=243) n (%)	Placebo (N=80) n (%)	Overall (N=323) n (%)
Patients with Any TEAE	131 (53.9)	47 (58.8)	178 (55.1)
Cardiac disorders	34 (14.0)	15 (18.8)	49 (15.2)
Angina pectoris	21 (8.6)	8 (10.0)	29 (9.0)
Coronary artery disease	6 (2.5)	4 (5.0)	10 (3.1)
Infections and infestations	32 (13.2)	10 (12.5)	42 (13.0)
Influenza	9 (3.7)	0 (0.0)	9 (2.8)
Bronchitis	3 (1.2)	2 (2.5)	5 (1.5)
Respiratory tract infection viral	2 (0.8)	2 (2.5)	4 (1.2)
Gastrointestinal disorders	30 (12.3)	8 (10.0)	38 (11.8)
Dyspepsia	6 (2.5)	1 (1.3)	7 (2.2)
Diarrhoea	4 (1.6)	3 (3.8)	7 (2.2)
Nausea	6 (2.5)	0 (0.0)	6 (1.9)
Abdominal pain	1 (0.4)	2 (2.5)	3 (0.9)
General disorders and administration site conditions	31 (12.8)	6 (7.5)	37 (11.5)
Non-cardiac chest pain	6 (2.5)	3 (3.8)	9 (2.8)
Oedema peripheral	7 (2.9)	0 (0.0)	7 (2.2)
Fatigue	5 (2.1)	1 (1.3)	6 (1.9)
Chest pain	4 (1.6)	2 (2.5)	6 (1.9)
Injury, poisoning and procedural complications	17 (7.0)	9 (11.3)	26 (8.0)
In-stent coronary artery restenosis	2 (0.8)	3 (3.8)	5 (1.5)
Procedural complication	0 (0.0)	2 (2.5)	2 (0.6)
Investigations	20 (8.2)	2 (2.5)	22 (6.8)
Alanine aminotransferase increased	5 (2.1)	0 (0.0)	5 (1.5)
Hepatic enzyme increased	5 (2.1)	0 (0.0)	5 (1.5)
Musculoskeletal and connective tissue disorders	17 (7.0)	4 (5.0)	21 (6.5)
Myalgia	5 (2.1)	0 (0.0)	5 (1.5)
Neck pain	0 (0.0)	2 (2.5)	2 (0.6)
Nervous system disorders	17 (7.0)	2 (2.5)	19 (5.9)
Dizziness	5 (2.1)	1 (1.3)	6 (1.9)
Respiratory, thoracic and mediastinal disorders	13 (5.3)	5 (6.3)	18 (5.6)
Cough	5 (2.1)	2 (2.5)	7 (2.2)
Metabolism and nutrition disorders	15 (6.2)	2 (2.5)	17 (5.3)
Diabetes mellitus	5 (2.1)	2 (2.5)	7 (2.2)
Vascular disorders	9 (3.7)	6 (7.5)	15 (4.6)
Hypertension	6 (2.5)	2 (2.5)	8 (2.5)
Arteriosclerosis	0 (0.0)	2 (2.5)	2 (0.6)
Skin and subcutaneous tissue	11 (4.5)	3 (3.8)	14 (4.3)

Body System/Organ Class Preferred Term	RVX000222 200 mg (N=243) n (%)	Placebo (N=80) n (%)	Overall (N=323) n (%)
disorders			
Dermatitis	0 (0.0)	2 (2.5)	2 (0.6)

Note: A TEAE was defined as any AE with an onset date on or after the first dose of study drug. Patients may have had more than 1 AE per SOC and preferred term. At each level (SOC and preferred term) a patient was counted only once if he/she experienced 1 or more AEs at that level. AEs were coded using MedDRA version 14.1.
Source Data: Table 14.3.1.4

Table 12.4: Incidence of Treatment-Emergent Related Adverse Events Reported for ≥1% of Patients in Any Treatment Group, by Body System/Organ Class and Preferred Term – Safety Population

Body System/Organ Class Preferred Term	RVX000222 200 mg (N=243) n (%)	Placebo (N=80) n (%)	Overall (N=323) n (%)
Patients with Any Treatment-Related TEAE	33 (13.6)	7 (8.8)	40 (12.4)
Investigations	16 (6.6)	0 (0.0)	16 (5.0)
Hepatic enzyme increase	5 (2.1)	0 (0.0)	5 (1.5)
Alanine aminotransferase increased	4 (1.6)	0 (0.0)	4 (1.2)
Aspartate aminotransferase increased	3 (1.2)	0 (0.0)	3 (0.9)
Gastrointestinal Disorders	11 (4.5)	2 (2.5)	13 (4.0)
Diarrhoea	3 (1.2)	1 (1.3)	4 (1.2)
Constipation	3 (1.2)	0 (0.0)	3 (0.9)
Abdominal pain	1 (0.4)	1 (1.3)	2 (0.6)
Musculoskeletal and connective tissue disorders	4 (1.6)	1 (1.3)	5 (1.5)
Neck pain	0 (0.0)	1 (1.3)	1 (0.3)
Skin and subcutaneous tissue disorders	3 (1.2)	1 (1.3)	4 (1.2)
Rash	1 (0.4)	1 (1.3)	2 (0.6)
Psychiatric disorders	0 (0.0)	2 (2.5)	2 (0.6)
Abnormal dreams	0 (0.0)	1 (1.3)	1 (0.3)
Sleep disorder	0 (0.0)	1 (1.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (1.3)	1 (0.3)
Cough	0 (0.0)	1 (1.3)	1 (0.3)

Note: Related included definite, probably, possibly and missing. A TEAE was defined as any AE with an onset date on or after the first dose of study drug. Patients may have had more than 1 AE per SOC and preferred term. At each level (SOC and preferred term) a patient was counted only once if he/she experienced 1 or more AEs at that level. AEs were coded using MedDRA version 14.1.
Source Data: Table 14.3.1.6

12.2.3 Listing of Adverse Events by Patient

Listings of pre-treatment AEs and TEAEs reported during this study are presented by patient in Listings 16.2.12.1 and 16.2.12.2.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Deaths

A by-patient listing of TEAEs resulting in death is presented in Listing 16.2.12.4. There were no deaths in the RVX000222 treated group. One patient in the placebo group died during the study. A narrative for this patient (Patient 403-006) is available in Section 14.3.3.

12.3.2 Other Serious Adverse Events

Table 12.5 provides a listing of the patients who experienced treatment-emergent SAEs during the study. A total of 51 (15.8%) patients reported 66 treatment-emergent SAEs (End-of-text Tables 14.3.1.7.1 and 14.3.1.7.2). A lower percentage of patients in the RVX000222 200 mg group experienced SAEs compared to the placebo group (33/243, 13.6% compared to 18/80, 22.5%), although this result was not statistically significant (p=0.076). All of the SAEs were assessed by the Investigator as being not related to treatment with the study drug (RVX000222 or placebo), with the exception of 2 events. Patient 705-021 experienced increased ALT that was considered by the Investigator to be possibly related to RVX000222. Patient 705-023 experienced rhabdomyolysis that was considered by the Investigator to be possibly related to RVX000222 (see narrative in Section 14.3.3 for further details). However, upon further review by the Sponsor the event was deemed related to rosuvastatin use, not to RVX000222.

A by-patient listing of all SAEs is provided in Listing 16.2.12.5. A by-patient listing of treatment-emergent SAEs is provided in Listing 16.2.12.3. Narratives for these patients are provided in Section 14.3.3.

Table 12.5: Listing of Patients who Experienced Treatment-Emergent Serious Adverse Events – Safety Population

Center/ Patient	Sex/Age/Race[a]	Onset Day[b]	End Day[b]	Adverse Event(s)[c]	Severity[d]	Relationship to Study Drug[d]
RVX000222 200 mg						
203-004	55/F/White	16 Jul 2012	24 Jul 2012	Pneumonia	Moderate	Not related
207-023	72/M/White	09 Jan 2013	18 Jan 2013	Vascular pseudoaneurysm	Moderate	Not related
401-007	58/M/White	07 March 2013	30 Apr 2013	Arteriosclerosis coronary artery	Moderate	Not related
501-001	45/F/White	21 Dec 2011	25 Dec 2011	Depression	Severe	Not related
		19 Jan 2012	03 Feb 2012	Depression	Mild	Not related
		08 Mar 2012	20 Mar 2012	Bipolar disorder	Mild	Not related
501-037	44/M/White	09 Oct 2012	09 Oct 2012	Non-cardiac chest pain	Mild	Not related
		20 Mar 2013	22 Mar 2013	Coronary artery disease	Severe	Not related
502-020	55/M/White	14 Dec 2012	14 Dec 2012	In-stent arterial restenosis	Moderate	Not related
502-026	68/F/White	05 Dec 2012	12 Dec 2012	Cholecystitis	Moderate	Not related
		10 Jan 2013	11 Jan 2013	Coronary artery disease	Moderate	Not related
505-018	55/F/White	13 Dec 2012	14 Dec 2012	Angina pectoris	Moderate	Not related
601-008	69/M/White	19 Jul 2012	20 Jul 2012	Chest pain	Moderate	Not related
601-015	71/M/White	18 Nov 2012	20 Nov 2012	Transient ischaemic attached	Severe	Not related
		07 Jan 2013	11 Jan 2013	Presyncope	Moderate	Not related
		30 Jan 2013	06 Feb 2013	Cerebrovascular accident	Severe	Not related
601-027	63/F/White	27 Nov 2012	30 Nov 2012	Acute myocardial infarction	Moderate	Not related
608-001	49/M/White	05 Nov 2012	06 Nov 2012	Angina pectoris	Moderate	Not related
608-016	54/M/White	29 Oct 2012	31 Oct 2012	Vascular pseudoaneursym	Moderate	Not related
608-018	48/M/White	06 Nov 2012	07 Nov 2012	Angina unstable	Moderate	Not related
		15 Nov 2012	30 Nov 2012	Acute coronary syndrome	Moderate	Not related
703-012	54/M/White	08 Oct 2012	16 Nov 2012	Coronary artery disease	Moderate	Not related
705-011	61/M/White	24 May 2012	28 May 2012	Peripheral vascular disorder	Moderate	Not related
705-013	62/M/White	19 Jul 2012	24 Jul 2012	Benign neoplasm of bladder	Severe	Not related
705-021	64/M/White	31 Jul 2012	07 Aug 2012	Alanine aminotransferase increased	Mild	Possible

Center/ Patient	Sex/Age/Race[a]	Onset Day[b]	End Day[b]	Adverse Event(s)[c]	Severity[d]	Relationship to Study Drug[d]
		02 Aug 2012	07 Aug 2012	Blood creatinine increased	Mild	Not related
705-023	65/F/White	04 Oct 2012	11 Oct 2012	Coronary artery disease	Moderate	Not related
		01 Nov 2012	19 Nov 2012	Cardiac failure	Moderate	Not related
		16 Dec 2012	28 Dec 2012	Rhabdomyolysis	Severe	Possible
705-028	61/F/White	07 Sep 2012	10 Sep 2012	Epistaxis	Moderate	Not related
802-017	62/F/White	07 Jun 2012	26 Jun 2012	Acute myocardial infarction	Severe	Not related
804-007	64/M/White	03 Oct 2012	09 Nov 2012	Angina unstable	Moderate	Not related
806-010	60/M/White	04 Oct 2012	11 Oct 2012	Myocardial infarction	Mild	Not related
806-019	63/M/White	30 Jan 2013	04 Feb 2013	Chest pain	Moderate	Not related
807-005	71/M/White	17 Apr 2012	23 Apr 2012	Pancreatitis acute	Moderate	Not related
809-011	64/M/White	19 Aug 2012	19 Aug 2012	Angioedema	Moderate	Not related
		06 Nov 2012	12 Nov 2012	Angina pectoris	Mild	Not related
810-013	53/M/White	30 Sep 2012	09 Oct 20123	Cholecystitis acute	Moderate	Not related
		10 Nov 2012	24 Nov 2012	Cholecystitis acute	Moderate	Not related
901-003	44/M/White	17 Oct 2012	17 Oct 2012	Chest pain	Mild	Not related
902-001	59/M/White	29 Jun 2012	19 Jul 2012	Head injury	Moderate	Not related
903-007	68/M/White	07 Nov 2012	20 Nov 2012	Acute myocardial infarction	Severe	Not related
		02 Feb 2013	15 Feb 2013	Gastritis erosive	Moderate	Not related
		02 Feb 2013	15 Feb 2013	Haemorrhoidal haemorrhage	Moderate	Not related
911-002	49/F/White	28 Mar 2012	28 Mar 2012	Coronary artery disease	Moderate	Not related
911-008	56/F/White	31 Aug 2012	03 Sep 2012	Fibula fracture	Moderate	Not related
911-012	66/M/White	19 Nov 2012	19 Nov 2012	Coronary artery disease	Moderate	Not related
Placebo						
207-002	64/F/White	03 Aug 2012	04 Aug 2012	Coronary artery disease	Mild	Not related
207-017	63/M/White	29 Jan 2013	30 Jan 2013	Coronary artery disease	Severe	Not related
302-010	73/M/White	04 Feb 2013	07 Feb 2013	Angina pectoris	Moderate	Not related
403-006	62/M/White	27 Oct 2012	27 Oct 2012	Acute myocardial infarction	Severe	Not related

Center/ Patient	Sex/Age/Race[a]	Onset Day[b]	End Day[b]	Adverse Event(s)[c]	Severity[d]	Relationship to Study Drug[d]
409-005	64/M/White	07 Dec 2012	12 Dec 2012	Haemorrhage	Moderate	Not related
501-008	50/F/White	06 Apr 2012	13 Apr 2012	Anaemia	Severe	Not related
501-014	40/F/White	23 Mar 2012	02 Apr 2012	Cough	Severe	Not related
		30 Mar 2012	02 Apr 2012	Dyspnoea	Moderate	Not related
501-020	59/M/White	30 Aug 2012	31 Aug 2012	Angina unstable	Moderate	Not related
502-018	58/M/White	27 Nov 2012	28 Nov 2012	Coronary artery disease	Moderate	Not related
502-035	64/M/White	15 Dec 2012	21 Dec 2012	Pneumonia	Mild	Not related
502-036	63/F/White	05 Mar 2013	06 Mar 2013	In-stent coronary artery restenosis	Moderate	Not related
502-041	58/M/White	03 Oct 2012	05 Oct 2012	Non-cardiac chest pain	Mild	Not related
506-003	61/M/White	28 Aug 2012	03 Oct 2012	Pancreatic carcinoma	Severe	Not related
705-007	55/M/White	08 Mar 2012	21 Mar 2012	Coronary artery disease	Moderate	Not related
804-003	55/M/White	30 Oct 2012	02 Nov 2012	Arteriosclerosis	Mild	Not related
908-004	57/M/White	10 Sep 2012	22 Oct 2012	Colon cancer	Severe	Not related
911-004	52/M/White	19 Mar 2012	10 May 2012	In-stent coronary artery restenosis	Mild	Not related
911-009	61/M/White	02 Oct 2012	02 Oct 2012	In-stent coronary artery restenosis	Moderate	Not related

a: Sex: M = male; F = female. Age is in years.
b: Treatment days for duration of event.
c: Preferred terms (literal terms, if required for clarification).
d: In the opinion of the Investigator.
Source Data: Listings 16.2.5 and 16.2.12.3

12.3.3 Other Significant Adverse Events

Treatment-emergent adverse events leading to withdrawal of study drug is provided in End-of-text Table 14.3.1.8. Overall, 4.3% (14/323) of patients discontinued study drug due to a TEAE, 4.9% (12/243) and 2.5% (2/80) in the treatment and placebo groups, respectively. Narratives for these patients are provided in Section 14.3.3.

12.3.4 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives for the patient who died, and for those patients who experienced SAEs, who discontinued study drug due to an AE, or who had ALT/AST increases >3X ULN are provided in Section 14.3.3.

12.4 Clinical Laboratory Evaluation

12.4.1 Evaluation of Each Laboratory Parameter

12.4.1.1 Laboratory Values over Time

Summaries of ALT, AST, and total bilirubin at each visit and the change from baseline are presented by treatment group in Table 12.6.

Summaries of additional safety laboratory results and fasting lipid profile at baseline, Week 14, and Week 26, and the change from baseline are presented by treatment group in Table 12.7 and Table 12.8, respectively.

No clinically significant observations were noted in laboratory values over the course of the study, with the exception of ALT and AST. A summary of patients with ALT/AST increases is provided in Table 12.9. Summaries of hematology, chemistry, liver function tests, fasting lipid, and urinalysis laboratory results and changes from baseline are provided in the End-of-Text Tables 14.3.2.1, 14.3.2.2, 14.3.2.3, 14.3.2.4, and 14.3.2.5. Laboratory assessments are listed for each patient by visit and date in Listing 16.2.14.1. By-patient listings for laboratory results for hematology, chemistry, liver function tests, and pregnancy test and urinalysis are provided in Listings 16.2.14.2-16.2.14.4 and 16.2.14.6, respectively.

Table 12.6: Summary of ALT, AST, and Total Bilirubin by Week and Change from Baseline by Treatment Group - Safety Population

	RVX000222 (N=243)						Placebo (N=80)					
	ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)		ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)	
	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline
Baseline												
n	243		243		243		80		80		80	
Mean	26.3		20.9		0.54		24.2		20.1		0.55	
(SD)	(11.85)		(8.55)		(0.215)		(11.25)		(8.80)		(0.235)	
Median	24.0		19.0		0.50		22.0		19.0		0.50	
Min, Max	5, 97		6, 103		0.2, 1.5		7, 67		9, 79		0.1, 1.4	
Week 2												
n	237	237	237	237	237	237	78	78	78	78	78	78
Mean	25.7	-0.4	20.9	0.2	0.62	0.07	23.5	-0.9	19.5	-0.4	0.53	-0.02
(SD)	(11.10)	(11.31)	(6.33)	(8.42)	(0.267)	(0.207)	(9.15)	(9.37)	(5.30)	(8.66)	(0.234)	(0.202)
Median	24.0	0.0	20.0	1.0	0.60	0.10	22.5	0.0	18.0	1.0	0.50	0.00
Min, Max	4, 73	-77, 28	9, 43	-88, 22	0.2, 1.6	-0.7, 1.1	5, 52	-45, 15	9, 31	-62, 10	0.2, 1.3	-0.6, 0.4
Week 4												
n	239	239	239	239	239	239	76	76	76	76	76	76
Mean	35.4	9.3	25.5	4.6	0.61	0.07	25.1	1.0	20.8	0.8	0.57	0.01
(SD)	(106.98)	(107.19)	(52.37)	(52.99)	(0.253)	(0.208)	(10.51)	(10.47)	(6.09)	(8.95)	(0.230)	(0.156)
Median	25.0	2.0	21.0	1.0	0.60	0.10	23.0	1.0	20.0	2.0	0.50	0.00
Min, Max	4, 1646	-82, 1625	8, 818	-89, 802	0.1, 2.0	-0.5, 1.1	8, 53	-46, 23	10, 39	-55, 21	0.2, 1.2	-0.4, 0.3
Week 6												
n	233	233	233	233	233	233	76	76	76	76	76	76
Mean	38.9	12.6	26.5	5.6	0.62	0.07	25.1	1.3	20.1	0.9	0.54	-0.01
(SD)	(56.23)	(55.99)	(23.62)	(23.99)	(0.255)	(0.221)	(11.92)	(11.69)	(6.33)	(6.43)	(0.214)	(0.199)
Median	26.0	2.0	22.0	2.0	0.60	0.10	23.0	1.0	19.0	1.0	0.50	0.00
Min, Max	4, 595	-84, 568	8, 263	-90, 242	0.1, 2.2	-0.7, 1.1	9, 66	-48, 40	9, 37	-22, 18	0.2, 1.2	-0.5, 0.5
Week 8												
n	234	234	234	234	234	234	77	77	77	77	77	77
Mean	42.1	15.9	28.3	7.3	0.61	0.07	23.8	-0.6	20.2	0.3	0.54	-0.01
(SD)	(50.18)	(49.93)	(21.69)	(21.92)	(0.244)	(0.215)	(10.74)	(12.22)	(5.62)	(9.10)	(0.234)	(0.170)
Median	28.5	3.0	23.0	3.0	0.60	0.10	22.0	0.0	19.0	1.0	0.50	0.00
Min, Max	2, 525	-73, 479	8, 217	-81, 190	0.2, 1.5	-0.7, 1.1	8, 79	-51, 51	11, 36	-57, 17	0.2, 1.3	-0.4, 0.4

	RVX000222 (N=243)						Placebo (N=80)					
	ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)		ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)	
	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline
Week 11												
n	232	232	232	232	231	231	75	75	75	75	75	75
Mean	35.4	9.2	25.3	4.4	0.63	0.08	26.2	1.7	21.6	1.7	0.55	0.00
(SD)	(30.16)	(30.66)	(12.82)	(14.27)	(0.259)	(0.225)	(11.59)	(12.44)	(6.14)	(9.35)	(0.249)	(0.205)
Median	27.0	3.0	22.0	3.0	0.60	0.10	23.0	1.0	21.0	2.0	0.50	0.00
Min, Max	6, 258	-70, 222	9, 117	-86, 92	0.2, 1.8	-0.7, 0.9	7, 59	-44, 37	11, 40	-56, 14	0.2, 1.3	-0.4, 0.8
Week 14												
n	227	227	227	227	228	228	76	76	76	76	76	76
Mean	32.9	6.5	25.2	4.2	0.63	0.08	25.4	0.9	21.7	1.7	0.54	-0.01
(SD)	(20.47)	(22.01)	(11.38)	(12.89)	(0.265)	(0.225)	(11.05)	(12.03)	(5.67)	(8.91)	(0.251)	(0.209)
Median	28.0	3.0	23.0	3.0	0.60	0.10	23.0	1.0	21.0	2.0	0.50	0.00
Min, Max	8, 167	-73, 145	9, 93	-84, 69	0.1, 2.2	-0.6, 1.3	8, 61	-38, 33	11, 37	-55, 15	0.2, 1.3	-0.5, 0.5
Week 17												
n	228	228	228	228	228	228	75	75	75	75	75	75
Mean	32.1	5.9	24.8	3.8	0.62	0.08	26.1	1.7	22.5	2.5	0.57	0.01
(SD)	(29.96)	(31.40)	(16.09)	(17.24)	(0.267)	(0.211)	(13.24)	(12.99)	(8.24)	(10.67)	(0.245)	(0.180)
Median	27.0	3.0	22.0	3.0	0.60	0.10	23.0	2.0	21.0	2.0	0.50	0.00
Min, Max	5, 415	-84, 393	9, 223	-87, 199	0.2, 1.8	-0.6, 0.7	8, 88	-35, 51	11, 76	-53, 54	0.2, 1.2	-0.5, 0.4
Week 20												
n	225	225	225	225	226	226	76	76	76	76	76	76
Mean	29.1	2.9	24.2	3.2	0.63	0.09	25.5	1.1	23.4	3.5	0.58	0.03
(SD)	(16.76)	(18.67)	(13.82)	(15.41)	(0.276)	(0.221)	(10.67)	(10.86)	(9.86)	(7.94)	(0.225)	(0.198)
Median	26.0	2.0	22.0	3.0	0.60	0.10	23.5	2.0	22.0	3.0	0.50	0.05
Min, Max	2, 173	-77, 162	9, 185	-83, 166	0.2, 1.6	-0.6, 1.0	9, 73	-47, 22	12, 87	-18, 43	0.2, 1.3	-0.5, 0.5
Week 23												
n	224	224	224	224	224	224	77	77	77	77	77	77
Mean	29.5	3.3	23.7	2.8	0.63	0.09	25.5	1.1	22.6	2.6	0.59	0.04
(SD)	(15.78)	(16.79)	(8.07)	(10.86)	(0.274)	(0.239)	(10.86)	(10.61)	(6.55)	(8.69)	(0.260)	(0.218)
Median	26.0	2.0	22.0	3.0	0.60	0.10	24.0	1.0	22.0	2.0	0.50	0.00
Min, Max	4, 109	-79, 86	10, 82	-90, 58	0.2, 1.9	-0.7, 1.1	8, 64	-33, 27	12, 38	-41, 28	0.2, 1.4	-0.4, 0.7
Week 26												
n	223	223	223	223	223	223	74	74	74	74	74	74
Mean	30.0	3.8	25.9	4.9	0.68	0.14	24.4	-0.3	22.3	2.3	0.61	0.06
(SD)	(24.37)	(23.26)	(20.59)	(19.44)	(0.290)	(0.222)	(9.19)	(11.20)	(6.96)	(9.48)	(0.269)	(0.196)

	RVX000222 (N=243)						Placebo (N=80)					
	ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)		ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)	
	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline	Value	Change from Baseline
Median	26.0	2.0	23.0	3.0	0.60	0.10	22.5	1.0	21.5	2.5	0.50	0.00
Min, Max	2, 337	-80, 274	13, 294	-85, 240	0.2, 1.8	-0.4, 1.1	6, 50	-48, 28	11, 50	-53, 28	0.2, 1.7	-0.3, 0.7

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SD = standard deviation
Source Data: Table 14.3.2.3

Table 12.7: Summary of Safety Laboratory Results at Baseline, Week 14, Week 26, and Change from Baseline– Safety Population

	RVX000222 (N=243)		Placebo (N=80)	
	Value	Change from Baseline	Value	Change from Baseline
Direct Bilirubin (mg/dL)				
Baseline				
n	242		80	
Mean (SD)	0.18 (0.078)		0.18 (0.075)	
Median	0.20		0.20	
Min, Max	0.0, 0.5		0.1, 0.4	
Week 14				
n	224	223	75	75
Mean (SD)	0.21 (0.100)	0.03 (0.095)	0.18 (0.085)	0.00 (0.074)
Median	0.20	0.00	0.20	0.00
Min, Max	0.1, 0.7	-0.3, 0.5	0.1, 0.4	-0.1, 0.2
Week 26				
n	221	220	73	73
Mean (SD)	0.23 (0.105)	0.05 (0.086)	0.21 (0.098)	0.02 (0.075)
Median	0.20	0.00	0.20	0.00
Min, Max	0.1, 0.6	-0.1, 0.3	0.1, 0.5	-0.1, 0.2
GGT (U/L)				
Baseline				
n	243		80	
Mean (SD)	32.8 (16.75)		32.7 (22.56)	
Median	29.0		28.0	
Min, Max	8, 120		12, 198	
Week 14				
n	228	228	76	76
Mean (SD)	36.2 (21.80)	3.4 (17.04)	34.1 (20.80)	1.1 (25.25)
Median	30.0	2.0	27.0	-1.0
Min, Max	7, 170	-63, 98	11, 131	-143, 86
Week 26				
n	223	223	74	74
Mean (SD)	34.4 (19.57)	1.6 (17.30)	31.2 (17.44)	-1.7 (23.15)
Median	30.0	0.0	27.5	0.0
Min, Max	7, 109	-66, 75	12, 119	-140, 98
BUN (mg/dL)				
Baseline				
n	243		80	
Mean (SD)	16.4 (4.54)		15.8 (3.96)	
Median	16.0		15.0	
Min, Max	8, 40		9, 26	
Week 14				
n	228	228	76	76
Mean (SD)	17.5 (5.38)	1.1 (5.67)	17.2 (4.88)	1.4 (4.20)
Median	17.0	1.0	17.0	1.0
Min, Max	7, 46	-13, 27	9, 34	-7, 13

	RVX000222 (N=243)		Placebo (N=80)	
	Value	Change from Baseline	Value	Change from Baseline
Week 26				
n	223	223	74	74
Mean (SD)	16.9 (4.37)	0.5 (4.93)	16.5 (3.85)	0.6 (3.27)
Median	16.0	0.0	16.0	1.0
Min, Max	8, 39	-13, 30	6, 25	-5, 8
Creatinine kinase (U/L)				
Baseline				
n	243		80	
Mean (SD)	114.2 (81.64)		102.9 (73.33)	
Median	91.0		84.0	
Min, Max	20, 609		29, 539	
Week 14				
n	228	228	76	76
Mean (SD)	144.3 (109.87)	29.4 (112.56)	125.2 (80.44)	20.3 (93.21)
Median	118.0	19.0	96.0	20.0
Min, Max	29, 914	-539, 692	38, 403	-474, 286
Week 26				
n	223	223	74	74
Mean (SD)	163.6 (371.66)	49.8 (375.35)	127.0 (82.45)	20.4 (84.21)
Median	118.0	25.0	105.0	19.5
Min, Max	37, 5574	-542, 5482	30, 570	-459, 311
Creatinine (mg/dL)				
Baseline				
n	242		80	
Mean (SD)	0.948 (0.1914)		0.911 (0.1820)	
Median	0.940		0.930	
Min, Max	0.51, 1.44		0.53, 1.30	
Week 14				
n	228	227	75	75
Mean (SD)	0.978 (0.2348)	0.028 (0.1875)	0.919 (0.1764)	0.009 (0.1148)
Median	0.950	0.010	0.900	0.010
Min, Max	0.50, 2.72	-0.43, 1.44	0.51, 1.32	-0.25, 0.31
Week 26				
n	222	221	73	73
Mean (SD)	0.942 (0.2788)	-0.006 (0.2423)	0.874 (0.1764)	-0.041 (0.1297)
Median	0.920	-0.010	0.880	-0.050
Min, Max	0.52, 3.91	-0.43, 2.96	0.54, 1.30	-0.39, 0.31
Glucose (mg/dL)				
Baseline				
n	243		80	
Mean (SD)	118.2 (47.39)		109.2 (35.66)	
Median	105.0		102.5	
Min, Max	68, 458		68, 305	
Week 14				
n	228	228	75	75
Mean (SD)	123.2 (46.15)	4.3 (40.94)	119.0 (43.30)	9.6 (32.87)
Median	110.0	3.5	108.0	5.0
Min, Max	68, 317	-287, 180	74, 357	-89, 191
Week 26				
n	223	223	74	74
Mean (SD)	124.3 (47.38)	6.0 (36.73)	120.1 (45.07)	11.2 (35.61)
Median	108.0	4.0	103.0	1.0

	RVX000222 (N=243)		Placebo (N=80)	
	Value	Change from Baseline	Value	Change from Baseline
Min, Max	72, 400	-222, 200	72, 292	-58, 191

BUN = blood urea nitrogen; GGT = gamma –glutamyl transferase; SD = standard deviation
Source Data: Tables 14.3.2.2 and 14.3.2.3

Table 12.8: Summary of Fasting Lipid Profile at Baseline, Week 14, Week 26, and Change from Baseline – Safety Population

	RVX000222 (N=243)		Placebo (N=80)	
	Value	Change from Baseline	Value	Change from Baseline
Cholesterol (mg/dL)				
Baseline				
n	242		80	
Mean (SD)	160.7 (39.18)		160.8 (42.41)	
Median	154.0		152.5	
Min, Max	86, 282		85, 286	
Week 14				
n	228	227	76	76
Mean (SD)	144.0 (29.04)	-15.3 (38.00)	145.3 (27.38)	-14.8 (38.56)
Median	139.0	-11.0	143.0	-12.0
Min, Max	85, 263	-139, 82	73, 216	-100, 111
Week 26				
n	223	222	74	74
Mean (SD)	148.6 (36.68)	-10.3 (41.26)	143.4 (31.18)	-16.9 (34.34)
Median	143.0	-8.0	143.0	-15.0
Min, Max	81, 328	-135, 143	77, 270	-108, 38
HDL Cholesterol (mg/dL)				
Baseline				
n	243		80	
Mean (SD)	38.0 (7.48)		38.2 (6.97)	
Median	39.0		39.0	
Min, Max	12, 58		23, 58	
Week 14				
n	228	228	76	76
Mean (SD)	42.4 (10.15)	4.5 (9.15)	41.6 (8.18)	3.6 (8.08)
Median	42.0	4.0	39.0	4.0
Min, Max	19, 116	-15, 70	19, 69	-14, 30
Week 26				
n	223	223	74	74
Mean (SD)	41.9 (9.51)	3.9 (8.70)	40.8 (7.27)	2.6 (7.02)
Median	42.0	4.0	39.5	3.0
Min, Max	19, 81	-27, 42	23, 62	-11, 23
LDL Cholesterol (mg/dL)				
Baseline				
n	243		80	
Mean (SD)	97.3 (34.33)		96.5 (35.10)	
Median	93.0		93.0	
Min, Max	35, 212		34, 201	
Week 14				
n	228	228	76	76

	RVX000222 (N=243)		Placebo (N=80)	
	Value	Change from Baseline	Value	Change from Baseline
Mean (SD)	76.5 (23.62)	-19.4 (32.44)	78.6 (20.92)	-17.3 (32.70)
Median	73.0	-15.0	77.0	-11.5
Min, Max	31, 185	-124, 73	33, 147	-93, 101
Week 26				
n	223	223	74	74
Mean (SD)	80.5 (30.30)	-15.0 (35.73)	77.8 (25.43)	-17.8 (27.30)
Median	73.0	-12.0	73.0	-13.5
Min, Max	27, 236	-123, 100	25, 201	-101, 31
Non-HDL Cholesterol (mg/dL)				
Baseline				
n	243		80	
Mean (SD)	122.8 (37.57)		123.0 (41.90)	
Median	117.0		114.0	
Min, Max	58, 239		58, 251	
Week 14				
n	228	228	76	76
Mean (SD)	101.6 (28.12)	-19.8 (35.34)	103.3 (26.05)	-19.3 (38.16)
Median	99.5	-15.0	98.5	-15.5
Min, Max	50, 220	-131, 73	54, 178	-97, 116
Week 26				
n	223	223	74	74
Mean (SD)	106.8 (35.61)	-14.2 (39.07)	102.7 (29.12)	-19.8 (33.54)
Median	100.0	-14.0	98.5	-15.0
Min, Max	42, 282	-131, 131	51, 212	-101, 38
Triglycerides (mg/dL)				
Baseline				
n	243		80	
Mean (SD)	147.2 (70.33)		152.4 (82.39)	
Median	135.0		132.5	
Min, Max	37, 358		41, 392	
Week 14				
n	228	228	76	76
Mean (SD)	152.2 (87.21)	4.9 (75.62)	150.0 (86.55)	-1.4 (68.91)
Median	134.5	4.0	133.0	-4.5
Min, Max	48, 760	-235, 402	46, 641	-155, 289
Week 26				
n	223	223	74	74
Mean (SD)	160.1 (100.71)	12.8 (83.20)	154.0 (85.37)	1.6 (80.63)
Median	129.0	6.0	133.5	-3.5
Min, Max	35, 746	-187, 455	60, 643	-228, 311

SD = standard deviation
Source Data: Table 14.3.2.4

12.4.1.2 Individual Patient Changes

Shifts in hematology, serum chemistry, liver function tests, fasting lipid profile, and urinalysis are presented in End-of-Text Tables 14.3.3.1, 14.3.3.2, 14.3.3.3, 14.3.3.4, and 14.3.3.5.

12.4.1.3 Individual Clinically Significant Abnormalities

A summary of patients with elevated ALT/AST levels at any time during the treatment period is presented in Table 12.9.

Per the protocol, study drug was to be interrupted if a patient had ALT or AST >5x ULN at any time. Study drug was to be permanently discontinued if a patient met any of the following criteria:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 consecutive weeks
- ALT or AST >3x ULN AND bilirubin (total) >2x ULN
- ALT or AST >3x ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%).

Repeat ALT or AST levels were to be drawn every 3 (+3) days after dose discontinuation until the abnormal liver function tests returned to either ULN or baseline, or for at least 30 days after drug discontinuation. Patients were to continue to follow the protocol defined assessments until study completion.

Summary of ALT Elevations

Among RVX000222-treated patients, 39.9% (97/243) had elevated ALT levels >ULN, compared with 17.5% (14/80) of patients in the placebo group. In the RVX000222 group, 7.0% (17/243) had ALT elevations >3x ULN; among patients with any ALT elevation, 9.3% (9/97) had elevations >5x ULN and 6.2% (6/97) had elevations >8x ULN. All these liver enzyme elevations began between Weeks 4 and 11.

Patients with ALT elevations >8xULN

Six patients had an ALT >8xULN and were permanently withdrawn from treatment per protocol stopping rules. Two patients were on medications or had an underlying medical history (hepatitis) (patient 203-004 was receiving treatment with clavulinic acid and patient 705-021 had a positive HepB serology), which confounded the relatedness of the assessment. Two patients initially had ALT elevations >3xULN, which at follow-up visits had elevated to >8xULN and were consequently permanently withdrawn from treatment. In 1 patient, the elevation in liver function enzymes was deemed an SAE.

Patients with ALT elevations >5xULN and <8xULN

Three patients had ALT elevations >5x and <8xULN. One patient had an ALT elevation at Visit 12, was hospitalized and obtained a diagnosis of rhabdomyolysis, which was considered possibly related to RVX000222 by the investigator. However, upon further review by the Sponsor the event was deemed related to rosuvastatin use, not to RVX000222. Another patient had underlying hepatitis and had ALT >5xULN for more than two consecutive weeks, so treatment was permanently withdrawn. In all cases after suspension of study drug the elevated transaminases returned to below the upper limit of normal.

Patients with ALT elevations >3xULN and <5xULN

Eight (8) patients had ALT elevations >3x and <5xULN. None of these were dose interrupted. One of these patients, patient 503-003 did not complete the study, while the other patients did complete the trial on study drug. One patient (patient 501-029) had underlying medical history (hepatitis) which may have confounded the assessment. Generally, in this patient the elevations in liver enzymes were transient and returned to normal ranges.

Narratives for all patients with ALT >3x ULN are provided in Section 14.3.3.

Summary of AST Elevations

A smaller proportion of patients in both groups had elevated AST compared to ALT. Approximately 29.2% (71/243) of patients treated with RVX000222 had an AST elevation, compared with 8.8% (7/80) of patients in the placebo group. In the RVX000222 group, 4.1% (10/243) had AST elevations >3x ULN; among patients with any AST elevation, 7.0% (5/71) had elevations >5x ULN and 1.4% (1/71) had elevations >8x ULN. Among patients treated

with RVX000222 who had AST elevations >3x ULN but less than 5x ULN, 100.0% (10/10) had AST levels that returned. Study drug discontinuation was not required in any of these cases. AST elevations followed a similar pattern to ALT elevations.

Table 12.9: **Patients with Elevated ALT/AST at Any Time during the Treatment Period – Safety Population**

	RVX000222 (N=243) n (%)	Placebo (N=80) n (%)	P-value
Patients with elevated ALT or AST levels[a]	102 (42.0)	18 (22.5)	0.002[e]
Patients with elevated ALT levels[a]	97 (39.9)	14 (17.5)	
1x ULN but ≤3x ULN[a]	80 (32.9)	14 (17.5)	0.005[f]
3x ULN but ≤5x ULN[a]	8 (3.3)	0 (0.0)	
5x ULN but ≤8x ULN[a]	3 (1.2)	0 (0.0)	
ALT elevation >8x ULN[a,b]	6 (2.5)	0 (0.0)	
ALT elevation >3x ULN[a]	17 (7.0)	0 (0.0)	0.009[e]
First occurrence of ALT >3x ULN before or at Week 11 (Visit 7)[c]	16 (94.1)	0 (0.0)	NE
First occurrence of ALT >3x ULN after Week 11 (Visit 7)[c]	1 (5.9)	0 (0.0)	
ALT Elevation >5x ULN[d]	9 (9.3)	0 (0.0)	0.600[e]
ALT Elevation >8x ULN[b,d]	6 (6.2)	0 (0.0)	>0.999[e]
Patients with elevated AST levels[a]	71 (29.2)	7 (8.8)	
1x ULN but ≤3x ULN[a]	61 (25.1)	7 (8.8)	0.007[f]
3x ULN but ≤5x ULN[a]	5 (2.1)	0 (0.0)	
5x ULN but ≤8x ULN[a]	4 (1.6)	0 (0.0)	
AST elevation >8x ULN[a]	1 (0.4)	0 (0.0)	
AST elevation >3x ULN[a]	10 (4.1)	0 (0.0)	0.128[e]
First occurrence of drug induced AST >3x ULN before or at Week 11 (Visit 7)[c]	7 (70.0)	0 (0.0)	NE
First occurrence of AST >3x ULN after Week 11 (Visit 7)[c]	3 (30.0)	0 (0.0)	
AST Elevation >5x ULN[d]	5 (7.0)	0 (0.0)	>0.999[e]
AST Elevation >8x ULN[d]	1 (1.4)	0 (0.0)	>0.999[d]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NE = not estimable; ULN = upper limit of normal.

a: Enzyme elevations >1x ULN. Percentages based on the number of patients in each respective treatment group.

b: Two patients (703-004 and 205-005) with initial ALT elevations of >3x ULN had subsequent elevations of >8x ULN, however, these subsequent elevations occurred after study drug was discontinued. See narratives in Section 14.3.3 for further details on these 2 patients.

c: Percentages based on the number of patients with ALT/AST elevation >3x ULN. One patient (502-026) had her first occurrence of ALT >3x ULN after Week 11 (Visit 7) (Week 20, Visit 10 =173 U/L). It should be noted that the elevation of ALT in this patient was due to cholecystitis. Three patients had a first occurrence of AST >3x ULN after Week 11 (Visit 7): 502-026 (Week 20, Visit 10 =185 U/L), 601-014 (Week 17, Visit 9 =223 U/L), and 705-023 (Week 26, Visit 12 =294 U/L). See narratives in Section 14.3.3 for further details on these patients.

d: Percentages based on the number of patients with elevated ALT/AST levels.

e: P-value based on the Fisher's exact test.

f: P -value from a Cochran Mantel-Haenszel test. Patients with no elevated ALT/AST levels were considered the lowest category.
Source Data: Table 14.3.4

12.5 Vital Signs, Physical Examination Findings, and Other Observations Related to Safety

12.5.1 Vital signs

A summary of vital signs and changes from baseline for the Safety Population is presented in End-of-Text Table 14.3.5. Vital signs are listed for patients in the Safety Population in Listing 16.2.16. No clinically significant observations were noted.

12.5.2 Electrocardiogram

Summaries of 12–lead ECG parameters and shifts for the Safety Population are presented in End-of-Text Tables 14.3.6.1 and 14.3.6.2, respectively. Results of 12-lead ECGs and abnormal ECGs are listed in Listings 16.2.17.1 and 16.2.17.2 respectively for all patients in the Safety Population. Most results were not clinically significant. Of the clinically significant results, most were present at baseline.

12.5.3 Physical Examinations

A by-patient listing of physical examination findings is provided in Listing 16.2.8. None of the findings were considered clinically significant by the Sponsor.

12.6 Safety Conclusions

- The proportion of patients reporting at least 1 TEAE was similar in the RVX000222 and placebo groups (53.9% and 58.8%, respectively).
- At least one MACE occurred in 8.7% of patients. Major adverse cardiac events occurred more frequently in the placebo group than in the RVX000222 200 mg group (p=0.083, 13.8% vs. 7.0%, respectively).
- The most frequently occurring TEAE in both the study drug and placebo groups was angina pectoris (8.6% and 10.0% in the RVX000222 and placebo groups, respectively).
- Overall, the majority of TEAEs were mild or moderate in severity. A similar pattern of results was observed for both RVX000222 and placebo groups.
- The frequency of treatment-related AEs was higher in the RVX000222 group (13.6%) compared to the placebo group (8.8%). The most common treatment-related AEs reported in the study drug group were hepatic enzyme increase (5 patients [2.1%]) and ALT increase (4 patients [1.6%]).
- Serious TEAEs were reported for 13.6% of RVX000222-treated patients and 22.5% of placebo patients; of these, only 2 were related to treatment (0.8% of patients in the RVX000222 group and none in the placebo group). The related events were ALT elevation (in patient 705-021) and rhabdomyolysis (in patient 705-023). However, upon further review by the Sponsor the event rhabdomyolysis was deemed related to rosuvastatin use, not to RVX000222.
- Overall, 4.3% of patients discontinued study drug due to a TEAE, 4.9% and 2.5% in the treatment and placebo groups, respectively.
- One patient in the placebo group died due to a TEAE; no patients in the RVX000222 group died due to a TEAE.
- There were no clinically significant observations in laboratory results, with the exception of ALT/AST elevations, which occurred more frequently in the RVX000222 group compared with placebo (42.0% vs. 22.5%, p=0.002). In the

RVX000222 group, 7.0% (17/243) had ALT elevations >3x ULN; among patients with any ALT elevation, 9.3% (9/97) had elevations >5x ULN. In the RVX000222 group, 4.1% (10/243) had AST elevations >3x ULN; among patients with any AST elevation, 7.0% (5/71) had elevations >5x ULN.

- No clinically significant observations were made by the Sponsor with regard to vital signs, physical examinations, or ECG results.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

This was a 26-week active treatment period, double-blind, placebo-controlled, 2-arm parallel-group (allocation ratio 3:1) study of RVX000222 at a daily dose of 200 mg or matching placebo administered to patients with a low HDL-C level who required coronary angiography for a clinical indication. The objective of the study was to determine the 26-week impact of the ApoA-I inducer, RVX000222, on the burden of coronary atherosclerosis in patients with coronary disease and low HDL cholesterol levels.

Overall, 324 patients were randomized to the study of whom 323 received study drug; 243 were randomized to receive 200 mg RVX000222 and 80 patients were randomized to receive placebo. Overall, the majority of patients were male and Caucasian. No clinically meaningful demographic or baseline differences were noted among the treatment groups. The medical history was also similar for patients in the RVX000222 200 mg and placebo groups.

The primary endpoint of this study was not met. However, a reduction in PAV from baseline to 26 weeks was observed and there was a trend toward decreased PAV with RVX000222 ($p=0.08$). The study met the secondary endpoints in that significant reductions from baseline to Week 26 in TAV and TAV for the 10 mm sub-segment with the greatest disease burden at baseline were observed within the RVX000222 treatment group ($p<0.001$, for both). However, there were no significant differences between the RVX000222 treatment group and placebo for TAV or TAV for the 10 mm sub segment with the greatest disease burden. Additional secondary efficacy analyses showed a significant percent change from baseline to Week 26 in HDL-C, ApoA-I, hs-CRP, and large HDL particles in the RVX000222 group ($p<0.001$).

Virtual histology findings suggested that the actions of RVX000222 improved the NC/DC ratio, pointing to less vulnerability of the atherosclerotic plaque for rupture.

However, PK modeling seemed to indicate that, for patients with measured plasma levels below LLOQ (i.e. <1 ng/mL), the compliance for regular dosing was questionable.

Pre-specified subgroup analyses demonstrated significant changes in PAV at Week 26 in RVX000222 treated patients that had PAV above the baseline median, in patients without a

history of diabetes mellitus, in patients with large HDL and HDL-C that were below the baseline median.

Post-hoc subgroup analyses were performed on the subgroups of patients with baseline hs-CRP >2.0 mg/dL and those with below median HDL-C who were treated with rosuvastatin in addition to the study drug. In the RVX000222-treated patients with baseline hs-CRP >2.0 mg/dL, significant reductions in hs-CRP as well as significant atheroma regression as measured by PAV, TAV, and the worst 10 mm TAV segment were observed. Furthermore, in RVX000222 treated patients with hs-CRP >2.0 mg/dL, the incidence of MACE was lower by 63% versus placebo (p=0.023). This observation is of value in that hs-CRP of >2.0 mg/dL is well known to be clinically important in predicting cardiovascular risk. In the post-hoc subgroup analysis of patients with below median HDL (<39 mg/dL) at baseline who were taking either rosuvastatin or atorvastatin together with RVX000222, a statistically significant (p<0.002) PAV plaque regression among the subgroup of patients taking rosuvastatin was observed. This PAV regression exceeded the trial's pre-specified PAV endpoint by more than two-fold; however, those patients taking atorvastatin together with RVX000222 did not show the same benefit. The responder population (i.e. patients with HDL <39 mg/dL taking rosuvastatin and RVX000222) also surpassed secondary endpoints (TAV and TAV for the 10-mm sub-segment with the greatest disease burden at baseline), reflecting regression in coronary atherosclerosis.

Overall, RVX000222 was well tolerated, with a similar proportion of patients reporting TEAEs and a smaller proportion of patients reporting SAEs compared to placebo. There were few MACEs observed, with events occurring more frequently in the placebo group than in the RVX000222 group, though the difference was not statistically significant (p=0.083). ALT/AST increases were more common in the RVX000222 group, observed mainly between Weeks 4 and 11; however, levels returned to normal after suspension of the study drug.

The main contributing factor that may have impacted the results of this study was study duration. This study was the shortest IVUS trial reported to date with a treatment duration of only 6 months, compared to most trials of this nature which are 18-24 months in duration.

13.2 Overall Conclusions

- Though the primary endpoint of this study was not met, a reduction in PAV was observed and there was a trend toward decreased PAV for change from baseline to Week 26 with RVX000222 (p=0.08). However, there were no significant differences between the RVX000222 treatment group and placebo for TAV or TAV for the 10 mm sub segment with the greatest disease burden.
- The study met the secondary endpoints in that significant reductions from baseline to Week 26 in TAV and TAV for the 10 mm sub-segment with the greatest disease burden at baseline were observed within the RVX000222 treatment group ($p<0.001$, for both).
- Additional secondary efficacy analyses showed a significant percent change from baseline to Week 26 in HDL-C, ApoA-I, hs-CRP, and large HDL particles in the RVX000222 group ($p<0.001$).
- RVX000222 was well tolerated, with a similar proportion of patients reporting TEAEs and a smaller proportion of patients reporting SAEs in the RVX000222 group compared to the placebo group.
- Major adverse cardiac events occurred more frequently in the placebo group than in the RVX000222 group, though the difference was not statistically significant (p=0.083).
- ALT/AST increases were more common in the RVX000222 group, observed mainly between Weeks 4 and 11; however, levels returned to normal after suspension of the study drug.

14 END-OF-TEXT TABLES, FIGURES, AND GRAPHS

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14.1 DEMOGRAPHIC DATA

Table 14.1.1 Analysis Populations and Subject Disposition by Treatment Group - All Randomized Subjects

	RVX000222 200 mg n (%)	Placebo n (%)	Overall n (%)
Subjects randomized	xxx	xxx	xxx
Safety population [1]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Modified Intent-to-Treat (mITT) population [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Full Analysis Set (FAS) [3]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Per Protocol (PP) population [4]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed active treatment (Visit 2 through 12)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed study (Visit 2 through 13)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued prematurely	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for discontinuation:			
Adverse event(s)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal laboratory values	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol violation(s)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: [1] The Safety population includes all subjects who received at least one dose of study drug (active or control). The actual treatment taken will be used to summarize the Safety population.
[2] The mITT population includes all randomized subjects who received at least one dose of study drug. The randomized treatment assignment will be used to summarize the mITT population.
[3] The FAS will consist of all randomized patients who have received at least one dose of study drug and completed both baseline (Visit 1) and Week 26 (Visit 12) IVUS.
[4] The PP population includes all subjects who completed all both a baseline and follow-up IVUS procedure with no major protocol violations, have a study drug compliance rate of 80%, and have no major protocol violations.
This table corresponds to Listing 16.x.

Table 14.1.2 Protocol Deviations - Safety Population

Protocol Deviation	RVX000222 200 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Did not meet inclusion/exclusion criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)
Visit not within protocol specified window	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study medication compliance less than 80%	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			

Notes: This table corresponds to Listing 16.x.

Table 14.1.3.1 Demographic and Baseline Characteristics - Safety Population

	RVX000222 200 mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
Gender			
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race			
Caucasian	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black/African American	xx (xx.x)	xx (xx.x)	xx (xx.x)
American Indian/Alaska Native	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian/Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity			
Hispanic/Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-hispanic/Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Age (years)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, max	xx, xx	xx, xx	xx, xx
Age group (years)			
< 50	xx (xx.x)	xx (xx.x)	xx (xx.x)
50 – 65	xx (xx.x)	xx (xx.x)	xx (xx.x)
>65	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: This table corresponds to Listing 16.x.

Table 14.1.3.1 Demographic and Baseline Characteristics - Safety Population

	RVX000222 200 mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
Height (cm)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Weight (kg)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Tobacco usage history			
Never consumed tobacco	xx (xx.x)	xx (xx.x)	xx (xx.x)
Previously consumed tobacco	xx (xx.x)	xx (xx.x)	xx (xx.x)
Currently consume tobacco	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alcohol usage history			
Never consumed tobacco	xx (xx.x)	xx (xx.x)	xx (xx.x)
Previously consumed tobacco	xx (xx.x)	xx (xx.x)	xx (xx.x)
Currently consume tobacco	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.1.3.2 Demographic and Baseline Characteristics – Modified Intent-to-Treat Population

Table 14.1.3.3 Demographic and Baseline Characteristics – Full Analysis Set

Table 14.1.4.1.1 Significant Cardiovascular Medical History - Safety Population

	RVX000222 200 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Myocardial infarction	xx (xx.x)	xx (xx.x)	xx (xx.x)
Coronary artery bypass graft (CABG) surgery	xx (xx.x)	xx (xx.x)	xx (xx.x)
Percutaneous coronary intervention (PCI)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hypertension	xx (xx.x)	xx (xx.x)	xx (xx.x)
Congestive heart failure	xx (xx.x)	xx (xx.x)	xx (xx.x)
Class			
1	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina	xx (xx.x)	xx (xx.x)	xx (xx.x)
Type			
Stable	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unstable	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hospitalization required	xx (xx.x)	xx (xx.x)	xx (xx.x)
Classification			
0	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)
Metabolic syndrome	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: This table corresponds to Listing 16.x.

Table 14.1.4.1.1 Significant Cardiovascular Medical History - Safety Population

	RVX000222 200 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Dislipidemia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diabetes	xx (xx.x)	xx (xx.x)	xx (xx.x)
Type			
1	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stroke	xx (xx.x)	xx (xx.x)	xx (xx.x)
Transient ischemic attack	xx (xx.x)	xx (xx.x)	xx (xx.x)
Peripheral vascular disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Arrhythmia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Atrial fibrillation	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.1.4.1.2 Significant Cardiovascular Medical History - Safety Population – mITT

Table 14.1.4.1.3 Significant Cardiovascular Medical History - Safety Population – FAS

Table 14.1.4.2 Other Significant Medical History by Body System - Safety Population

	RVX000222 200 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Subjects with any significant/past medical conditions	xx (xx.x)	xx (xx.x)	xx (xx.x)
Body System	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 4	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			

Notes: Medical history coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 14.1.
This table corresponds to Listing 16.x.

Table 14.1.5 Study Drug Exposure and Compliance - Safety Population

	RVX000222 200 mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
Days on Treatment [1]			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Active treatment phase duration (days) [2]			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Study duration (days) [3]			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Percent compliance [4]			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx

Notes: [1] Days on treatment = last dose date – first dose date +1.
[2] Active treatment phase duration = last visit date (through Visit 12) – randomization date +1.
[3] Study duration = last visit date (through Visit 13) – randomization date +1.
[4] Percent compliance = 100 x [(capsules dispensed–capsules returned)/(4 x (last dose date - first dose date+1))].
This table corresponds to Listing 16.x.

Table 14.1.6.1 Prior Medications - Safety Population

ATC Level 4 Term/ Standardized Drug Name	RVX000222 200 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Subjects with at least one prior medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			
ATC Level 4 Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			

Notes: Prior medications are defined as non-study medications with an end date prior to the first dose of study drug. Subjects reporting a prior medication more than once are only counted once for that medication.
Medications coded using the WHO Drug Dictionary 2001Q1.
This table corresponds to Listing 16.x.

Table 14.1.6.2 Concomitant Medications - Safety Population

ATC Level 4 Term/ Standardized Drug Name	RVX000222 200 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Subjects with at least one concomitant medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			
ATC Level 4 Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			

Notes: Concomitant medications are defined as non-study medications with a start date or end date on the first dose of study drug through the patient's last visit in the study. Medications with partial onset dates that indicate usage from the first study drug date or medications with completely missing start or stop dates will be classified as concomitant. Subjects reporting concomitant medications more than once are only counted once for that medication. Medications coded using the WHO Drug Dictionary 2011Q1.
This table corresponds to Listing 16.x.

Table 14.1.6.3 Concomitant Statin Medications - Safety Population

ATC Level 4 Term/ Standardized Drug Name	RVX000222 200 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Subjects with at least one statin medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			
ATC Level 4 Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standardized Drug Name 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .			

Notes: Concomitant statin medications are defined as study medications with a start date or end date on the first dose of study drug through the patient’s last visit in the study. Medications with partial onset dates that indicate usage from the first study drug date or medications with completely missing start or stop dates will be classified as concomitant. Subjects reporting concomitant statin medications more than once are only counted once for that medication. Statin medications coded using the WHO Drug Dictionary 2011Q1. This table corresponds to Listing 16.x.

14.2 EFFICACY DATA

Table 14.2.1.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - mITT Population

	RVX000222 200 mg (N =xxx)	Placebo (N =xx)
Baseline (Visit 1)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 26 (Visit 12)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 26 change from baseline		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)
P-value [1]	0.xxx*	0.xxx
ANCOVA [2]		
LS Mean (SE)	x.x (x.x)	x.x (x.x)
95% CI of LS Mean	(x.x, x.x)	(x.x, x.x)
P-value	0.xxx	

Notes: *Primary efficacy endpoint.
[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.2.1.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) – FAS

Table 14.2.1.3 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) – Per Protocol Population

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.0. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS
Full FAS Dataset - Replicate

	RVX000222 200 mg daily (N=208)	Placebo (N=73)
Baseline (Visit 1)		
n	208	73
Mean (SD)	38.35 ± (8.366)	36.83 ± (9.374)
Median	38.13	36.19
Min, Max	17.91, 60.46	20.41, 64.39
Week 26 (Visit 12)		
n	208	73
Mean (SD)	38.16 ± (8.440)	36.49 ± (9.184)
Median	37.83	36.11
Min, Max	17.45, 65.88	19.35, 62.66
Week 26 change from baseline		
n	208	73
Mean (SD)	-0.20 ± (2.419)	-0.34 ± (2.275)
Median	-0.40	-0.30
Min, Max	-7.21, 8.29	-8.24, 5.49
95% CI	(-0.53, 0.13)	(-0.87, 0.19)
P-value[1]	0.0801	0.2279
ANCOVA [2]		
LS Mean (SE)	-0.18 (0.164)	-0.38 (0.277)
95% CI of LS Mean	(-0.50, 0.14)	(-0.93, 0.16)
P-value	0.5338	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.5. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS Below Median HDL-c at Baseline

	RVX000222 200 mg daily (N=92)	Placebo (N=34)
Baseline (Visit 1)		
n	92	34
Mean (SD)	39.05 ± (8.667)	39.13 ± (9.975)
Median	39.02	36.51
Min, Max	19.14, 58.46	21.14, 64.39
Week 26 (Visit 12)		
n	92	34
Mean (SD)	38.68 ± (8.851)	38.30 ± (9.478)
Median	39.48	35.70
Min, Max	19.20, 56.60	21.30, 62.66
Week 26 change from baseline		
n	92	34
Mean (SD)	-0.37 ± (2.613)	-0.83 ± (1.964)
Median	-0.66	-0.79
Min, Max	-5.06, 8.29	-5.58, 3.72
95% CI	(-0.91, 0.17)	(-1.52, -0.15)
P-value[1]	0.0362	0.0163
ANCOVA [2]		
LS Mean (SE)	-0.37 (0.255)	-0.83 (0.419)
95% CI of LS Mean	(-0.88, 0.13)	(-1.66, 0.00)
P-value	0.3545	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.6. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS At or Above Median HDL-c at Baseline

	RVX000222 200 mg daily (N=114)	Placebo (N=39)
Baseline (Visit 1)		
n	114	39
Mean (SD)	37.81 ± (8.059)	34.83 ± (8.443)
Median	37.43	35.09
Min, Max	17.91, 60.46	20.41, 49.71
Week 26 (Visit 12)		
n	114	39
Mean (SD)	37.74 ± (8.079)	34.92 ± (8.738)
Median	37.09	36.19
Min, Max	17.45, 65.88	19.35, 51.18
Week 26 change from baseline		
n	114	39
Mean (SD)	-0.06 ± (2.272)	0.09 ± (2.460)
Median	-0.09	0.53
Min, Max	-7.21, 5.49	-8.24, 5.49
95% CI	(-0.48, 0.36)	(-0.71, 0.89)
P-value[1]	0.7097	0.6413
ANCOVA [2]		
LS Mean (SE)	-0.04 (0.218)	0.02 (0.374)
95% CI of LS Mean	(-0.47, 0.39)	(-0.72, 0.76)
P-value	0.8815	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.7. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS Rosuvastatin

	RVX000222 200 mg daily (N=115)	Placebo (N=44)
Baseline (Visit 1)		
n	115	44
Mean (SD)	38.56 ± (8.629)	36.33 ± (9.946)
Median	37.84	35.91
Min, Max	17.91, 58.46	21.14, 64.39
Week 26 (Visit 12)		
n	115	44
Mean (SD)	37.99 ± (8.430)	35.68 ± (9.801)
Median	37.87	34.49
Min, Max	17.45, 56.60	19.35, 62.66
Week 26 change from baseline		
n	115	44
Mean (SD)	-0.57 ± (2.253)	-0.65 ± (1.978)
Median	-0.61	-0.61
Min, Max	-6.72, 8.25	-8.24, 4.07
95% CI	(-0.98, -0.15)	(-1.25, -0.05)
P-value[1]	0.0017	0.0265
ANCOVA [2]		
LS Mean (SE)	-0.54 (0.200)	-0.73 (0.324)
95% CI of LS Mean	(-0.93, -0.14)	(-1.37, -0.09)
P-value	0.6130	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.8. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS Atorvastatin

	RVX000222 200 mg daily (N=97)	Placebo (N=31)
Baseline (Visit 1)		
n	97	31
Mean (SD)	38.24 ± (8.066)	36.65 ± (8.215)
Median	38.24	35.39
Min, Max	19.14, 60.46	20.41, 51.44
Week 26 (Visit 12)		
n	97	31
Mean (SD)	38.48 ± (8.491)	36.62 ± (7.997)
Median	37.79	36.11
Min, Max	18.43, 65.88	20.14, 54.64
Week 26 change from baseline		
n	97	31
Mean (SD)	0.23 ± (2.527)	-0.02 ± (2.623)
Median	0.19	0.02
Min, Max	-7.21, 8.29	-5.58, 5.49
95% CI	(-0.28, 0.74)	(-0.99, 0.94)
P-value[1]	0.5376	0.9087
ANCOVA [2]		
LS Mean (SE)	0.24 (0.260)	-0.04 (0.461)
95% CI of LS Mean	(-0.28, 0.75)	(-0.95, 0.87)
P-value	0.5960	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.9. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter

	RVX000222 200 mg daily (N=81)	Placebo (N=33)
Baseline (Visit 1)		
n	81	33
Mean (SD)	39.27 ± (8.251)	37.79 ± (9.400)
Median	38.79	36.15
Min, Max	20.75, 60.46	20.41, 51.44
Week 26 (Visit 12)		
n	81	33
Mean (SD)	38.89 ± (8.637)	36.73 ± (9.194)
Median	38.84	35.28
Min, Max	18.43, 65.88	20.14, 54.64
Week 26 change from baseline		
n	81	33
Mean (SD)	-0.39 ± (2.685)	-1.06 ± (2.473)
Median	-0.60	-1.37
Min, Max	-7.21, 8.29	-8.24, 3.72
95% CI	(-0.98, 0.21)	(-1.94, -0.18)
P-value[1]	0.0692	0.0130
ANCOVA [2]		
LS Mean (SE)	-0.38 (0.293)	-1.08 (0.459)
95% CI of LS Mean	(-0.96, 0.20)	(-1.99, -0.17)
P-value	0.1965	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.10. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter

	RVX000222 200 mg daily (N=127)	Placebo (N=40)
Baseline (Visit 1)		
n	127	40
Mean (SD)	37.77 ± (8.419)	36.04 ± (9.398)
Median	37.50	36.44
Min, Max	17.91, 58.46	21.14, 64.39
Week 26 (Visit 12)		
n	127	40
Mean (SD)	37.69 ± (8.313)	36.29 ± (9.288)
Median	37.71	36.24
Min, Max	17.45, 56.60	19.35, 62.66
Week 26 change from baseline		
n	127	40
Mean (SD)	-0.08 ± (2.236)	0.25 ± (1.932)
Median	-0.19	0.33
Min, Max	-5.06, 8.25	-4.08, 5.49
95% CI	(-0.47, 0.32)	(-0.36, 0.87)
P-value[1]	0.4350	0.3817
ANCOVA [2]		
LS Mean (SE)	-0.06 (0.190)	0.20 (0.340)
95% CI of LS Mean	(-0.43, 0.32)	(-0.47, 0.87)
P-value	0.5131	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.11. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS Prior Statin

	RVX000222 200 mg daily (N=198)	Placebo (N=72)
Baseline (Visit 1)		
n	198	72
Mean (SD)	38.13 ± (8.410)	36.45 ± (8.847)
Median	37.83	36.17
Min, Max	17.91, 60.46	20.41, 56.40
Week 26 (Visit 12)		
n	198	72
Mean (SD)	38.02 ± (8.530)	36.13 ± (8.704)
Median	37.75	35.89
Min, Max	17.45, 65.88	19.35, 55.50
Week 26 change from baseline		
n	198	72
Mean (SD)	-0.11 ± (2.389)	-0.32 ± (2.285)
Median	-0.27	-0.30
Min, Max	-7.21, 8.29	-8.24, 5.49
95% CI	(-0.44, 0.23)	(-0.86, 0.22)
P-value[1]	0.2189	0.2769
ANCOVA [2]		
LS Mean (SE)	-0.09 (0.167)	-0.36 (0.278)
95% CI of LS Mean	(-0.42, 0.24)	(-0.91, 0.19)
P-value	0.4062	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.12. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS Statin Naive

	RVX000222 200 mg daily (N=10)	Placebo (N=1)
Baseline (Visit 1)		
n	10	1
Mean (SD)	42.83 ± (6.190)	64.39 ± (----)
Median	42.24	64.39
Min, Max	34.29, 53.60	64.39, 64.39
Week 26 (Visit 12)		
n	10	1
Mean (SD)	40.83 ± (6.133)	62.66 ± (----)
Median	41.51	62.66
Min, Max	32.47, 50.64	62.66, 62.66
Week 26 change from baseline		
n	10	1
Mean (SD)	-2.00 ± (2.413)	-1.73 ± (----)
Median	-2.31	-1.73
Min, Max	-6.72, 1.59	-1.73, -1.73
95% CI	(-3.73, -0.28)	(,)
P-value[1]	0.0195	1.0000
ANCOVA [2]		
LS Mean (SE)	-2.17 (0.833)	-0.06 (3.631)
95% CI of LS Mean	(-4.09, -0.25)	(-8.43, 8.32)
P-value	0.6036	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.13. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter and Rosuvastatin

	RVX000222 200 mg daily (N=40)	Placebo (N=16)
Baseline (Visit 1)		
n	40	16
Mean (SD)	40.08 ± (8.168)	37.40 ± (9.036)
Median	38.91	35.91
Min, Max	25.78, 56.64	24.19, 50.08
Week 26 (Visit 12)		
n	40	16
Mean (SD)	38.84 ± (8.102)	35.85 ± (8.746)
Median	38.36	34.41
Min, Max	25.18, 55.39	21.88, 49.57
Week 26 change from baseline		
n	40	16
Mean (SD)	-1.25 ± (2.062)	-1.56 ± (2.164)
Median	-1.31	-1.46
Min, Max	-6.72, 4.38	-8.24, 1.41
95% CI	(-1.90, -0.59)	(-2.71, -0.40)
P-value[1]	0.0002	0.0034
ANCOVA [2]		
LS Mean (SE)	-1.21 (0.329)	-1.65 (0.522)
95% CI of LS Mean	(-1.87, -0.55)	(-2.69, -0.60)
P-value	0.4855	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.14. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter and Atorvastatin

	RVX000222 200 mg daily (N=44)	Placebo (N=19)
Baseline (Visit 1)		
n	44	19
Mean (SD)	38.41 ± (8.084)	37.30 ± (9.843)
Median	38.77	35.32
Min, Max	20.75, 60.46	20.41, 51.44
Week 26 (Visit 12)		
n	44	19
Mean (SD)	38.78 ± (8.955)	36.56 ± (9.746)
Median	38.35	35.28
Min, Max	18.43, 65.88	20.14, 54.64
Week 26 change from baseline		
n	44	19
Mean (SD)	0.37 ± (2.929)	-0.75 ± (2.634)
Median	0.14	-0.78
Min, Max	-7.21, 8.29	-5.58, 3.72
95% CI	(-0.52, 1.26)	(-2.02, 0.52)
P-value[1]	0.5347	0.2579
ANCOVA [2]		
LS Mean (SE)	0.37 (0.432)	-0.74 (0.658)
95% CI of LS Mean	(-0.50, 1.23)	(-2.05, 0.58)
P-value	0.1659	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.15. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter and Rosuvastatin

	RVX000222 200 mg daily (N=75)	Placebo (N=28)
Baseline (Visit 1)		
n	75	28
Mean (SD)	37.74 ± (8.810)	35.71 ± (10.541)
Median	37.50	35.64
Min, Max	17.91, 58.46	21.14, 64.39
Week 26 (Visit 12)		
n	75	28
Mean (SD)	37.54 ± (8.619)	35.58 ± (10.510)
Median	37.71	34.88
Min, Max	17.45, 56.60	19.35, 62.66
Week 26 change from baseline		
n	75	28
Mean (SD)	-0.21 ± (2.280)	-0.13 ± (1.694)
Median	-0.31	-0.26
Min, Max	-5.06, 8.25	-4.08, 4.07
95% CI	(-0.73, 0.32)	(-0.79, 0.52)
P-value[1]	0.2015	0.6896
ANCOVA [2]		
LS Mean (SE)	-0.18 (0.244)	-0.20 (0.401)
95% CI of LS Mean	(-0.67, 0.30)	(-0.99, 0.60)
P-value	0.9792	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.1.2.16. Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter and Atorvastatin

	RVX000222 200 mg daily (N=53)	Placebo (N=12)
Baseline (Visit 1)		
n	53	12
Mean (SD)	38.10 ± (8.127)	35.61 ± (4.859)
Median	37.82	36.16
Min, Max	19.14, 53.70	26.05, 44.85
Week 26 (Visit 12)		
n	53	12
Mean (SD)	38.22 ± (8.165)	36.73 ± (4.356)
Median	37.79	36.57
Min, Max	20.89, 54.19	26.67, 44.76
Week 26 change from baseline		
n	53	12
Mean (SD)	0.12 ± (2.159)	1.12 ± (2.255)
Median	0.48	1.25
Min, Max	-4.36, 5.49	-3.60, 5.49
95% CI	(-0.48, 0.71)	(-0.31, 2.55)
P-value[1]	0.8103	0.1099
ANCOVA [2]		
LS Mean (SE)	0.14 (0.298)	1.03 (0.630)
95% CI of LS Mean	(-0.46, 0.73)	(-0.23, 2.29)
P-value	0.2051	

[1] P-value comparing within group change using the Wilcoxon signed-rand test.
[2] P-value from an ANCOVA with change in PAV as the response variable, baseline PAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_pav (Date Generated 01AUG13:20:34)

Table 14.2.2.1 Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) – mITT Population

	RVX000222 200 mg (N =xxx)	Placebo (N =xx)
Baseline (Visit 1)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 26 (Visit 12)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 26 change from baseline		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)
P-value [1]	0.xxx	0.xxx
ANCOVA [2]		
LS Mean (SE)	x.x (x.x)	x.x (x.x)
95% CI of LS Mean	(x.x, x.x)	(x.x, x.x)
P-value	0.xxx	

Notes: [1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.2.2.2 Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) – FAS

Table 14.2.2.3 Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) – Per Protocol Population

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.0. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS
Full FAS Dataset - Replicate

	RVX000222 200 mg daily (N=208)	Placebo (N=73)
Baseline (Visit 1)		
n	208	73
Mean (SD)	210.4 ± (83.273)	173.6 ± (74.362)
Median	199.91	154.78
Min, Max	37.57, 517.22	68.96, 367.20
Week 26 (Visit 12)		
n	208	73
Mean (SD)	206.2 ± (83.738)	169.8 ± (69.683)
Median	198.60	156.59
Min, Max	37.83, 504.87	67.34, 346.80
Week 26 change from baseline		
n	208	73
Mean (SD)	-4.18 ± (17.228)	-3.78 ± (12.622)
Median	-3.20	-3.77
Min, Max	-58.93, 44.17	-38.63, 28.78
95% CI	(-6.54, -1.83)	(-6.72, -0.83)
P-value[1]	0.0006	0.0127
ANCOVA [2]		
LS Mean (SE)	-3.91 (1.117)	-4.56 (1.903)
95% CI of LS Mean	(-6.10, -1.71)	(-8.31, -0.81)
P-value	0.8649	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.5. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Below Median HDL-c at Baseline

	RVX000222 200 mg daily (N=92)	Placebo (N=34)
Baseline (Visit 1)		
n	92	34
Mean (SD)	211.9 ± (91.789)	193.0 ± (86.225)
Median	199.01	178.22
Min, Max	37.57, 517.22	71.90, 367.20
Week 26 (Visit 12)		
n	92	34
Mean (SD)	204.1 ± (92.359)	184.9 ± (79.125)
Median	190.53	173.82
Min, Max	37.83, 504.87	74.74, 346.80
Week 26 change from baseline		
n	92	34
Mean (SD)	-7.81 ± (15.421)	-8.12 ± (13.990)
Median	-7.79	-6.92
Min, Max	-50.67, 31.53	-38.63, 28.78
95% CI	(-11.0, -4.61)	(-13.0, -3.24)
P-value[1]	<.0001	0.0019
ANCOVA [2]		
LS Mean (SE)	-7.66 (1.555)	-8.51 (2.563)
95% CI of LS Mean	(-10.7, -4.58)	(-13.6, -3.43)
P-value	0.8147	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.6. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS At or Above Median HDL-c at Baseline

	RVX000222 200 mg daily (N=114)	Placebo (N=39)
Baseline (Visit 1)		
n	114	39
Mean (SD)	208.2 ± (76.411)	156.7 ± (58.211)
Median	200.11	140.61
Min, Max	52.30, 423.63	68.96, 273.50
Week 26 (Visit 12)		
n	114	39
Mean (SD)	207.2 ± (76.978)	156.7 ± (58.156)
Median	200.58	144.47
Min, Max	53.14, 425.11	67.34, 281.59
Week 26 change from baseline		
n	114	39
Mean (SD)	-1.05 ± (18.121)	0.01 ± (10.018)
Median	1.23	0.56
Min, Max	-58.93, 44.17	-19.79, 23.96
95% CI	(-4.41, 2.32)	(-3.24, 3.26)
P-value[1]	0.5386	0.9955
ANCOVA [2]		
LS Mean (SE)	-0.79 (1.560)	-0.75 (2.729)
95% CI of LS Mean	(-3.87, 2.30)	(-6.15, 4.64)
P-value	0.9560	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.7. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Rosuvastatin

	RVX000222 200 mg daily (N=115)	Placebo (N=44)
Baseline (Visit 1)		
n	115	44
Mean (SD)	215.2 ± (87.318)	176.3 ± (73.808)
Median	201.35	162.76
Min, Max	51.77, 473.98	68.96, 350.84
Week 26 (Visit 12)		
n	115	44
Mean (SD)	209.3 ± (87.564)	172.1 ± (68.546)
Median	200.39	162.40
Min, Max	53.14, 469.29	67.34, 323.15
Week 26 change from baseline		
n	115	44
Mean (SD)	-5.89 ± (17.350)	-4.22 ± (12.573)
Median	-5.24	-3.54
Min, Max	-50.67, 44.17	-38.63, 28.78
95% CI	(-9.09, -2.68)	(-8.04, -0.40)
P-value[1]	0.0004	0.0312
ANCOVA [2]		
LS Mean (SE)	-5.55 (1.503)	-5.09 (2.453)
95% CI of LS Mean	(-8.52, -2.58)	(-9.94, -0.25)
P-value	0.6445	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.8. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Atorvastatin

	RVX000222 200 mg daily (N=97)	Placebo (N=31)
Baseline (Visit 1)		
n	97	31
Mean (SD)	205.9 ± (79.267)	163.7 ± (76.090)
Median	196.51	138.33
Min, Max	37.57, 517.22	71.90, 367.20
Week 26 (Visit 12)		
n	97	31
Mean (SD)	203.8 ± (80.346)	160.2 ± (72.636)
Median	195.39	138.89
Min, Max	37.83, 504.87	74.74, 346.80
Week 26 change from baseline		
n	97	31
Mean (SD)	-2.11 ± (16.769)	-3.55 ± (12.627)
Median	0.32	-3.88
Min, Max	-58.93, 35.54	-30.48, 23.96
95% CI	(-5.49, 1.27)	(-8.18, 1.08)
P-value[1]	0.2188	0.1277
ANCOVA [2]		
LS Mean (SE)	-1.91 (1.622)	-4.18 (2.908)
95% CI of LS Mean	(-5.12, 1.30)	(-9.94, 1.57)
P-value	0.4266	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.9. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter

	RVX000222 200 mg daily (N=81)	Placebo (N=33)
Baseline (Visit 1)		
n	81	33
Mean (SD)	206.6 ± (76.514)	171.4 ± (82.880)
Median	199.72	153.72
Min, Max	69.81, 406.16	71.90, 367.20
Week 26 (Visit 12)		
n	81	33
Mean (SD)	201.6 ± (76.244)	165.3 ± (75.943)
Median	198.40	147.35
Min, Max	62.19, 388.16	74.74, 346.80
Week 26 change from baseline		
n	81	33
Mean (SD)	-5.00 ± (15.421)	-6.09 ± (12.358)
Median	-3.53	-6.62
Min, Max	-58.93, 35.54	-35.69, 19.07
95% CI	(-8.41, -1.59)	(-10.5, -1.71)
P-value[1]	0.0046	0.0080
ANCOVA [2]		
LS Mean (SE)	-4.53 (1.591)	-7.22 (2.515)
95% CI of LS Mean	(-7.69, -1.38)	(-12.2, -2.24)
P-value	0.3404	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.10. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter

	RVX000222 200 mg daily (N=127)	Placebo (N=40)
Baseline (Visit 1)		
n	127	40
Mean (SD)	212.9 ± (87.519)	175.4 ± (67.564)
Median	200.10	157.65
Min, Max	37.57, 517.22	68.96, 350.84
Week 26 (Visit 12)		
n	127	40
Mean (SD)	209.2 ± (88.351)	173.5 ± (64.813)
Median	198.80	165.10
Min, Max	37.83, 504.87	67.34, 323.15
Week 26 change from baseline		
n	127	40
Mean (SD)	-3.66 ± (18.327)	-1.87 ± (12.671)
Median	-3.06	0.18
Min, Max	-53.61, 44.17	-38.63, 28.78
95% CI	(-6.88, -0.44)	(-5.92, 2.19)
P-value[1]	0.0261	0.3570
ANCOVA [2]		
LS Mean (SE)	-3.49 (1.527)	-2.42 (2.748)
95% CI of LS Mean	(-6.50, -0.47)	(-7.85, 3.01)
P-value	0.6523	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.11. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Prior Statin

	RVX000222 200 mg daily (N=198)	Placebo (N=72)
Baseline (Visit 1)		
n	198	72
Mean (SD)	211.0 ± (84.429)	171.2 ± (72.002)
Median	201.12	154.51
Min, Max	37.57, 517.22	68.96, 367.20
Week 26 (Visit 12)		
n	198	72
Mean (SD)	206.8 ± (84.930)	167.7 ± (67.737)
Median	200.58	156.42
Min, Max	37.83, 504.87	67.34, 346.80
Week 26 change from baseline		
n	198	72
Mean (SD)	-4.17 ± (17.353)	-3.51 ± (12.510)
Median	-3.20	-3.09
Min, Max	-58.93, 44.17	-38.63, 28.78
95% CI	(-6.60, -1.74)	(-6.45, -0.57)
P-value[1]	0.0009	0.0198
ANCOVA [2]		
LS Mean (SE)	-3.88 (1.151)	-4.30 (1.929)
95% CI of LS Mean	(-6.15, -1.62)	(-8.10, -0.51)
P-value	0.9443	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.12. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Statin Naive

	RVX000222 200 mg daily (N=10)	Placebo (N=1)
Baseline (Visit 1)		
n	10	1
Mean (SD)	198.7 ± (57.448)	345.8 ± (----)
Median	180.20	345.76
Min, Max	116.18, 300.53	345.76, 345.76
Week 26 (Visit 12)		
n	10	1
Mean (SD)	194.3 ± (56.764)	323.2 ± (----)
Median	182.12	323.15
Min, Max	137.69, 309.32	323.15, 323.15
Week 26 change from baseline		
n	10	1
Mean (SD)	-4.35 ± (15.324)	-22.6 ± (----)
Median	-6.02	-22.60
Min, Max	-21.77, 21.51	-22.60, -22.60
95% CI	(-15.3, 6.61)	(,)
P-value[1]	0.3922	
ANCOVA [2]		
LS Mean (SE)	-4.99 (5.208)	-16.3 (20.24)
95% CI of LS Mean	(-17.0, 7.02)	(-62.9, 30.42)
P-value	0.3412	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.13. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter and Rosuvastatin

	RVX000222 200 mg daily (N=40)	Placebo (N=16)
Baseline (Visit 1)		
n	40	16
Mean (SD)	205.6 ± (75.501)	171.9 ± (81.300)
Median	202.52	162.23
Min, Max	73.26, 394.14	75.96, 341.30
Week 26 (Visit 12)		
n	40	16
Mean (SD)	197.1 ± (74.157)	164.7 ± (74.124)
Median	200.07	156.42
Min, Max	62.19, 368.17	74.74, 316.37
Week 26 change from baseline		
n	40	16
Mean (SD)	-8.55 ± (13.376)	-7.22 ± (11.666)
Median	-7.78	-7.66
Min, Max	-32.34, 21.51	-35.69, 14.91
95% CI	(-12.8, -4.27)	(-13.4, -1.01)
P-value[1]	0.0002	0.0257
ANCOVA [2]		
LS Mean (SE)	-8.05 (1.971)	-8.48 (3.143)
95% CI of LS Mean	(-12.0, -4.09)	(-14.8, -2.18)
P-value	0.9012	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.14. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter and Atorvastatin

	RVX000222 200 mg daily (N=44)	Placebo (N=19)
Baseline (Visit 1)		
n	44	19
Mean (SD)	205.8 ± (75.965)	162.2 ± (85.982)
Median	195.45	134.75
Min, Max	69.81, 406.16	71.90, 367.20
Week 26 (Visit 12)		
n	44	19
Mean (SD)	204.1 ± (76.540)	157.0 ± (79.967)
Median	193.14	119.09
Min, Max	70.31, 388.16	74.74, 346.80
Week 26 change from baseline		
n	44	19
Mean (SD)	-1.71 ± (16.476)	-5.21 ± (12.500)
Median	0.30	-6.21
Min, Max	-58.93, 35.54	-30.48, 19.07
95% CI	(-6.72, 3.30)	(-11.2, 0.81)
P-value[1]	0.4940	0.0858
ANCOVA [2]		
LS Mean (SE)	-1.22 (2.321)	-6.36 (3.578)
95% CI of LS Mean	(-5.86, 3.42)	(-13.5, 0.80)
P-value	0.1862	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.15. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter and Rosuvastatin

	RVX000222 200 mg daily (N=75)	Placebo (N=28)
Baseline (Visit 1)		
n	75	28
Mean (SD)	220.3 ± (93.087)	178.9 ± (70.609)
Median	200.90	165.32
Min, Max	51.77, 473.98	68.96, 350.84
Week 26 (Visit 12)		
n	75	28
Mean (SD)	215.9 ± (93.751)	176.3 ± (66.174)
Median	200.39	165.10
Min, Max	53.14, 469.29	67.34, 323.15
Week 26 change from baseline		
n	75	28
Mean (SD)	-4.46 ± (19.068)	-2.51 ± (12.952)
Median	-4.68	0.18
Min, Max	-50.67, 44.17	-38.63, 28.78
95% CI	(-8.85, -0.08)	(-7.53, 2.52)
P-value[1]	0.0462	0.3149
ANCOVA [2]		
LS Mean (SE)	-4.18 (2.044)	-3.26 (3.379)
95% CI of LS Mean	(-8.24, -0.13)	(-9.96, 3.45)
P-value	0.6223	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.16. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter and Atorvastatin

	RVX000222 200 mg daily (N=53)	Placebo (N=12)
Baseline (Visit 1)		
n	53	12
Mean (SD)	206.0 ± (82.631)	166.2 ± (60.677)
Median	197.12	149.42
Min, Max	37.57, 517.22	81.43, 273.50
Week 26 (Visit 12)		
n	53	12
Mean (SD)	203.5 ± (84.102)	165.2 ± (62.283)
Median	198.80	159.56
Min, Max	37.83, 504.87	85.87, 281.59
Week 26 change from baseline		
n	53	12
Mean (SD)	-2.43 ± (17.159)	-0.93 ± (12.918)
Median	0.32	-0.92
Min, Max	-53.61, 28.55	-24.35, 23.96
95% CI	(-7.16, 2.29)	(-9.13, 7.28)
P-value[1]	0.3064	0.8086
ANCOVA [2]		
LS Mean (SE)	-2.41 (2.292)	-1.02 (4.876)
95% CI of LS Mean	(-7.00, 2.17)	(-10.8, 8.73)
P-value	0.8072	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.5. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Below Median HDL-c at Baseline

	RVX000222 200 mg daily (N=92)	Placebo (N=34)
Baseline (Visit 1)		
n	92	34
Mean (SD)	211.9 ± (91.789)	193.0 ± (86.225)
Median	199.01	178.22
Min, Max	37.57, 517.22	71.90, 367.20
Week 26 (Visit 12)		
n	92	34
Mean (SD)	204.1 ± (92.359)	184.9 ± (79.125)
Median	190.53	173.82
Min, Max	37.83, 504.87	74.74, 346.80
Week 26 change from baseline		
n	92	34
Mean (SD)	-7.81 ± (15.421)	-8.12 ± (13.990)
Median	-7.79	-6.92
Min, Max	-50.67, 31.53	-38.63, 28.78
95% CI	(-11.0, -4.61)	(-13.0, -3.24)
P-value[1]	<.0001	0.0019
ANCOVA [2]		
LS Mean (SE)	-7.66 (1.555)	-8.51 (2.563)
95% CI of LS Mean	(-10.7, -4.58)	(-13.6, -3.43)
P-value	0.8147	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.6. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS At or Above Median HDL-c at Baseline

	RVX000222 200 mg daily (N=114)	Placebo (N=39)
Baseline (Visit 1)		
n	114	39
Mean (SD)	208.2 ± (76.411)	156.7 ± (58.211)
Median	200.11	140.61
Min, Max	52.30, 423.63	68.96, 273.50
Week 26 (Visit 12)		
n	114	39
Mean (SD)	207.2 ± (76.978)	156.7 ± (58.156)
Median	200.58	144.47
Min, Max	53.14, 425.11	67.34, 281.59
Week 26 change from baseline		
n	114	39
Mean (SD)	-1.05 ± (18.121)	0.01 ± (10.018)
Median	1.23	0.56
Min, Max	-58.93, 44.17	-19.79, 23.96
95% CI	(-4.41, 2.32)	(-3.24, 3.26)
P-value[1]	0.5386	0.9955
ANCOVA [2]		
LS Mean (SE)	-0.79 (1.560)	-0.75 (2.729)
95% CI of LS Mean	(-3.87, 2.30)	(-6.15, 4.64)
P-value	0.9560	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.7. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Rosuvastatin

	RVX000222 200 mg daily (N=115)	Placebo (N=44)
Baseline (Visit 1)		
n	115	44
Mean (SD)	215.2 ± (87.318)	176.3 ± (73.808)
Median	201.35	162.76
Min, Max	51.77, 473.98	68.96, 350.84
Week 26 (Visit 12)		
n	115	44
Mean (SD)	209.3 ± (87.564)	172.1 ± (68.546)
Median	200.39	162.40
Min, Max	53.14, 469.29	67.34, 323.15
Week 26 change from baseline		
n	115	44
Mean (SD)	-5.89 ± (17.350)	-4.22 ± (12.573)
Median	-5.24	-3.54
Min, Max	-50.67, 44.17	-38.63, 28.78
95% CI	(-9.09, -2.68)	(-8.04, -0.40)
P-value[1]	0.0004	0.0312
ANCOVA [2]		
LS Mean (SE)	-5.55 (1.503)	-5.09 (2.453)
95% CI of LS Mean	(-8.52, -2.58)	(-9.94, -0.25)
P-value	0.6445	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.8. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Atorvastatin

	RVX000222 200 mg daily (N=97)	Placebo (N=31)
Baseline (Visit 1)		
n	97	31
Mean (SD)	205.9 ± (79.267)	163.7 ± (76.090)
Median	196.51	138.33
Min, Max	37.57, 517.22	71.90, 367.20
Week 26 (Visit 12)		
n	97	31
Mean (SD)	203.8 ± (80.346)	160.2 ± (72.636)
Median	195.39	138.89
Min, Max	37.83, 504.87	74.74, 346.80
Week 26 change from baseline		
n	97	31
Mean (SD)	-2.11 ± (16.769)	-3.55 ± (12.627)
Median	0.32	-3.88
Min, Max	-58.93, 35.54	-30.48, 23.96
95% CI	(-5.49, 1.27)	(-8.18, 1.08)
P-value[1]	0.2188	0.1277
ANCOVA [2]		
LS Mean (SE)	-1.91 (1.622)	-4.18 (2.908)
95% CI of LS Mean	(-5.12, 1.30)	(-9.94, 1.57)
P-value	0.4266	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.9. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter

	RVX000222 200 mg daily (N=81)	Placebo (N=33)
Baseline (Visit 1)		
n	81	33
Mean (SD)	206.6 ± (76.514)	171.4 ± (82.880)
Median	199.72	153.72
Min, Max	69.81, 406.16	71.90, 367.20
Week 26 (Visit 12)		
n	81	33
Mean (SD)	201.6 ± (76.244)	165.3 ± (75.943)
Median	198.40	147.35
Min, Max	62.19, 388.16	74.74, 346.80
Week 26 change from baseline		
n	81	33
Mean (SD)	-5.00 ± (15.421)	-6.09 ± (12.358)
Median	-3.53	-6.62
Min, Max	-58.93, 35.54	-35.69, 19.07
95% CI	(-8.41, -1.59)	(-10.5, -1.71)
P-value[1]	0.0046	0.0080
ANCOVA [2]		
LS Mean (SE)	-4.53 (1.591)	-7.22 (2.515)
95% CI of LS Mean	(-7.69, -1.38)	(-12.2, -2.24)
P-value	0.3404	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.10. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter

	RVX000222 200 mg daily (N=127)	Placebo (N=40)
Baseline (Visit 1)		
n	127	40
Mean (SD)	212.9 ± (87.519)	175.4 ± (67.564)
Median	200.10	157.65
Min, Max	37.57, 517.22	68.96, 350.84
Week 26 (Visit 12)		
n	127	40
Mean (SD)	209.2 ± (88.351)	173.5 ± (64.813)
Median	198.80	165.10
Min, Max	37.83, 504.87	67.34, 323.15
Week 26 change from baseline		
n	127	40
Mean (SD)	-3.66 ± (18.327)	-1.87 ± (12.671)
Median	-3.06	0.18
Min, Max	-53.61, 44.17	-38.63, 28.78
95% CI	(-6.88, -0.44)	(-5.92, 2.19)
P-value[1]	0.0261	0.3570
ANCOVA [2]		
LS Mean (SE)	-3.49 (1.527)	-2.42 (2.748)
95% CI of LS Mean	(-6.50, -0.47)	(-7.85, 3.01)
P-value	0.6523	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.11. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Prior Statin

	RVX000222 200 mg daily (N=198)	Placebo (N=72)
Baseline (Visit 1)		
n	198	72
Mean (SD)	211.0 ± (84.429)	171.2 ± (72.002)
Median	201.12	154.51
Min, Max	37.57, 517.22	68.96, 367.20
Week 26 (Visit 12)		
n	198	72
Mean (SD)	206.8 ± (84.930)	167.7 ± (67.737)
Median	200.58	156.42
Min, Max	37.83, 504.87	67.34, 346.80
Week 26 change from baseline		
n	198	72
Mean (SD)	-4.17 ± (17.353)	-3.51 ± (12.510)
Median	-3.20	-3.09
Min, Max	-58.93, 44.17	-38.63, 28.78
95% CI	(-6.60, -1.74)	(-6.45, -0.57)
P-value[1]	0.0009	0.0198
ANCOVA [2]		
LS Mean (SE)	-3.88 (1.151)	-4.30 (1.929)
95% CI of LS Mean	(-6.15, -1.62)	(-8.10, -0.51)
P-value	0.9443	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.12. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS Statin Naive

	RVX000222 200 mg daily (N=10)	Placebo (N=1)
Baseline (Visit 1)		
n	10	1
Mean (SD)	198.7 ± (57.448)	345.8 ± (----)
Median	180.20	345.76
Min, Max	116.18, 300.53	345.76, 345.76
Week 26 (Visit 12)		
n	10	1
Mean (SD)	194.3 ± (56.764)	323.2 ± (----)
Median	182.12	323.15
Min, Max	137.69, 309.32	323.15, 323.15
Week 26 change from baseline		
n	10	1
Mean (SD)	-4.35 ± (15.324)	-22.6 ± (----)
Median	-6.02	-22.60
Min, Max	-21.77, 21.51	-22.60, -22.60
95% CI	(-15.3, 6.61)	(,)
P-value[1]	0.3922	
ANCOVA [2]		
LS Mean (SE)	-4.99 (5.208)	-16.3 (20.24)
95% CI of LS Mean	(-17.0, 7.02)	(-62.9, 30.42)
P-value	0.3412	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.13. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter and Rosuvastatin

	RVX000222 200 mg daily (N=40)	Placebo (N=16)
Baseline (Visit 1)		
n	40	16
Mean (SD)	205.6 ± (75.501)	171.9 ± (81.300)
Median	202.52	162.23
Min, Max	73.26, 394.14	75.96, 341.30
Week 26 (Visit 12)		
n	40	16
Mean (SD)	197.1 ± (74.157)	164.7 ± (74.124)
Median	200.07	156.42
Min, Max	62.19, 368.17	74.74, 316.37
Week 26 change from baseline		
n	40	16
Mean (SD)	-8.55 ± (13.376)	-7.22 ± (11.666)
Median	-7.78	-7.66
Min, Max	-32.34, 21.51	-35.69, 14.91
95% CI	(-12.8, -4.27)	(-13.4, -1.01)
P-value[1]	0.0002	0.0257
ANCOVA [2]		
LS Mean (SE)	-8.05 (1.971)	-8.48 (3.143)
95% CI of LS Mean	(-12.0, -4.09)	(-14.8, -2.18)
P-value	0.9012	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.14. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS S5 Catheter and Atorvastatin

	RVX000222 200 mg daily (N=44)	Placebo (N=19)
Baseline (Visit 1)		
n	44	19
Mean (SD)	205.8 ± (75.965)	162.2 ± (85.982)
Median	195.45	134.75
Min, Max	69.81, 406.16	71.90, 367.20
Week 26 (Visit 12)		
n	44	19
Mean (SD)	204.1 ± (76.540)	157.0 ± (79.967)
Median	193.14	119.09
Min, Max	70.31, 388.16	74.74, 346.80
Week 26 change from baseline		
n	44	19
Mean (SD)	-1.71 ± (16.476)	-5.21 ± (12.500)
Median	0.30	-6.21
Min, Max	-58.93, 35.54	-30.48, 19.07
95% CI	(-6.72, 3.30)	(-11.2, 0.81)
P-value[1]	0.4940	0.0858
ANCOVA [2]		
LS Mean (SE)	-1.22 (2.321)	-6.36 (3.578)
95% CI of LS Mean	(-5.86, 3.42)	(-13.5, 0.80)
P-value	0.1862	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.15. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter and Rosuvastatin

	RVX000222 200 mg daily (N=75)	Placebo (N=28)
Baseline (Visit 1)		
n	75	28
Mean (SD)	220.3 ± (93.087)	178.9 ± (70.609)
Median	200.90	165.32
Min, Max	51.77, 473.98	68.96, 350.84
Week 26 (Visit 12)		
n	75	28
Mean (SD)	215.9 ± (93.751)	176.3 ± (66.174)
Median	200.39	165.10
Min, Max	53.14, 469.29	67.34, 323.15
Week 26 change from baseline		
n	75	28
Mean (SD)	-4.46 ± (19.068)	-2.51 ± (12.952)
Median	-4.68	0.18
Min, Max	-50.67, 44.17	-38.63, 28.78
95% CI	(-8.85, -0.08)	(-7.53, 2.52)
P-value[1]	0.0462	0.3149
ANCOVA [2]		
LS Mean (SE)	-4.18 (2.044)	-3.26 (3.379)
95% CI of LS Mean	(-8.24, -0.13)	(-9.96, 3.45)
P-value	0.6223	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Resverlogix Corp.
Protocol: RVX222-CS-007

Table 14.2.2.2.16. Total Atheroma Volume (TAV) Change from Baseline to Week 26 (Visit 12) - FAS ILAB Catheter and Atorvastatin

	RVX000222 200 mg daily (N=53)	Placebo (N=12)
Baseline (Visit 1)		
n	53	12
Mean (SD)	206.0 ± (82.631)	166.2 ± (60.677)
Median	197.12	149.42
Min, Max	37.57, 517.22	81.43, 273.50
Week 26 (Visit 12)		
n	53	12
Mean (SD)	203.5 ± (84.102)	165.2 ± (62.283)
Median	198.80	159.56
Min, Max	37.83, 504.87	85.87, 281.59
Week 26 change from baseline		
n	53	12
Mean (SD)	-2.43 ± (17.159)	-0.93 ± (12.918)
Median	0.32	-0.92
Min, Max	-53.61, 28.55	-24.35, 23.96
95% CI	(-7.16, 2.29)	(-9.13, 7.28)
P-value[1]	0.3064	0.8086
ANCOVA [2]		
LS Mean (SE)	-2.41 (2.292)	-1.02 (4.876)
95% CI of LS Mean	(-7.00, 2.17)	(-10.8, 8.73)
P-value	0.8072	

[1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with rank transformed data with change in TAV as the response variable, baseline TAV as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.2.11.2.

Source:/d/consult/resassur/sasprog/t_tav (Date Generated 01AUG13:21:58)

Table 14.2.3.1 Total Atheroma Volume (TAV), 10-mm Subsegment with the Greatest Disease Burden at Baseline, Change from Baseline to Week 26 (Visit 12) – mITT Population

	RVX000222 200 mg (N =xxx)	Placebo (N =xx)
Baseline (Visit 1)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 26 (Visit 12)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 26 change from baseline		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)
P-value [1]	0.xxx	0.xxx
ANCOVA [2]		
LS Mean (SE)	x.x (x.x)	x.x (x.x)
95% CI of LS Mean	(x.x, x.x)	(x.x, x.x)
P-value	0.xxx	

Notes: [1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with change in TAV for the 10-mm subsegment with the greatest disease burden at baseline as the response variable, baseline TAV for the 10-mm subsegment with the greatest disease burden as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.2.3.2 Total Atheroma Volume (TAV), 10-mm Subsegment with the Greatest Disease Burden at Baseline, Change from Baseline to Week 26 (Visit 12) – FAS

Table 14.2.3.3 Total Atheroma Volume (TAV), 10-mm Subsegment with the Greatest Disease Burden at Baseline, Change from Baseline to Week 26 (Visit 12) – Per Protocol Population

Table 14.2.4.1.1 HDL-C Percent Change from Baseline to Week 26 (Visit 12) LOCF - mITT Population

	RVX000222 200 mg (N =xxx)	Placebo (N =xx)
Baseline (Visit 1)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 8 (Visit 14)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 8 percent change from baseline		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)
P-value [1]	0.xxx	0.xxx
ANCOVA [2]		
LS Mean (SE)	x.x (x.x)	x.x (x.x)
95% CI of LS Mean	(x.x, x.x)	(x.x, x.x)
P-value	0.xxx	

Notes: [1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with percent change in HDL-C as the response variable, baseline HDL-C as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.x.

Table 14.2.4.1.1 HDL-C Percent Change from Baseline to Week 26 (Visit 12) LOCF - mITT Population

	RVX000222 200 mg (N =xxx)	Placebo (N =xx)
Week 26 (Visit 26) (LOCF)		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Week 26 percent change from baseline		
n	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)
P-value [1]	0.xxx	0.xxx
ANCOVA [2]		
LS Mean (SE)	x.x (x.x)	x.x (x.x)
95% CI of LS Mean	(x.x, x.x)	(x.x, x.x)
P-value	0.xxx	

Notes: [1] P-value comparing within group change using the paired t-test.
[2] P-value from an ANCOVA with percent change in HDL-C as the response variable, baseline HDL-C as a covariate, and treatment group as a factor.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.2.4.1.2 HDL-C Percent Change from Baseline to Week 26 (Visit 12) LOCF – FAS
Table 14.2.4.1.3 HDL-C Percent Change from Baseline to Week 26 (Visit 12) LOCF – Per Protocol Population

Table 14.2.4.2.1 ApoA-I Percent Change from Baseline to Week 26 (Visit 12) LOCF – mITT Population
Table 14.2.4.2.2 ApoA-I Percent Change from Baseline to Week 26 (Visit 12) LOCF – FAS
Table 14.2.4.2.3 ApoA-I Percent Change from Baseline to Week 26 (Visit 12) LOCF – Per Protocol Population

Table 14.2.4.3.1 HDL Subclass 1 Percent Change from Baseline to Week 26 (Visit 12) LOCF - mITT Population
Table 14.2.4.3.2 HDL Subclass 1 Percent Change from Baseline to Week 26 (Visit 12) LOCF – FAS
Table 14.2.4.3.3 HDL Subclass 1 Percent Change from Baseline to Week 26 (Visit 12) LOCF – Per Protocol Population

Table 14.2.4.4.1 HDL Subclass 2 Percent Change from Baseline to Week 26 (Visit 12) LOCF – mITT Population
Table 14.2.4.4.2 HDL Subclass 2 Percent Change from Baseline to Week 26 (Visit 12) LOCF – FAS
Table 14.2.4.4.3 HDL Subclass 2 Percent Change from Baseline to Week 26 (Visit 12) LOCF - Per Protocol Population

Table 14.2.5.1.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline PAV - FAS Population

	Below Baseline PAV Median		Above Baseline PAV Median	
	RVX000222 200 mg (N =xxx)	Placebo (N =xx)	RVX000222 200 mg (N =xxx)	Placebo (N =xx)
Baseline (Visit 1)				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 26 (Visit 12)				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 26 change from baseline				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)
P-value [1]	0.xxx	0.xxx	0.xxx	0.xxx

Notes: [1] P-value comparing within group change using the paired t-test.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables: The first row header will be replaced by table specified subgroups.
For subgroups referencing the median (xx.x), below median will be <xx.x and above median will be ≥xx.x.

Table 14.2.5.1.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline PAV – Per Protocol Population

Note to programmer: Subgroups will be Below Baseline HDL-C Median and At or Above Baseline HDL-C Median. The median will be determined by the overall baseline values from the respective population.
Table 14.2.5.2.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline HDL-C – Per Protocol Population
Table 14.2.5.2.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline HDL-C – Per Protocol Population

Note to programmer: Subgroups will be History with Diabetes Mellitus (indicated by 'Yes' for diabetic history from the significant cardiovascular medical history eCRF) and No History of Diabetes Mellitus (indicated by 'No' for diabetic history from the significant cardiovascular medical history eCRF).
Table 14.2.5.3.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for History of Diabetes Mellitus - FAS
Table 14.2.5.3.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for History of Diabetes Mellitus - Per Protocol Population

Note to programmer: Subgroups will be Male and Female (from the demography eCRF)
Table 14.2.5.4.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Gender - FAS
Table 14.2.5.4.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Gender - Per Protocol Population

Note to programmer: Subgroups will be Age < 65 and Age ≥ 65 (calculated based on DOB from demography eCRF).
Table 14.2.5.5.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Age - FAS
Table 14.2.5.5.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Age - Per Protocol Population

Note to programmer: Subgroups will be Atorvastatin and Rosuvastatin. The medications will be captured in the concomitant medication eCRF.
Table 14.2.5.6.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Statin Use - FAS
Table 14.2.5.6.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Statin Use - Per Protocol Population

Note to programmer: Subgroups will be Below Baseline ApoA-1 Median and At or Above Baseline ApoA-1 Median. The median will be determined by the overall baseline values from the respective population.
Table 14.2.5.7.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline Apo-A1 – FAS
Table 14.2.5.7.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline Apo-A1 – Per Protocol Population

Note to programmer: Subgroups will be Below Baseline Large HDL (NMR) Median and At or Above Baseline Large HDL (NMR) Median. The median will be determined by the overall baseline values from the respective population.
Table 14.2.5.8.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline Large HDL (NMR) – FAS
Table 14.2.5.8.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline Large HDL (NMR) – Per Protocol Population

Note to programmer: Subgroups will be Below Baseline CRP Median and At or Above Baseline CRP Median. The median will be determined by the overall baseline values from the respective population.
Table 14.2.5.9.1 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline CRP – FAS
Table 14.2.5.9.2 Percent Atheroma Volume (PAV) Change from Baseline to Week 26 (Visit 12) Subgroup Analysis for Baseline CRP - Per Protocol Population

Table 14.2.6.1 Correlation Between Changes in Atheroma Burden and Percent Changes in Lipid Biomarkers – FAS

	Change from Baseline at Week 26			
	HDL-C (N=xx)	ApoA-I (N=xx)	HDL-S (N=xx)	HDL-L (N=xx)
Percent change from baseline at Week 26 of Percent Atheroma Volume(PAV)				
Correlation [1]	x.xxx	x.xxx	x.xxx	x.xxx
p-value [2]	x.xxxx	x.xxxx	x.xxxx	x.xxxx
Percent change from baseline at Week 26 of Total Atheroma Volume(TAV)				
Correlation [1]	x.xxx	x.xxx	x.xxx	x.xxx
p-value [2]	x.xxxx	x.xxxx	x.xxxx	x.xxxx

Notes: [1] Correlation based on Pearson correlation coefficient.
[2] P-value from the t-test for zero correlation.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.2.6.2 Correlation Between Changes in Atheroma Burden and Percent Changes in Lipid Biomarkers – Per Protocol Population

Table 14.2.7.1 Regression of Coronary Atheroscerosis – FAS

	RVX000222 200 mg (N =xxx) n (%)	Placebo (N =xxx) n (%)
Change in PAV < 0 [1]		
Yes	xx(xx.x)	xx(xx.x)
No	xx(xx.x)	xx(xx.x)
P-value [2]	0.xxx	

Notes: [1] Regression of coronary atherosclerosis is defined as a change in PAV from baseline (Visit 1) to Week 26 (Visit 12) less than zero.
[2] P-value based on the chi-square test.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.2.7.2 Regression of Coronary Atheroscerosis – Per Protocol Population

Table 14.2.8.1 Summary of Change from Baseline at Week 26 (Visit 12) by Treatment Group: Radio Frequency Analysis (RFA) – mITT Population

	RVX000222 200 mg (N=xxx)	Placebo (N=xx)
Fibrous		
Baseline (Visit 1)		
n	xxx	xx
Mean (SD)	xx.x (xx.xx)	xx.x
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)
Week 26 (Visit 12)		
n	xxx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)
Week 26 change from baseline		
n	xxx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
95% CI	(x.x, x.x)	(x.x, x.x)

Continue table for fibro-fatty, necrotic core and dense calcium.

Note to Programmer: Please use same table format for the following tables:

Table 14.2.8.2 Summary of Change from Baseline at Week 26 (Visit 12) by Treatment Group: Radio Frequency Analysis (RFA) – FAS
Table 14.2.8.3 Summary of Change from Baseline at Week 26 (Visit 12) by Treatment Group: Radio Frequency Analysis (RFA) – Per Protocol Population

Table 14.2.9.1 Correlation Between Pharmcokinetic Trough Values (C-min) and Change in Percent Atheroma (PAV) Burden – FAS

	RVX000222 200 mg (N=xxx)
Correlation [1]	x.xxx
p-value [2]	x.xxxx

Notes: [1] Correlation based on Pearson correlation coefficient.
[2] P-value from the t-test for zero correlation.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:
Table 14.2.9.2 Correlation Between Pharmcokinetic Trough Values (C-min) and Change in Percent Atheroma (PAV) Burden – Per Protocol Population

14.3 SAFETY DATA

Table 14.3.1.1.1 Major Adverse Cardiac Events (MACE) – Safety Population

	RVX000222 200mg (N=xxx)		Placebo (N=xxx)			Overall (N=xxx)	
	n (%)	95% CI	n (%)	95% CI	p-value [1]	n (%)	95% CI
At least one major adverse cardiac event [1]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	0.xxx	xx (xx.x)	(xx.x, xx.x)
Myocardial infarction	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	0.xxx	xx (xx.x)	(xx.x, xx.x)
Stroke	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	0.xxx	xx (xx.x)	(xx.x, xx.x)
Coronary revascularization	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	0.xxx	xx (xx.x)	(xx.x, xx.x)
Hospitalization for ACS or heart failure	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	0.xxx	xx (xx.x)	(xx.x, xx.x)
Death	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	0.xxx	xx (xx.x)	(xx.x, xx.x)

Notes: [1] P-value from Fisher’s Exact Test comparing RVX000222 and placebo treatment groups.
This table corresponds to Listing 16.x.

Table 14.3.1.2 Adverse Events (AEs) – Safety Population

	RVX000222 200mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
At least one pre-treatment adverse event [1]	xx (xx.x)	xx (xx.x)	xx (xx.x)
At least one treatment-emergent adverse event [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-emergent adverse event by severity [3]			
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
At least one treatment-emergent serious adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)
At least one treatment-emergent treatment-related adverse event [4]	xx (xx.x)	xx (xx.x)	xx (xx.x)
At least one treatment-emergent treatment-related serious adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)
At least one treatment-emergent adverse event leading to study drug withdrawal	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death due to treatment-emergent adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: [1] A pre-treatment AE is defined as any AE that ended prior to the first dose of study drug.
[2] A treatment-emergent adverse event is defined as any AE with an onset date on or after the first dose of study drug.
[3] A patient is counted only once in the most severe category when multiple treatment-emergent AEs were reported.
[4] A treatment-related AE is defined as a relationship of possibly, probably and definitely related to study drug.
This table corresponds to Listing 16.x.

Table 14.3.1.3 Pre-Treatment Adverse Events – Safety Population

System Organ Class (SOC) Preferred Term	RVX000222 200mg (N=xxx)		Placebo (N=xxx)		Overall (N=xxx)	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Any pre-treatment AE	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 3	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
…						
SYSTEM ORGAN CLASS 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 3	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
…						

Notes: A pre-treatment AE is defined as any AE that ended prior to the first dose of study drug.
Patients may have more than one AE per SOC and preferred term. At each level (SOC and preferred term) a patient is counted only once if he/she experienced one or more AE at that level. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1).
This table corresponds to Listing 16.x.

Table 14.3.1.4 Treatment-Emergent Adverse Events (TEAE) – Safety Population

System Organ Class (SOC) Preferred Term	RVX000222 200mg (N=xxx)		Placebo (N=xxx)		Overall (N=xxx)	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Any TEAE	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 3	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
…						
SYSTEM ORGAN CLASS 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 3	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
…						

Notes: A treatment-emergent adverse event is defined as any AE with an onset date on or after the first dose of study drug. Patients may have more than one AE per SOC and preferred term. At each level (SOC and preferred term) a patient is counted only once if he/she experienced one or more AE at that level. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1).
This table corresponds to Listing 16.x.

Table 14.3.1.5 Treatment-Emergent Adverse Events (TEAE) by Severity – Safety Population

System Organ Class (SOC) Preferred Term	RVX000222 200mg (N=xxx) Events n	 Subjects n (%)	Placebo (N=xxx) Events n	 Subjects n (%)	Overall (N=xxx) Events n	 Subjects n (%)
Any TEAE	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Mild	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Moderate	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Severe	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Mild	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Moderate	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Severe	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 1	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Mild	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Moderate	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Severe	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
PREFERRED TERM 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
…						

Notes: A treatment-emergent adverse event is defined as any AE with an onset date on or after the first dose of study drug. Patients may have more than one AE per SOC and preferred term. At each level (SOC and preferred term) a patient is counted only once if he/she experienced one or more AE at that level, with the maximum severity reported. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1).
This table corresponds to Listing 16.x.

Table 14.3.1.6 Treatment-Emergent Adverse Events (TEAEs) by Relationship to Treatment – Safety Population

System Organ Class (SOC) Preferred Term	RVX000222 200mg (N=xxx)		Placebo (N=xxx)		Overall (N=xxx)	
	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)
Any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…						
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…						

Notes: Related includes definite, probably, possibly and missing.
A treatment-emergent adverse event is defined as any AE with an onset date on or after the first dose of study drug. Patients may have more than one AE per SOC and preferred term. At each level (SOC and preferred term) a patient is counted only once if he/she experienced one or more AE at that level, with the maximum relatedness reported. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1).
This table corresponds to Listing 16.x.This table corresponds to Listing 16.x.

Table 14.3.1.7 Treatment-Emergent Serious Adverse Events (SAEs) – Safety Population

System Organ Class (SOC) Preferred Term	RVX000222 200mg (N=xxx) n(%)	Placebo (N=xxx) n(%)	Overall (N=xxx) n(%)
Any SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			

Notes: A treatment-emergent adverse event is defined as any AE with an onset date on or after the first dose of study drug. Patients may have more than one AE per SOC and preferred term. At each level (SOC and preferred term) a patient is counted only once if he/she experienced one or more AE at that level. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1).
This table corresponds to Listing 16.x.

Table 14.3.1.8 Treatment-Emergent Adverse Events (TEAEs) Leading to Withdrawal of Study Drug – Safety Population

System Organ Class (SOC) Preferred Term	RVX000222 200mg (N=xxx) n(%)	Placebo (N=xxx) n(%)	Overall (N=xxx) n(%)
Any TEAE leading to withdrawal of study drug	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			

Notes: A treatment-emergent adverse event is defined as any AE with an onset date on or after the first dose of study drug. Patients may have more than one AE per SOC and preferred term. At each level (SOC and preferred term) a patient is counted only once if he/she experienced one or more AE at that level. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1).
This table corresponds to Listing 16.x.

Table 14.3.1.9 Listing of Deaths – Safety Population

Treatment Group	Patient ID	Age/Sex/Race	Date of First Dose	Date of Last Dose	Date of Death	Cause of Death
Placebo RVX000222	xxx-xxx	xx/xxxxx/xxxxxxxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	Xxxxxxxxx xxxxxxxx xxxxx

Notes: This table corresponds to Listing 16.x.

Table 14.3.2.1 Summary of Hematology Laboratory Results – Safety Population

	RVX000222 200 mg (N=xxx)		Placebo (N=xxx)	
	Value	Change from Baseline	Value	Change from Baseline
Parameter 1 (unit)				
Baseline				
n	xxx		xxx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx.x, xx.x		xx.x, xx.x	
Week 14				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 26				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

continue for all hematology parameters

Notes: This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.3.2.2 Summary of Chemistry Laboratory Results – Safety Population

Note to programmer: Safety labs include: ALT (SGPT), AST (SGOT), GGT, billirubin (direct and total), if indicated INR.
Table 14.3.2.3 Summary of Safety Laboratory Results – Safety Population

Table 14.3.2.4 Summary of Fasting Lipid Profile Laboratory Results – Safety Population

Table 14.3.2.5 Summary of Urinalysis Laboratory Results – Safety Population

Table 14.3.3.1 Shift Tables of Hematology Laboratory Results – Safety Population

		Baseline					
		RVX000222 200 mg (N=xxx)			Placebo (N=xxx)		
		Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Parameter 1 (unit)							
Week 14	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 26	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

continue for all hematology parameters

Notes: Percentages are based on the total number of subjects within a treatment who have both a baseline and post-baseline data.
This table corresponds to Listing 16.x.

Note to Programmer: Please use same table format for the following tables:

Table 14.3.3.2 Shift Tables of Chemistry Laboratory Results – Safety Population

Note to programmer: Safety labs include: ALT (SGPT), AST (SGOT), GGT, billirubin (direct and total), if indicated INR.

Table 14.3.3.3 Shift Tables of Safety Laboratory Results – Safety Population

Table 14.3.3.4 Shift Tables of Fasting Lipid Profile Laboratory Results – Safety Population

Table 14.3.3.5 Shift Tables of Urinalysis Laboratory Results – Safety Population

Table 14.3.4 Subjects with Elevated ALT/AST at Any Time During the Treatment Period – Safety Population

	RVX000222 200 mg (N=xxx)	Placebo (N=xxx)	P-value[1]
Subjects with elevated ALT levels	xxx	xxx	xxx
1x ULN < ALT elevation <= 3x ULN	xx(xx.x)	xx(xx.x)	0.xxx
3x ULN < ALT elevation <= 5x ULN	xx(xx.x)	xx(xx.x)	0.xxx
5x ULN < ALT elevation <= 8x ULN	xx(xx.x)	xx(xx.x)	0.xxx
ALT elevation > 3x ULN	xx(xx.x)	xx(xx.x)	0.xxx
ALT elevation> 3x ULN in patients who without study drug discontinuation return to normal transaminase levels	xx(xx.x)	xx(xx.x)	0.xxx
First occurrence of ALT > 3x ULN before or at Week 11 (Visit 7)	xx(xx.x)	xx(xx.x)	0.xxx
First occurrence of ALT > 3x ULN after Week 11 (Visit 7)	xx(xx.x)	xx(xx.x)	0.xxx
ALT Elevation > 5x ULN	xx(xx.x)	xx(xx.x)	0.xxx
ALT Elevation > 8x ULN	xx(xx.x)	xx(xx.x)	0.xxx
Subjects with elevated AST levels	xxx	xxx	xxx
1x ULN < AST elevation <= 3x ULN	xx(xx.x)	xx(xx.x)	0.xxx
3x ULN < AST elevation <= 5x ULN	xx(xx.x)	xx(xx.x)	0.xxx
5x ULN < AST elevation <= 8x ULN	xx(xx.x)	xx(xx.x)	0.xxx
AST elevation > 3x ULN	xx(xx.x)	xx(xx.x)	0.xxx
AST elevation > 3x ULN in patients who without study drug discontinuation return to normal transaminase levels	xx(xx.x)	xx(xx.x)	0.xxx
AST elevation > 3x ULN	xx(xx.x)	xx(xx.x)	0.xxx
AST elevation > 5x ULN	xx(xx.x)	xx(xx.x)	0.xxx
AST elevation > 8x ULN	xx(xx.x)	xx(xx.x)	0.xxx

Notes: [1] P-value based on the Fisher's Exact test.
This table corresponds to Listing 16.x.

Table 14.3.5 Vital Signs – Safety Population

Visit	RVX000222 200 mg (N=xxx)		Placebo (N=xxx)	
	Value	Change from Baseline	Value	Change from Baseline
Temperature (C)				
Baseline				
n	xxx		xxx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx.x, xx.x		xx.x, xx.x	
Week 3				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 4				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 5				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

continue for all visits and parameters (systolic blood pressure, diastolic blood pressure, pulse, respiration rate)

Notes: This table corresponds to Listing 16.x.

Table 14.3.6.1 Summary of ECG results (PR Interval) – Safety Population

	RVX000222 200 mg (N=xxx)		Placebo (N=xxx)	
	Value	Change from Baseline	Value	Change from Baseline
PR interval (msec)				
Baseline				
n	xxx		xxx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx.x, xx.x		xx.x, xx.x	
Week 14				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 26				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

continue for QRS interval and QT interval

Notes: This table corresponds to Listing 16.x.

Table 14.3.6.2 Shift Tables of ECG Results – Safety Population

		Baseline					
		RVX000222 200 mg (N=xxx)			Placebo (N=xxx)		
		Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
PR interval (msec)							
Week 14	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 26	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

continue for all QRS interval and QT interval

Notes: Percentages are based on the total number of subjects within a treatment who have both a baseline and post-baseline data.
This table corresponds to Listing 16.x.

Table 14.3.7.1 Summary of Pharmacokinetic Trough Plasma Concentration of RVX000222 – FAS

	RVX000222 200mg (N=xxx)
Steady State Trough Concentration [1]	
n	xxx
Mean (SD)	xx.x (xx.xx)
Coefficient of Variation	xx.xx
Geometric Mean	xx.x
Median	xx.x
Min, Max	xx.x, xx.x

Notes: [1] Trough for each subject is calculated as the mean of Visit 4, Visit 8, and Visit 12.

Note to Programmer: Please use same table format for the following tables:

Table 14.3.7.1 Summary of Pharmacokinetic Trough Plasma Concentration of RVX000222 – Per Protocol Population

14.3.3 Narratives of Death, Other Serious and Certain Other Significant Adverse Events

RVX222-CS-007-203-004
RVX222-CS-007-203-008
RVX222-CS-007-205-005
RVX222-CS-007-207-002
RVX222-CS-007-207-007
RVX222-CS-007-207-017
RVX222-CS-007-207-023
RVX222-CS-007-302-010
RVX222-CS-007-401-007
RVX222-CS-007-403-006
RVX222-CS-007-409-003
RVX222-CS-007-409-005
RVX222-CS-007-501-001
RVX222-CS-007-501-008
RVX222-CS-007-501-014
RVX222-CS-007-501-020
RVX222-CS-007-501-029
RVX222-CS-007-501-037
RVX222-CS-007-502-018
RVX222-CS-007-502-020
RVX222-CS-007-502-022
RVX222-CS-007-502-026
RVX222-CS-007-502-035
RVX222-CS-007-502-036
RVX222-CS-007-502-041
RVX222-CS-007-503-002
RVX222-CS-007-505-014
RVX222-CS-007-505-018
RVX222-CS-007-506-003
RVX222-CS-007-601-008
RVX222-CS-007-601-014
RVX222-CS-007-601-015
RVX222-CS-007-601-027
RVX222-CS-007-608-001
RVX222-CS-007-608-003
RVX222-CS-007-608-014
RVX222-CS-007-608-016
RVX222-CS-007-608-018
RVX222-CS-007-703-004
RVX222-CS-007-703-012
RVX222-CS-007-705-007
RVX222-CS-007-705-011
RVX222-CS-007-705-013
RVX222-CS-007-705-021
RVX222-CS-007-705-023
RVX222-CS-007-705-028
RVX222-CS-007-802-017
RVX222-CS-007-804-003
RVX222-CS-007-804-007
RVX222-CS-007-806-010
RVX222-CS-007-806-019
RVX222-CS-007-807-005
RVX222-CS-007-809-011
RVX222-CS-007-810-013
RVX222-CS-007-811-004
RVX222-CS-007-901-003
RVX222-CS-007-902-001

RVX222-CS-007-903-007
RVX222-CS-007-908-004
RVX222-CS-007-911-002
RVX222-CS-007-911-004
RVX222-CS-007-911-008
RVX222-CS-007-911-009
RVX222-CS-007-911-012
RVX222-CS-007-911-015

14.3.3 Narratives of Death, Other Serious and Certain Other Significant Adverse Events

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 203/004
Age: 55	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason(s) for Narrative:	Serious Adverse Event Clinically Significant Event
Event(s):	Pneumonia Elevated liver enzymes

Narrative:

Patient 203-004, a 55-year-old female with a history of hypertension, unstable angina, dyslipidemia, diverticulum intestinal and hypothyroidism enrolled in the study on 31 MAY 2012. She was randomized to RVX000222 200 mg on 13 JUN 2012; the first dose of study drug was administered on the same date. Concomitant medications included valsartan 160 mg QD (hypertension), rosuvastatin 20 mg QD (dyslipidemia), acetylsalicylic acid 100 mg QD (myocardial infarction), and levothyroxine sodium 50 µg QD (hypothyroidism).

On 16 JUL 2012 (Day 34), the patient was hospitalized in the intensive care unit (ICU) for pneumonia that was moderate in severity. Treatment for the event included norepinephrine 8 mg continuous IV from 16 JUL 2012 to 20 JUL 2012, Unacid® (ampicillin/sulbactam) 3 g QID from 16 JUL 2012 to 24 JUL 2012, clarithromycin 500 mg BID from 16 JUL 2012 to 30 JUL 2012, potassium chloride 8 mEq QID from 23 JUL 2012 to 27 JUL 2012, and amoxicillin with clavulanic acid 625 mg BID from 24 JUL 2012 to 30 JUL 2012. Treatment with the study drug was not changed. The patient remained in the ICU until 22 JUL 2012 and then was transferred to a common room. On 24 JUL 2012 (Day 42), the event of pneumonia was considered resolved and the patient was discharged from the hospital on the same day.

On 27 JUL 2012 (Day 45), at Visit 5, laboratory tests revealed elevated liver enzymes with ALT >8x upper limit of normal (ULN), AST >3x ULN, and elevated GGT (see table below); this event was not reported as an adverse event. Treatment with study drug was permanently discontinued on 30 JUL 2012 (Day 48) due to the event. Liver enzymes returned to normal after discontinuation of the study drug.

The investigator considered the event of pneumonia to be unrelated to study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	31MAY2012	17	16	19	0.2	0.5	
Week 0	13JUN2012	17	16	23	0.3	0.8	

Week 2	27JUN2012	25	18	19	0.2	0.7
Week 4	11JUL2012	20	13 (L)	17	0.2	0.6
Week 6	27JUL2012	424 (H)	181 (H)	186 (H)	0.3	0.8
Unscheduled 1	03AUG2012	185 (H)	63 (H)	119 (H)	0.2	0.8
Week 8	09AUG2012	58 (H)	29	86 (H)	0.1	0.6
Week 11	03SEP2012	16	15	28	0.1	0.4
Week 14	20SEP2012	23	19	27	0.2	0.5
Week 17	10OCT2012	44	26	55 (H)	0.2	0.4
Week 20	06NOV2012	24	22	17	0.2	0.5
Week 23	22NOV2012	20	20	22	0.3	0.7
Week 26	12DEC2012	22	21	18	0.2	0.7
Follow-Up	09JAN2013	81 (H)	38	87 (H)	0.1	0.4

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 203/008
Age: 59	**Sex:** Female
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Discontinuation Due to Adverse Event	
Event(s): Hepatitis A antibody positive	

Narrative:

Patient 203-008, a 59-year-old female with a history of hypertension, angina, dyslipidemia, and uterine cancer enrolled in the study on 23 JUL 2012. She was randomized to RVX000222 200 mg on 03 AUG 2012; the first dose of study drug was administered on the same date. Concomitant medications included Micardis® (telmisartan) 40 mg QD (hypertension), and Crestor® (rosuvastatin) 20 mg QD and aspirin 100 mg QD (primary prevention).

On 29 AUG 2012 (Day 27), laboratory tests revealed elevated liver enzymes >8X upper limit of normal (see table below). No treatment was given for the event. Treatment with study drug was permanently discontinued on 02 SEP 2012 (Day 31).

The investigator considered the liver enzyme elevations to be probably related to study drug; the positive hepatitis A antibody was probably due to remote exposure to hepatitis A, which is very common in Latin America. At the time of discontinuation, the patient had received 31 days of study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	23JUL2012	21	17	20	0.1	0.5	
Week 0	03AUG2012	21	16	22	0.1	0.5	
Week 2	17AUG2012	33	25	21	0.2	0.8	
Week 4	29AUG2012	1646 (H)	818 (H)	130 (H)	0.4 (H)	1.0	
Unscheduled 1	29AUG2012	1636 (H)	848 (H)	126 (H)	0.5 (H)	0.9	
Unscheduled 4	07SEP2012	144 (H)	36			0.6	1.12 (H)
Week 6	13SEP2012	67 (H)	23	68 (H)	0.2	0.6	
Week 8	27SEP2012	27	20	44	0.2	0.6	
Week 11	17OCT2012	29	20	31	0.1	0.4	
Week 14	13NOV2012	25	19	26	0.2	0.6	
Week 17	28NOV2012	74 (H)	49 (H)	64 (H)	0.3	0.9	
Week 20	19DEC2012	33	24	47	0.3	0.5	
Week 23	09JAN2013	80 (H)	38	87 (H)	0.1	0.4	
Week 26	30JAN2013	24	25	20	0.1	0.6	
Follow-Up	26FEB2013	22	24	34	0.3	0.9	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 205/005
Age: 47	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative:	Discontinuation Due to Adverse Event
Event(s):	Hepatic enzyme increase

Narrative:

Patient 205-005, a 47-year-old male with a history of hypertension, stable angina, and dyslipidemia enrolled in the study on 30 JUL 2012. He was randomized to RVX000222 200 mg on 16 AUG 2012; the first dose of study drug was administered on the same date. Concomitant medications included Coreg® (carvedilol) 3.125 mg BID and aspirin 100 mg QD (coronary heart disease) and Lipitor® (atorvastatin) 10 mg QD (dyslipidemia).

On 17 SEP 2012 (Day 33), laboratory tests revealed hepatic enzyme increases (see table below). No treatment was given for the event. Treatment with study drug was permanently discontinued on 20 SEP 2012 (Day 36). The event of hepatic enzyme increase resolved on 29 OCT 2012 (Day 75).

The investigator considered the hepatic enzyme increase to be probably related to study drug. At the time of discontinuation, the patient had received 36 days of study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	30JUL2012	34	23	31	0.3	0.7	
Week 0	16AUG2012	45	19	34	0.3	0.7	
Week 2	31AUG2012	73 (H)	41 (H)	46	0.4 (H)	1.0	
Week 4	17SEP2012	320 (H)	119 (H)	54	0.5 (H)	1.0	
Unscheduled 3	25SEP2012	450 (H)	92 (H)			0.9	1.14 (H)
Week 6	28SEP2012	255 (H)	51 (H)	61	0.3	0.8	
Unscheduled 4	01OCT2012	135 (H)	33			0.8	
Week 8	09OCT2012	56 (H)	25			0.6	
Unscheduled 8	22OCT2012	42	26			0.8	
Week 11	29OCT2012	37	24	36	0.2	0.7	
Week 14	21NOV2012	34	19	32	0.2	0.9	
Week 17	13DEC2012	32	19	28	0.2	0.5	
Week 20	04JAN2013	33	29	30	0.3	0.8	
Week 23	28JAN2013	30	26	29	0.3	0.9	
Week 26	25FEB2013	35	27	33	0.3	0.9	
Unscheduled 9	15APR2013	32	20	30	0.2	0.6	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 207/002
Age: 64	**Sex:** Female
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event:	Coronary artery disease

Narrative:

Patient 207-002, a 64-year-old female with a history of hypertension, dyslipidemia, and type 2 diabetes mellitus enrolled in the study on 17 JAN 2012. She was randomized to placebo on 02 FEB 2012; the first dose of placebo was administered on the same date. Concomitant medications included Lotrial® (enalapril) 2.5 mg BID (hypertension), Clonagin® (clonazepam) 2 mg QD (ansiolitic), metformin 850 mg TID and Humulin® (human recombinant NPH insulin) 60 IU TID (diabetes), rosuvastatin 10 mg QD (dyslipidemia), and aspirin (acetylsalicylic acid) 100 mg QD (antiplatelet).

On 03 AUG 2012 (Day 184), the patient presented for Visit 12 and follow-up intravascular ultrasound where progression of atheroma in the target lesion was found. The patient was admitted to the hospital due to worsening of coronary disease. The event was considered mild in intensity and the investigator reported that he would continue to perform percutaneous coronary intervention (PCI) of the right coronary artery. The patient received heparin 10,000 IU once, glyceryl trinitrate 100 µg once, and prasugrel 60 mg once for the intravascular ultrasound. On 04 AUG 2012 (Day 185), the event of worsening coronary artery disease was considered resolved and the patient was discharged from the hospital on the same date. Study drug had been discontinued on 02 AUG 2012 (Day 183), prior to the onset of the SAE, when the patient completed study drug treatment.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 207/007
Age: 71	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 207-007, a 71-year-old male with no reported relevant medical history enrolled in the study on 25 JAN 2012. He was randomized to RVX000222 200 mg on 16 FEB 2012; the first dose of study drug was administered on the same date. Concomitant medications included Aldactone® (spironolactone) 25 mg QD, Aproval® (irbesartan) 300 mg QD, losartan 25 mg QD, and Pelmec® (amlodipine) 5 and 10 mg QD (hypertension), amiodarone HCl 200 mg QD (arrhythmia), heparin 10,000 IU and glyceryl trinitrate 100 g (IVUS), Crestor® (rosuvastatin) 5 mg QD (dyslipidemia), and aspirin (acetylsalicylic acid) 100 mg QD (antiplatelet).

On 02 MAY 2012 (Day 77), at Visit 7, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal (see table below). Treatment with study drug was not changed. Despite continuous dosing with study drug, hepatic enzyme levels gradually improved, such that by the follow-up visit on 20 SEP 2012 (Day 218), enzyme levels were within normal limits.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	07FEB2012	23	21	13	0.3	0.8	
Week 0	16FEB2012	29	22	13	0.3	0.7	
Week 2	01MAR2012	49	24	23	0.5 (H)	1.1	
Week 4	15MAR2012	61 (H)	31	21	0.5 (H)	1.1	
Week 6	29MAR2012	40	30	18	0.3	0.7	
Week 8	12APR2012	60 (H)	34	15	0.3	0.8	
Week 11	02MAY2012	170 (H)	62 (H)	23	0.4 (H)	0.9	
Week 14	23MAY2012	139 (H)	47 (H)	27	0.5 (H)	1.1	
Week 17	19JUN2012	62 (H)	34	15	0.6 (H)	1.4 (H)	
Week 20	05JUL2012	53 (H)	31	15	0.4 (H)	0.9	
Week 23	26JUL2012	50 (H)	23	8	0.3	0.6	
Week 26	21AUG2012	58 (H)	33	11	0.5 (H)	1.2	
Follow-Up	20SEP2012	25	24	4	0.3	0.7	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 207/017
Age: 63	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event:	Coronary artery disease

Narrative:

Patient 207-017, a 63-year-old male with a history of hypertension, stable angina, dyslipidemia, and obesity enrolled in the study on 18 JUN 2012. He was randomized to placebo on 16 JUL 2012; the first dose of placebo was administered on the same date. Concomitant medications included telmisartan 40 mg QD (hypertension), Crestor® (rosuvastatin) 10 mg QD (dyslipidemia), and aspirin (acetylsalicylic acid) 100 mg QD and Nefazan® (clopidogrel) 75 mg QD (antiplatelet).

On 29 JAN 2013 (Day 198), the patient presented for Visit 12 and follow-up intravascular ultrasound where worsening of coronary lesions and intra-stent restenosis (ISR) were observed. The patient was admitted to the hospital due to worsening of coronary disease. The event was considered severe in intensity. The patient received heparin 10,000 IU and prasugrel 60 mg once for the intravascular ultrasound. Corrective treatment included percutaneous coronary intervention with drug-eluting stent and balloon. While the patient was hospitalized, clopidogrel was stopped and replaced with prasugrel 10 mg QD due to ISR. On 30 JAN 2013 (Day 199), the event of worsening coronary artery disease was considered resolved and the patient was discharged from the hospital on the same date. Study drug had been discontinued on 28 JAN 2013 (Day 197), prior to the onset of the SAE, when the patient finalized study drug treatment.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 207/023
Age: 72	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event:	Femoral artery pseudoaneurysm

Narrative:

Patient 207-023, a 72-year-old male with a history of percutaneous coronary intervention, hypertension, dyslipidemia, type 2 diabetes mellitus, peripheral vascular disease, arrhythmia, and intermittent claudication enrolled in the study on 22 JUN 2012. He was randomized to RVX000222 200 mg on 11 JUL 2012; the first dose of study drug was administered on the same date. Concomitant medications included bisoprolol 5 mg QD (hypertension), metformin hydrochloride 850 mg Q12H and Endial® (glimepiride) 2 mg BID (diabetes), atorvastatin 10 mg QD (dyslipidemia), and aspirin (acetylsalicylic acid) 100 mg QD and clopidogrel 75 mg QD (antiplatelet).

On 09 JAN 2013 (Day 183), the patient was admitted to the hospital due to femoral pseudoaneurysm. The event was considered moderate in intensity. Femoral pseudoaneurysm was diagnosed by Doppler ultrasound and showed resolution after manual and bandage compression. On 18 JAN 2013 (Day 192), the event of femoral pseudoaneurysm was considered resolved and the patient was discharged from the hospital on the same day. Study drug had been discontinued on 07 JAN 2013 (Day 181), prior to the onset of the SAE, when the patient completed study drug treatment.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 302/010
Age: 73	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Angina pectoris

Narrative:

Patient 302-010, a 73-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, stable angina, dyslipidemia, and Type 2 diabetes mellitus enrolled in the study on 27 AUG 2012. He was randomized to placebo on 31 AUG 2012; the first dose of placebo was administered on the same date. Concomitant medications included Symbicort® (budesonide with formoterol fumarate) 4.5 µg BID, antibiotics NOS, and Lysox® (acetylcysteine) 400 mg BID (lower airway infection), Terazosine® (terazosin hydrochloride) 10 mg QD (benign prostate hypertrophia), Biselect® (Co-Bisoprolol 10/25) 10 mg QD (arterial hypertension), metformin hydrochloride 500 mg QD (Type 2 diabetes mellitus), Crestor® (rosuvastatin calcium) 5 mg QD (dyslipidemia), glucosamine 500 mg PRN (bilateral knee arthrosis), Asaflow® (acetylsalicylic acid) 80 mg QD, clopidogrel 75 mg QD (coronary artery disease), Zyloric® (allopurinol) 300 mg QD (hyperuricemia).

On 05 FEB 2013 (Day 159), the patient was admitted to the hospital due to angina pectoris that was moderate in severity. An electrocardiogram did not show any evidence of ischemia and laboratory values included creatinine kinase 43 U/L (normal range: <190) and troponin 14 ng/L (normal range: <100). The patient left the hospital on 05 FEB 2013 for personal reasons but returned on 06 FEB 2013 (Day 160) for a scheduled angiography, which showed similar stenotic lesions to the index angiography performed on 27 AUG 2012. The patient received lidocaine, enoxaparin, glyceryl trinitrate, and Visipaque 270 (Iodixanol) for the angiography. Percutaneous transluminal coronary angioplasty was not performed and it was noted that medical therapy was the preferred method of treatment. The patient was instructed to use molsidomine 16 mg for symptomatic treatment of nighttime symptoms. No action was taken with study drug as a result of the event. On 07 FEB 2013 (Day 161), the event of angina pectoris was considered resolved with sequelae (lesions in the coronary arteries could not be removed) and the patient was discharged the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 401/007
Age: 58	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event:	Arteriosclerosis coronary artery

Narrative:

Patient 401-007, a 58-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, unstable angina, dyslipidemia, and gastritis enrolled in the study on 13 AUG 2012. He was randomized to RVX000222 200 mg on 05 SEP 2012; the first dose of study drug was administered on the same date. Concomitant medications included losartan 50 mg BID and hydrochlorothiazide 25 mg QD (hypertension), propranolol 40 mg BID (coronary ischemic heart), rosuvastatin 20 mg QD and simvastatin 40 mg QD (dyslipidemia), aspirin (acetylsalicylic acid) 100 mg QD (ischemic coronary artery disease), and omeprazole 20 mg QD (gastritis).

On 07 MAR 2013 (Day 184), the patient presented for Visit 12 and follow-up intravascular ultrasound. The target vessel for the study was unchanged; however, progression of atherosclerotic plaque in the left anterior descending artery was observed, with an increase from 60% to 70-80%. The event was considered moderate in intensity. The patient was given lidocaine 2% 20 mL, atropine 0.75 mg, protamine 100 IU, Rivotrol® (clonazepam) 5 gtt, Dormonid® (midazolam) 5 mg, heparin 10 mL, Tridil® (glyceryl trinitrate) 25 mg, and Plasil® (metoclopramide) 1 vial for the angiography. On 30 APR 2013 (Day 238), the patient underwent percutaneous coronary intervention with implantation of 2 stents. On the same date, the event of progression of atherosclerotic plaque in the left anterior descending artery was reported as resolved and the patient was discharged from the hospital. Study drug had been discontinued on 06 MAR 2013 (Day 183), prior to the onset of the SAE, when the patient finalized study drug treatment.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 403/006
Age: 62	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative: Death	
Event(s): Death	

Narrative:

Patient 403-006, a 62-year-old male with a history of hypertension, unstable angina, dyslipidemia, Type 2 diabetes mellitus and psoriasis enrolled in the study on 20 SEP 2012. He was randomized to placebo on 03 OCT 2012; the first dose of placebo was administered on the same date. Concomitant medications included captopril 50 mg BID and atenolol 50 mg BID (hypertension), metformin 850 mg TID (hypoglycemia), rosuvastatin 10 mg QD (dyslipidemia), acetylsalicylic acid 100 mg QD (antiplatelet), and omeprazole 20 mg QD (antacid).

On 26 NOV 2012 (Day 55), the patient's wife informed the site that the patient had died on 27 OCT 2012 (Day 25) at approximately 02:30. He was a night watchman and was found by his colleague in the morning after his shift. An autopsy was performed and the cause of death was determined as acute myocardial infarction.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 409/003
Age: 61	**Sex:** Male
Race: Asian	**Study Drug:** RVX000222
Reason for Narrative: Discontinuation Due to Adverse Event	
Event(s): Hepatic enzyme increase	

Narrative:

Patient 409-003, a 61-year-old male with a history of dyslipidemia and hepatitis A enrolled in the study on 27 AUG 2012. He was randomized to RVX000222 200 mg on 11 SEP 2012; the first dose of study drug was administered on 12 SEP 2012. Concomitant medications included Valium® (diazepam) 3 mL QD (IVUS), heparin 0.5 mL QD (angiography), Crestor® (rosuvastatin) 10 mg QD (dyslipidemia), and aspirin 100 mg QD and Plavix® (clopidogrel) 75 mg QD (antiplatelet).

On 23 OCT 2012 (Day 42), laboratory tests revealed hepatic enzyme increases >5-8X upper limit of normal (see table below). No treatment was given for the event. Treatment with study drug was permanently discontinued on 25 OCT 2012 (Day 44). The event of hepatic enzyme increase resolved on 23 NOV 2012 (Day 73).

The investigator considered the hepatic enzyme increase to be possibly related to study drug. At the time of discontinuation, the patient had received 44 days of study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	28AUG2012	33	29	22	0.2	0.7	
Week 0	11SEP2012	26	29	18	0.2	0.6	
Week 2	24SEP2012	33	27	21	0.4 (H)	0.9	
Week 4	09OCT2012	44	30	24	0.3	0.8	
Week 6	23OCT2012	292 (H)	145 (H)	29	0.4 (H)	0.9	
Unscheduled 3	29OCT2012	359 (H)	178 (H)			1.1	
Unscheduled 5	01NOV2012	328 (H)	160 (H)			0.9	
Week 8	06NOV2012	278 (H)	129 (H)	39	0.3	0.7	
Week 8	06NOV2012	273 (H)	134 (H)			0.8	
Unscheduled 6	09NOV2012	220 (H)	101 (H)			0.8	
Unscheduled 7	23NOV2012	67 (H)	44 (H)			0.9	
Week 11	27NOV2012	54 (H)	30	33	0.4 (H)	0.9	
Unscheduled 8	27NOV2012	52 (H)	36			0.9	
Week 14	18DEC2012	28	30	23	0.2	0.6	
Week 17	08JAN2013	26	26	29	0.2	0.8	
Week 20	29JAN2013	20	24	24	0.3	0.7	
Week 23	19FEB2013	22	24	23	0.3	0.8	1.18 (H)
Week 26	12MAR2013	21	25	21	0.4 (H)	0.8	
Follow-Up	11APR2013	22	21	19	0.4 (H)	0.9	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 409/005
Age: 64	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Haemorrhage

Narrative:

Patient 409-005, a 64-year-old male with a history of hypertension, stable angina, dyslipidemia, and intervertebral disc protrusion enrolled in the study on 04 SEP 2012. He was randomized to placebo on 19 SEP 2012; the first dose of placebo was administered on 20 SEP 2012. Concomitant medications included carvedilol 3.125 mL QD, losartan 50 mg BID, atenolol 50 mg QD, amlodipine 5 mg QD, and furosemide 40 mg QD (hypertension), folic acid 5 mg QD and ferrous sulfate 300 mg BID (anemia post bleeding) heparin 1.1 mL QD (angiography), rosuvastatin 10 mg QD (dyslipidemia), aspirin 100 mg QD and clopidogrel 75 mg QD (antiplatelet), and omeprazole 20 mg QD and 20 mg BID (bleeding and gastric protection).

On 07 DEC 2012 (Day 79), the patient was hospitalized due to severe dyspnea and was diagnosed with chronic coronary insufficiency that was moderate in intensity. Laboratory data revealed hemoglobin 7 g/dL, hematocrit 25%, and platelet count 180,000/mm^3 (normal ranges not provided). Treatment with study drug was not changed. At the time of the last report, the patient underwent endoscopy on 11 DEC 2012 as investigation of bleeding was confirmed. The patient was treated with ferrous sulphate and folic acid. On 12 DEC 2012 (Day 84), the event was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 501/001
Age: 45	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Depression Depression Bipolar disorder

Narrative:

Patient 501-001, a 45-year-old female with a history of percutaneous coronary intervention, hypertension, stable angina, dyslipidemia, Type 2 diabetes mellitus, chronic obstructive pulmonary disease, depression, gastroesophageal reflux disease, and myocardial ischemia enrolled in the study on 23 NOV 2011. She was randomized to RVX000222 200 mg on 05 DEC 2011; the first dose of study drug was administered on the same date. Concomitant medications included ramipril 5 mg BID (hypertension), Spiriva® (tiotroprium bromide) 2.5 mg BID and Theospirex® (theophylline) 150 mg BID (chronic obstructive pulmonary disease), Xanax SR® (alprazolam) 0.5 and 1 mg QD, Olzin® (olanzapine) 10 mg QD, and Rexetin® (paroxetine hydrochloride) 20 mg QD (depression), Atoris® and Sortis® (atorvastatin) 40 mg QD (dyslipidemia), Olicard® (isosorbine mononitrate) 40 mg QD, Mezitan MR® (trimetazidine) 35 mg BID, and Aspirin Protect® (acetylsalicylic acid) 100 mg QD (chronic ischemic heart disease), Kerberan® (clopidogrel) 75 mg QD (percutaneous coronary intervention), and Nolpaza® (pantoprazole sodium sesquihydrate) 20 mg BID (gastroesophageal reflux disease).

On 21 DEC 2011 (Day 17), the patient was admitted to the hospital due to worsening of depression of severe intensity. The investigator stated that the depressive state had aggravated around Christmas. The patient's antidepressant therapy was adjusted and treatment for the event was as follows: Olzin® (olanzapine) was decreased from 10 mg QD to 5 mg QD, Rexetin® was discontinued, and Aurorix® (miclobemide) 150 mg QD was initiated. Treatment with the study drug was not changed. On 25 DEC 2011 (Day 21), the event was considered resolved, and the patient was discharged from the hospital on the same date.

On 19 JAN 2012 (Day 46), the patient was admitted to the hospital due to recurring symptoms of worsening depression that was mild in severity. The patient's antidepressant therapy was adjusted and treatment for the event was as follows: Cipralex® (escitalopram) 10 mg QD was initiated, Aurorix® was discontinued, Olzin® (olanzapine) was increased to 10 mg QD, and Xanax SR® (alprazolam) therapy was increased to 0.5 mg in the morning and 1 mg in the evening. Treatment with the study drug was not changed. The

event of depression was considered resolved on 03 FEB 2012 (Day 61) and the patient was discharged from the hospital on the same date.

On 08 MAR 2012 (Day 95), the patient was admitted to the hospital due to worsening of bipolar affective disorder that was mild in severity. The patient had experienced recurrent symptoms of depression after familial conflict and financial problems. No treatment was given for the event and treatment with study drug was not changed. On 20 MAR 2012 (Day 107), the event of bipolar disorder was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered all of the events to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 501/008
Age: 50	**Sex:** Female
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Anaemia

Narrative:

Patient 501-008, a 50-year-old female with a history of myocardial infarction (myocardial ischemia), coronary artery bypass graft surgery, percutaneous coronary intervention, hypertension, congestive heart failure, stable angina, dyslipidemia, Type 2 diabetes mellitus, anemia, anxiety, gastroesophageal reflux disease, female sterilization, and metrorrhagia enrolled in the study on 10 JAN 2012. She was randomized to placebo on 16 JAN 2012; the first dose of placebo was administered on the same date. Concomitant medications included Coverex AS Komb® (indapmide and perindopril) 5/1.25 mg QD, Coverex AS® (perindopril erbumine) 5 mg QD, Tenox® (temazepam) 5 mg QD, Nebispes® (nebivolol) 5 mg BID, and Procorolan® (ivabradine hydrochloride) 7.5 mg QD (hypertension), Noacid® (dihydroxyaluminum sodium carbonate) 40 mg QD (gastroesophageal reflux disease), Frontin® (alprazolam) 0.25 mg TID (anxiety), blood transfusion 2 units PRN (anemia), Crestor® (rosuvastatin) 20 mg QD and Ezetrol® (ezetimibe) 10 mg QD (dyslipidemia), Humulin R (insulin) 24 units TID and Humulin N 22 units QD (diabetes mellitus), Mezitan® (trimetazidine) 35 mg BID, Astrix® (acetylsalicylic acid) 100 mg QD, and Plagrel® (clopidogrel bisulfate) 75 mg QD (ischemic heart disease), Kaldyum® (potassium chloride) 600 mg TIS and furosemide 20 mg TIS (heart failure), glyceryl trinitrate 200 µg QD (premedication) and warfarin sodium 10 mg QD (aortic valve replacement).

On 06 APR 2012 (Day 82), the patient was urgently admitted to hospital for cardiac chest pain Canadian Cardiovascular Society classification 4 (CCS 4) and anemia. On 10 APR 2012 (Day 86), laboratory tests revealed severe anemia with hemoglobin of 66 g/L (normal range: 118-148 g/L) and hematocrit of 0.24 L/L (normal range: 0.36-0.44 L/L). Cardiac chest pain was considered to be a symptom of anemia. The patient received blood transfusions of 800 mL PRN from 10 APR 2012 to 12 APR 2012. Treatment with study drug was not changed. On 13 APR 2012 (Day 89), the event of anemia was considered to be resolved and the patient was discharged on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 501/014
Age: 40	**Sex:** Female
Race: White	**Study Drug:** Placebo
Reason(s) for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Event(s):	Coughing Dyspnoea

Narrative:

Patient 501-014, a 40-year-old female with a history of myocardial infarction (myocardial ischaemia), percutaneous coronary intervention, hypertension, congestive heart failure, stable angina, dyslipidemia, anxiety, appendicectomy, cholecystectomy, and thyroidectomy enrolled in the study on 20 JAN 2012. She was randomized to RVX000222 200 mg on 25 JAN 2012; the first dose of study drug was administered on the same date. Concomitant medications included ramipril 2.5 mg QD, Co-Diovan® (valsartan/hydrocholorothiazide) 80/6.125 mg QD and Procoralan® (ivabradine hydrochloride) 5 mg BID (hypertension), alprazolam 0.25 mg TID (anxiety), Crestor® (rosuvastatin) 20 mg QD (dyslipidemia), glyceryl trinitrate 200 µg QD (premedication) and 8 mg PRN (ischemic heart disease), Olicard® (isosorbide mononitrate) 60 mg QD, Aspirin Protect® (acetylsalicylic acid) 100 mg QD (ischemic heart disease), trimetazidine 35 mg BID, Kaldyum® (potassium chloride) 600 mg QOD, and furosemide 40 mg QOD (heart failure), Augmentin duo (spektramox) 1000 mg BID (bronchitis), and Zimpax® (pantoprazole sodium sesquihydrate) 20 mg BID (gastrointestinal protection).

On 23 MAR 2012 (Day 59), the patient experienced the serious event of coughing that was severe in intensity, which progressed over the next 7 days. On 30 MAR 2012 (Day 66), the patient was hospitalized for the serious event of dyspnea that was moderate in intensity. Laboratory tests and plain chest x-ray revealed no signs of inflammation, pneumonia, or heart failure. Ramipril therapy was withdrawn and Tensart® (valsartan) 40 mg QD was initiated. At the patient's request, study drug was permanently discontinued on 31 MAR 2012 (last dose taken on 30 MAR 2012) and the symptoms improved on the next day. On 02 APR 2012 (Day 69), the coughing and dyspnoea resolved, and the patient was discharged from the hospital the same day. The patient refused to attempt reintroduction of the study drug.

The investigator considered the events of coughing and dyspnoea to be unrelated to study drug. At the time of discontinuation, the patient had received 66 days of study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 501/020
Age: 59	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Angina unstable

Narrative:

Patient 501-020, a 59-year-old male with a history of hypertension, unstable angina, dyslipidemia, epilepsy, gastroesophageal reflux disease, hyperuricaemia, and myocardial ischemia enrolled in the study on 27 FEB 2012. He was randomized to placebo on 05 MAR 2012; the first dose of placebo was administered on the same date. Concomitant medications included Hartil® (ramipril) 5/25 mg QD, Concor® (bisopropolol fumarate) 7.5 mg QD, and glyceryl trinitrate 5 mg QD (hypertension), Noacid® (dihydroxyaluminum sodium carbonate) 40 mg BID (gastroesophageal reflux disease), Sortis® (atorvastatin calcium) 40 mg QD (dyslipidemia), Mezitan® (trimetazidine) 35 mg BID, Aspirin Protect® (acetylsalicylic acid) 100 mg QD, and Egitromb® (clopidogrel) 75 mg QD (ischemic heart disease).

On 30 AUG 2012 (Day 179), the patient reported moderate chest pain at rest lasting for 10 minutes, and symptoms were relieved by sublingual glyceryl trinitrate. Angina recurred 3 times. On 31 AUG 2012 (Day 180) the patient was hospitalized for unstable angina and underwent urgent cardiac catheterization. Coronary angiography showed no significant lesions, and follow-up intravascular ultrasound was also performed as per protocol. The patient did not receive any treatment for the event, and treatment with study drug was not changed. On 31 AUG 2012 (Day 180), the event of unstable angina was considered resolved; the patient was discharged from the hospital on 03 SEP 2012 (Day 183).

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 501/029
Age: 56	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 501-029, a 56-year-old male with a history of hypertension, stable angina, dyslipidemia, Type 2 diabetes mellitus, and psoriasis enrolled in the study on 14 MAY 2012. He was randomized to RVX000222 200 mg on 23 MAY 2012; the first dose of study drug was administered on the same date. Concomitant medications included irbesartan/hydrochlorothiazide 100/6.25 mg QD, metoprolol 25 mg QD (hypertension), metformin 1000 mg BID and gliclazide 90 mg QD (diabetes), atorvastatin 40 mg QD (atherosclerosis), glyceryl trinitrate 200 µg (IVUS), acetylsalicylic acid 100 mg QD (ischemic heart disease), and allopurinol 300 mg QD (hyperuricemia).

On 17 JUL 2012 (Day 56), at Visit 6, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal (ULN), AST >1x ULN, and GGT >2x ULN (see table below). Despite continuous dosing with study drug, hepatic enzyme levels gradually improved, such that by Visit 11 on 31 OCT 2012 (Day 162), all liver enzyme levels were within normal limits and remained normal through the follow-up visits.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	15MAY2012	21	20	40	0.2	0.6	
Week 0	23MAY2012	20	17	37	0.2	0.5	
Week 2	06JUN2012	20	17	35	0.1	0.4	
Week 4	18JUN2012	20	21	44	0.1	0.5	
Week 6	02JUL2012	27	21	40	0.2	0.6	
Week 8	17JUL2012	166 (H)	67 (H)	149 (H)	0.2	0.6	
Week 11	08AUG2012	130 (H)	62 (H)	164 (H)	0.3 (H)	0.9	
Week 14	29AUG2012	39	24	100 (H)	0.3	0.6	
Week 17	18SEP2012	28	21	64	0.2	0.6	
Week 20	10OCT2012	50 (H)	30	82 (H)	0.3	0.7	
Week 23	31OCT2012	30	23	55	0.2	0.5	
Week 26	21NOV2012	21	22	47	0.2	0.7	
Follow-Up	19DEC2012	25	26	45	0.2	0.7	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H = high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 501/037
Age: 44	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Non-cardiac chest pain

Narrative:

Patient 501-037, a 44-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, dyslipidemia, myocardial ischemia, and epilepsy enrolled in the study on 11 SEP 2012. He was randomized to RVX000222 200 mg on 19 SEP 2012; the first dose of study drug was administered on the same date. Concomitant medications included perindopril 4 mg BID, nebivolol 5 mg QD, and glyceryl trinitrate 0.4 mg QD (hypertension), clonazepam 0.5 mg TID and Tegretol® (carbamazepine) 200 mg BID (epileptic disease), rosuvastatin 20 mg QD (dyslipidemia), glyceryl trinitrate 200 µg QD (intravascular ulstrasound), acetylsalicylic acid 100 mg QD and clopidogrel 75 mg QD (ischemic heart disease), and pantoprazole 40 mg QD (gastrointestinal protection).

On 09 OCT 2012 (Day 21), the patient was urgently hospitalized after experiencing mild non-cardiac chest pain which lasted for 1 hour. Electrocardiogram, echocardiography, and laboratory tests showed no abnormalities. Drug treatment (not specified) was given for the event; treatment with study drug was not changed. On 09 OCT 2012, the event of non-cardiac chest pain was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 502/018
Age: 58	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Coronary artery disease

Narrative:

Patient 502-018, a 58-year-old male with a history of unstable angina, dyslipidemia, duodenal ulcer, and gastroesophageal reflux disease enrolled in the study on 27 MAY 2012. He was randomized to placebo on 01 JUN 2012; the first dose of placebo was administered on the same date. Concomitant medications included Coverex AS Komb Forte® (indapmide and perindopril) 10/2.5 mg QD, Nebibeta® (nebivolol) 2.5 mg QD, Normodipine® (amlodipine besilate) 2.5 mg QD (hypertension), Crestor® (rosuvastatin) 10 mg QD (dyslipidemia), Nootropil® (piracetam) 1200 mg BID (neurological prophylaxis), Aspirin Protect® (acetylsalicylic acid) 100 mg QD (angina pectoris), and rabeprazole 20 mg QD (gastroesophageal reflux disease).

On 27 NOV 2012 (Day 180), the patient was hospitalized for follow-up intravascular ultrasound and angiogram. A marked worsening of coronary artery disease that was moderate in severity was noted and previously non-significant left circumflex coronary artery (LCX) lesion progressed which was causing a significant stenosis. Percutaneous coronary intervention of the LCX was done and the patient was started on clopidogrel 75 mg QD. Treatment with the study drug was not changed. On 28 NOV 2012 (Day 181), the event of coronary artery disease was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 502/020
Age: 55	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	In-stent arterial restenosis

Narrative:

Patient 502-020, a 55-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, stable angina, dyslipidemia, and benign prostatic hyperplasia enrolled in the study on 05 JUN 2012. He was randomized to RVX000222 200 mg on 12 JUN 2012; the first dose of study drug was administered on the same date. Concomitant medications included Vidotin Comb® (perindopril erbumine) 4/1.25 mg QD, Nebibeta® (nebivolol) 5 mg QD (hypertension), Noacid® (dihydroxyaluminum sodium carbonate) 40 mg QD (gastrointestinal bleeding prophylaxis), Xeter® (Crestor®; rosuvastatin calcium) 20 mg QD (dyslipidemia), Aspirin Protect® (acetylsalicylic acid) 100 mg QD and Plavix® (clopidogrel bisulfate) 75 mg QD (prior myocardial infarction).

On 14 DEC 2012 (Day 186), the patient went to the site for his Visit 12 follow-up intravascular ultrasound (IVUS). Coronary angiogram showed moderate diffuse in-stent restenosis of the previously implanted right coronary artery (RCA) stent and the patient was admitted to the hospital. Target coronary IVUS was done and afterwards percutaneous coronary intervention of the RCA with drug-eluting stent implantation was performed. The event of in-stent arterial restenosis was considered resolved on 14 DEC 2012, and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 502/022
Age: 63	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 502-022, a 63-year-old male with a history of myocardial infarction, percutaneous coronary intervention, dyslipidemia, Type 2 diabetes mellitus, and peptic ulcer hemorrhage enrolled in the study on 19 JUN 2012. He was randomized to RVX000222 200 mg on 26 JUN 2012; the first dose of study drug was administered on the same date. Concomitant medications included Lendormin® (brotizolam) 0.25 mg QD (sleep aid), Lokren® (betaxolol HCl) 20 mg QD, Moduxin MR® (trimetazidine) 35 mg BID, and Aspirin Protect® (acetylsalicylic acid) 100 mg QD (prior acute myocardial infarction), Meforal (metformin) 850 mg BID (diabetes), Crestor® (rosuvastatin) 20 mg QD (coronary artery disease, prior myocardial infarction), Thrombex® (clopidogrel) 75 mg QD (prior acute myocardial infarction with stent implantation), and Pafenon® (pantoprazole) 40 mg QD (prior peptic ulcer and gastrointestinal bleed).

On 12 SEP 2012 (Day 79), at Visit 7, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal (ULN), AST >1x ULN, and slight elevation in bilirubin (see table below). Despite continuous dosing with study drug, hepatic enzyme levels gradually improved, such that by Visit 8 on 24 OCT 2012 (Day 121), ALT and AST levels were within normal limits and remained normal through the follow-up visits. Direct bilirubin remained slightly elevated until the follow-up visit on 24 JAN 2013 (Day 213), when levels returned to normal.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	19JUN2012	15	19	12	0.3 (H)	1.0	
Week 0	26JUN2012	13	16	10	0.2	0.7	
Week 2	11JUL2012	15	17	9	0.4 (H)	1.2	
Week 4	25JUL2012	16	19	10	0.4 (H)	1.0	
Week 6	08AUG2012	22	19	10	0.4 (H)	1.1	
Week 8	22AUG2012	18	16	11	0.4 (H)	1.2	
Week 11	12SEP2012	186 (H)	75 (H)	20	0.5 (H)	1.6 (H)	
Unscheduled 2	25SEP2012	54 (H)	27	20	0.3 (H)	1.1	0.97
Week 17	24OCT2012	31	22	17	0.3 (H)	0.9	
Week 20	14NOV2012	24	22	16	0.3 (H)	0.7	
Week 23	06DEC2012	27	20	17	0.4 (H)	1.1	
Week 26	06JAN2013	32	30	11	0.3 (H)	0.9	
Follow-Up	24JAN2013	15	19	11	0.2	0.6	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 502/026
Age: 68	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason(s) for Narrative:	Clinically Significant Event Serious Adverse Event
Event(s):	Elevated liver enzymes Cholecystitis Coronary artery disease

Narrative:

Patient 502-026, a 68-year-old female with a history of myocardial infarction, coronary artery bypass graft (CABG) surgery, hypertension, stable angina, dyslipidemia, and malignant breast lump removal enrolled in the study on 05 JUL 2012. She was randomized to RVX000222 200 mg on 10 JUL 2012; the first dose of study drug was administered on the same date. Concomitant medications included Tensiomin® (captopril) 25 mg PRN, Coverex AS® (perindopril erbumine) 10 mg QD, Cardura XL® (doxazosin mesilate) 4 mg QD, Frontin® (alprazolam) 0.5 mg PRN, Concor® (bisoprolol fumarate) 10 mg QD, and Normodipine® (amlodipine besilate) 10 mg QD (hypertension), Atoris® (Sortis®; atorvastatin calcium) 20 mg QD, Olicard® (isosorbide mononitrate) 60 mg QD, Preductal MR® (trimetazidine) 35 mg BID, and Aspirin Protect® (acetylsalicylic acid) 100 mg QD, (post-CABG surgery), clopidogrel 75 mg QD (stent implantation), and Controloc® (pantoprazole) 20 mg BID (gastrointestinal bleeding prophylaxis).

On 28 NOV 2012 (Day 142), at Visit 10, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal (ULN), AST >3x ULN, GGT >8x ULN, and slight elevation in bilirubin (see table below). The liver enzyme elevation was not reported as an adverse event. Treatment with study drug was not changed.

On 05 DEC 2012 (Day 149), the patient was admitted to the hospital due to cholecystitis that was moderate in severity. Belt-like abdominal pain was present and the patient's laboratory values showed increased liver and biliary obstruction enzymes including: AST 108 U/L (normal range: <31), ALT 277 U/L (normal range: <34) and alkaline phosphatase 936 U/L (normal range: 98-279). Treatment with study drug was not changed. On 12 DEC 2012 (Day 156), the event of cholecystitis was considered resolved and the patient was discharged from the hospital on the same date.

On 10 JAN 2013 (Day 185), the patient presented for scheduled Visit 12 and follow up intravascular ultrasound (IVUS) and was admitted to the hospital for percutaneous coronary intervention (PCI) due to worsening of coronary artery disease that was moderate in severity. All laboratory values were within

normal ranges. Intravascular ultrasound was performed followed by PCI of the left circumflex artery. Treatment with the study drug was not changed due to the event, however, study drug was discontinued on 10 JAN 2013 at Visit 12 per protocol. On 11 JAN 2013 (Day 186), the event of coronary artery disease was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered both events to be unrelated to study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	05JUL2012	14	19	34	0.1	0.5	
Week 0	10JUL2012	11	19	39	0.2	0.7	
Week 2	25JUL2012	20	22	31	0.3	0.9	
Week 4	08AUG2012	21	20	33	0.3	1.0	
Week 6	22AUG2012	18	20	36	0.2	0.5	
Week 8	05SEP2012	24	15	58 (H)	0.2	0.6	
Week 11	26SEP2012	19	17	37	0.2	0.6	
Week 14	17OCT2012	20	22	41	0.3	0.8	
Week 17	07NOV2012	41	21	106 (H)	0.3 (H)	1.0	
Week 20	28NOV2012	173 (H)	185 (H)	487 (H)	0.5 (H)	1.0	
Unscheduled 2	04DEC2012	144 (H)	54 (H)	472 (H)	0.3	0.7	
Week 23	20DEC2012	30	29	342 (H)	0.4 (H)	0.7	
Week 26	10JAN2013	26	25	91 (H)	0.4 (H)	1.0	
Follow-Up	14FEB2013	21	22	37	0.3	0.7	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 502/035
Age: 64	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Pneumonia

Narrative:

Patient 502-035, a 64-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, dyslipidemia, and Type 2 diabetes mellitus enrolled in the study on 23 AUG 2012. He was randomized to placebo on 04 SEP 2012; the first dose of placebo was administered on the same date. Concomitant medications included Talliton® (carvedilol) 12.5 mg BID, Tanydon® (telmisartan) 80 mg QD, and Narva SR® (indapamide) 1.5 mg QD (hypertension), Merckformin® (metformin hydrochloride) 1 g BID, Lantus® (insulin glargine) 28 units QD, and Diaprel MR® (gliclazide) 60 mg BID (diabetes), Atoris® (Sortis®, atorvastatin calcium) 40 mg QD (dyslipidemia), and acetylsalicylic acid 100 mg QD (prior myocardial infarction)

On 15 DEC 2012 (Day 103), the patient experienced fever and shortness of breath and after referral from the general practitioner to the hospital, he was diagnosed with pneumonia that was mild in severity. Laboratory data included C-reactive protein 9 mg/L on 15 DEC 2012, 7 mg/L on 17 DEC 2012 and 4 mg/L on 20 DEC 2012 (normal range: 5 mg/L). All other laboratory values were within normal limits. Treatment for the event included oral clarithromycin 1000 mg from 15 DEC 2012 to 26 DEC 2012, and treatment with the study drug was not changed. On 21 DEC 2012 (Day 109), the event of pneumonia was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 502/036
Age: 63	**Sex:** Female
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	In-stent coronary artery restenosis

Narrative:

Patient 502-036, a 63-year-old female with a history of myocardial infarction, percutaneous coronary intervention, hypertension, dyslipidemia, Type 2 diabetes mellitus, and hypothyroidism enrolled in the study on 30 AUG 2012. She was randomized to placebo on 04 SEP 2012; the first dose of placebo was administered on the same date. Concomitant medications included Tritace® (ramipril) 1.25 mg BID and Lokren® (betaxololhydrochloride) 20 mg QD (hypertension), Noacid® (dihydroxyaluminum sodium carbonate) 40 mg QD (bleeding prophylaxis), Merckformin® (metformin hydrochloride) 500 mg BID (diabetes), Atoris® (Sortis®, atorvastatin calcium) 40 mg QD (dyslipidemia), Nitroderm® (glyceryl trinitrate) 5 mg QD, acetylsalicylic acid 100 mg QD, and Kardogrel® (clopidogrel) 75 mg QD (prior myocardial infarction, coronary artery disease), Kalydum® (postassium chloride) 600 mg QD (furosemide supplement), furosemide 40 mg QD (prophylaxis of ankle edema), and Euthyrox® (levothyroxine sodium) 100 µg QD (hypothyreosis).

On 05 Mar 2013 (Day 183), the patient was admitted to the site hospital for Visit 12 and follow-up intravascular ultrasound. Coronary angiography showed moderate diffuse in-stent restenosis of left anterior descending (LAD) stent implanted at Visit 1. On the same day, percutaneous coronary intervention of LAD stent was performed and a drug eluting stent was implanted. Treatment with study drug was not changed. On 06 MAR 2013 (Day 184), the event of in-stent restenosis was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 502/041
Age: 58	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Non-cardiac chest pain

Narrative:

Patient 502-041, a 58-year-old male with a history of myocardial infarction, hypertension, stable angina, dyslipidemia, cardiac pacemaker insertion, epilepsy, paranoia, and sick sinus syndrome enrolled in the study on 25 SEP 2012. He was randomized to placebo on 28 SEP 2012; the first dose of placebo was administered on the same date. Concomitant medications included Co-Prenessa® (indapamide and perindopril) 4/1.25 mg QD and doxazosin 4 mg QD (hypertension), Frisium® (clobazam) 250 mg BID, Depakin Chrono® (valproate sodium) 750 mg BID, Keppra® (levetiracetam) 500 mg BID, and Hunperdal® (risperidone) 2 mg QD (epilepsy), Nebilet® (nebivolol hydrochloride) 5 mg QD, Adexor MR® (trimetazidine hydrochloride) 35 mg BID, and acetylsalicylic acid 100 mg QD (prior myocardial infarction), and Sortis® (atorvastatin calcium) 40 mg QD (dyslipidemia).

On 03 OCT 2012 (Day 7), the patient presented with complaints of severe abdominal pain and chest pain and was hospitalized due to non-cardiac chest pain that was mild in severity. Laboratory tests showed no abnormalities, cardiac necro-enzymes remained negative, and a chest/abdomen CT was negative. Upper gastrointestinal endoscopy revealed a peptic ulcer that was not of acute nature. Treatment for the event included Flector® (diclofenac sodium) 50 mg PRN, Ulcogant® (sucralfate) 4 g TID and Contoroloc® (pantoprazole) 40 mg BID. Treatment with the study drug was not changed. On 05 OCT 2012 (Day 8), the event of non-cardiac chest pain was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 503-002
Age: 48	**Sex:** Female
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 503-002, a 48-year-old female with a history of hypertension, stable angina, metabolic syndrome, dyslipidemia, and Type 2 diabetes mellitus enrolled in the study on 12 JAN 2012. She was randomized to RVX000222 200 mg on 18 JAN 2012; the first dose of study drug was administered on the same date. Concomitant medications included Co-Diovan® (valsartan and hydrochlorothiazide) 80/12.5 mg QD (hypertension), amoxicillin and clavulanic acid 875/125 mg BID (pneumonia), rosuvastatin 20 mg QD (hypercholesterolemia), carbocisteine 375 mg TID and clenbuterol 0.005 mL/mg TID (bronchitis), trimetazidine 35 mg BID and acetylsalicylic acid 100 mg QD (angina pectoris), and lansoprazole 30 mg QD (prevention of hyperacidity).

On 02 MAR 2012 (Day 45), at Visit 5, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal (ULN) and AST >1x ULN (see table below). The study drug was temporarily discontinued from 06 MAR 2012 (Day 49) to 22 MAR 2012 (Day 65) due to an ALT value >3x ULN. Study drug was restarted on 23 MAR 2012 (Day 66). Despite continuation of study drug, hepatic enzyme levels gradually improved, such that by 04 APR 2012 (Day 78), all enzyme levels were within normal ranges. On 26 APR 2012 (Day 100), the patient refused to continue treatment and the study drug was permanently discontinued.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	12JAN2012	15	15	31	0.1	0.3 (L)	
Week 0	18JAN2012	17	14	28	0.1	0.3	
Week 2	01FEB2012	19	17	21	0.1	0.3	
Week 4	15FEB2012	19	15	19	0.1	0.4	
Week 6	02MAR2012	153 (H)	81 (H)	34	0.2	0.5	
Unscheduled 3	07MAR2012	125 (H)	72 (H)	40	0.2	0.6	
Week 8	13MAR2012	66 (H)	33	42	0.1	0.4	
Week 11	04APR2012	17	17	30	0.1	0.3 (L)	
Week 14	26APR2012	18	24	30	0.1	0.4	
Week 17	16MAY2012	16	15	23	0.1	0.2 (L)	
Week 20	06JUN2012	15	14	22	0.1	0.2 (L)	
Week 23	27JUN2012	17	16	23	0.2	0.4	
Week 26	06AUG2012	15	14	23	0.1	0.3	
Follow-Up	04SEP2012	13	15	21	0.1	0.3	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 505/014
Age: 48	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Discontinuation Due to Adverse Event	
Event(s): Weight increased	

Narrative:

Patient 505-014, a 48-year-old male with a history of hypertension, percutaneous coronary intervention, stable angina, dyslipidemia, and anxiety enrolled in the study on 24 APR 2012. He was randomized to RVX000222 200 mg on 04 MAY 2012; the first dose of study drug was administered on the same date. Concomitant medications included enalapril 10 mg BID (hypertonia), alprazolam 0.25 mg QD (anxiety), Concor® (bisoprolol fumarate) 5 mg QD and Olicard® (isosorbide mononitrate) 40 mg QD (angina), Obradon® (atorvastatin) 20 mg QD (dyslipidemia), aspirin 100 mg QD and Plavix® (clopidogrel) 75 mg QD (prior PCI), and Nolpaza® (pantoprazole sodium sesquihydrate) 40 mg BID (ulcer prophylaxis).

On 01 JUL 2012 (Day 59), the patient experienced an increase in weight. No treatment was given for the event. Treatment with study drug was permanently discontinued on 31 JUL 2012 (Day 89). The event of increase in weight was considered ongoing.

The investigator considered the weight increase to be possibly related to study drug. At the time of discontinuation, the patient had received 85 days of study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 505/018
Age: 55	**Sex:** Female
Race: White	**Study Drug :** RVX000222
Reason for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Event(s):	Fatigue Myalgia Transaminases Increased Pyrexia Nausea Angina Pectoris

Narrative:

Patient 505-018, a 55-year-old female with a history of myocardial infarction, percutaneous coronary intervention, hypertension, dyslipidemia, Type 2 diabetes mellitus, and peripheral vascular disorder enrolled in the study on 16 MAY 2012. She was randomized to RVX000222 200 mg on 31 MAY 2012; the first dose of study drug was administered on the same date. Concomitant medications included Renitec® (enalapril) 10 mg BID, Atoris® (atorvastatin calcium) 40 mg QD, Betaloc Zok® (metoprolol succinate) 50 mg BID, Aspirin Protect® (acetylsalicylic acid) 100 mg QD, and Kardogrel® (clopidogrel) 75 mg QD (prior NSTEMI), Nolpaza® (pantoprazole sodium sesquihydrate) 40 mg BID (ulcer prophylaxis), and metformin 500 mg BID (diabetes).

On 01 JUN 2012 (Day 2), the patient experienced fatigue and myalgia. No treatment was given for the events. The events were considered resolved on 30 Jun 2012 (Day 31).

On 12 JUL 2012 (Day 43), laboratory tests revealed elevated transaminase enzymes (see Table). Non-drug treatment (not specified) was given for the event. The event was considered resolved on 12 AUG 2012 (Day 74).

On 17 JUL 2012 (Day 48), the patient experienced pyrexia and nausea. No treatment was given for the events. The pyrexia resolved on 25 JUL 2012 (Day 56) and the nausea resolved on 27 JUL 2012 (Day 58).

Due to the events, the study drug was permanently discontinued on 23 JUL 2012 (Day 54).

The investigator considered all of the events to be possibly related to study drug. At the time of discontinuation, the patient had received 54 days of

study drug.

On 13 DEC 2012 (Day 197), the patient was admitted to the hospital because of angina pectoris, which was moderate in severity. On the same day, she underwent percutaneous coronary intervention due to significant left anterior descending ostial stenosis. Post-intervention, the patient was kept under overnight observation. Treatment with ongoing medications including metoprolol succinate (50 mg BID), acetylsalicylic acid (100 mg QD), and clopidogrel (75 mg QD) was continued. The investigator considered the event of angina pectoris to be unrelated to study drug. On 14 DEC 2012 (Day 198), the event was considered as resolved and the patient was discharged from the hospital.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	16MAY2012	36	25	39	0.2	0.5	
Week 0	31MAY2012	27	19	39	0.2	0.5	
Week 2	14JUN2012	28	18	37	0.2	0.6	
Week 4	02JUL2012	40	27	48	0.2	0.4	
Week 6	12JUL2012	135 (H)	52 (H)	62 (H)	0.3	0.7	
Week 8	24JUL2012	106 (H)	46 (H)	44	0.4 (H)	1.0	
Week 11	10AUG2012	22	19	31	0.1	0.5	
Week 14	11SEP2012	18	15	24	0.1	0.4	
Week 17	27SEP2012	21	14	20	0.1	0.4	
Week 20	18OCT2012	18	17	21	0.1	0.4	
Week 23	06NOV2012	25	20	25	0.1	0.4	
Week 26	06DEC2012	30	18	27	0.2	0.6	
Follow-Up	04JAN2013	23	21	22	0.1	0.5	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 506/003
Age: 61	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Event(s):	Pancreatic carcinoma

Narrative:

Patient 506-003, a 61-year-old male with a history of myocardial infarction, hypertension, stable angina, and Type 2 diabetes mellitus enrolled in the study on 17 APR 2012. He was randomized to RVX000222 200 mg on 02 MAY 2012; the first dose of study drug was administered on the same date. Concomitant medications included rosuvastatin 20 mg (prophylaxis of hypercholesterolemia).

On 28 AUG 2012 (Day 118), the patient underwent gastrointestinal examination and computerized tomography after complaints of stomach pain and was diagnosed with pancreatic carcinoma that was severe in intensity. On 26 SEP 2012 (Day 148) the patient was hospitalized and underwent surgery. Non-operable pancreatic carcinoma was diagnosed by histology. The patient was treated with cytostatic therapy (not specified) and his pain decreased. On 03 OCT 2012 (Day 155) the patient was discharged from the hospital and the event of pancreatic carcinoma was considered resolved with sequelae (pancreatic carcinoma).

At the request of the surgeon, study drug was interrupted on 13 SEP 2012 (Day 135) before the operation and was restarted on 12 OCT 2012 (Day 164) at the same dose; the study drug was permanently discontinued on 14 NOV 2012 (Day 197).

The investigator considered the pancreatic carcinoma to be unrelated to study drug. At the time of discontinuation, the patient had received 168 days of study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 601/008
Age: 69	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Chest pain

Narrative:

Patient 601-008, a 69-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, stable angina, dyslipidemia, Type 2 diabetes mellitus, nephropathy, retinopathy, and fatigue enrolled in the study on 02 MAR 2012. He was randomized to RVX000222 200 mg on 29 MAR 2012; the first dose of study drug was administered on the same date. Concomitant medications included Atacand® (candesartan cilexetil) 32 mg QD and amlodipine 10 mg QD (hypertension), metoprolol 50 mg QD, rosuvastatin 20 mg QD, glyceryl trinitrate 0.4 mg PRN, Promocard® (isosorbide mononitrate) 30 mg QD, triamterene 25 and 50 mg QD, Ascal® (acetylsalicylate calcium) 100 mg QD, ticagrelor 90 mg BID, and hydrochlorothiazide 12.5 mg QD (coronary artery disease), metformin hydrochloride 850 mg BID, and insulin (diabetes), heparin 5000 IU, glyceryl trinitrate 0.2 mg, and Isoptin® (verapamil hydrochloride) 5 mg (coronary angiogram), and Pantozol® (pantoprazole sodium sesquihydrate) 40 mg QD (oesophageal reflux).

On 19 JUL 2012 (Day 113), the patient called his general practitioner with complaints of moderate chest pain. He was admitted to the hospital due to non-specific thoracal pain and remained in the hospital overnight for observation. He was restarted on Promocard® (iosorbide mononitrate) 30 mg QD from 14 JUL 2012 to ongoing; treatment with the study drug was not changed. Laboratory test results included CK-MB 10 µg/L (normal range: <7.6). On 20 JUL 2012 (Day 114), the event of chest pain was considered resolved, and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 601/014
Age: 65	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative:	Discontinuation Due to Adverse Event
Event(s):	Aspartate aminotransferase increased Alanine aminotransferase increased

Narrative:

Patient 601-014, a 65-year-old male with a history of hypertension and stable angina enrolled in the study on 18 JUN 2012. He was randomized to RVX000222 200 mg on 29 JUN 2012; the first dose of study drug was administered on the same date. Concomitant medications included lisinopril 10 mg QD, metoprolol 100 mg QD, rosuvastatin 20 mg QD, and Ascal® (acetylsalicylate calcium) 80 mg QD (coronary artery disease), nifedipine 30 mg and 60 mg QD and furosemide 40 mg QD (hypertension), heparin 5000 IU and glyceryl trinitrate 200 µg PRN (coronary angiography), omeprazole 20 mg QD (stomach complaints), and diclofenac 50 mg TID (achilles tendon injury).

On 14 SEP 2012 (Day 78), laboratory tests revealed increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <8x upper limit of normal (see Table). No treatment was given for the events. Treatment with study drug was permanently discontinued on 29 OCT 2012 (Day 123). The events of AST and ALT increased were considered resolved on 12 NOV 2012 (Day 137) and 07 DEC 2012 (Day 162), respectively.

The investigator considered the events to be probably related to study drug. At the time of discontinuation, the patient had received 123 days of study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	18JUN2012	27	22	24	0.1	0.4	
Week 0	29JUN2012	22	24	22	0.1	0.4	
Week 2	13JUL2012	26	21	20	0.2	0.6	
Week 4	27JUL2012	35	31	18	0.1	0.4	
Week 6	10AUG2012	30	29	16	0.1	0.5	
Week 8	24AUG2012	56 (H)	46 (H)	15	0.2	0.5	
Week 11	14SEP2012	212 (H)	94 (H)	45	0.2	0.6	
Unscheduled 2	26SEP2012	130 (H)	59 (H)	41	0.2	0.4	
Week 14	05OCT2012	167 (H)	86 (H)	34	0.2	0.4	
Week 17	26OCT201	415 (H)	223 (H)	69	0.2	0.6	

	2					
Unscheduled 4	01NOV2012	344 (H)	137 (H)	77 (H)	0.2	0.5
Unscheduled 5	12NOV2012	61 (H)	31	56	0.2	0.5
Week 20	16NOV2012	42	27	47	0.2	0.5
Week 23	07DEC2012	37	30	31	0.1	0.5
Week 26	04JAN2013	14	15	16	0.1	0.3 (L)
Follow-Up	08FEB2013	39	31	33	0.1	0.5

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 601/015
Age: 71	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason(s) for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Event(s):	Transient ischemic attack Presyncope

Narrative:

Patient 601-015, a 71-year-old male with a history of percutaneous coronary intervention, hypertension, congestive heart failure, stable angina, and Type 2 diabetes mellitus enrolled in the study on 19 JUN 2012. He was randomized to RVX000222 200 mg on 02 JUL 2012; the first dose of study drug was administered on the same date. Concomitant medications included irbesartan 150 mg QD, diltiazem 90 mg QD, metoprolol 50 mg and 150 mg QD, rosuvastatin calcium 20 mg QD, glyceryl trinitrate 0.4 mg PRN, Promocard® (isosorbide mononitrate) 120 mg QD, and Ascal® (acetylsalicylate calcium) 80 mg QD (coronary artery disease), irbesartan 300 mg QD and hydrochlorothiazide 12.5 mg QD (hypertension), metformin hydrochloride 850 mg TID and insulin 300 IU PRN (diabetes), and Pantoprazol® (pantoprazole sodium sesquihydrate) 40 mg QD and 40 mg BID (esophageal reflux).

On 18 NOV 2012 (Day 140), the patient was admitted to the hospital due to possible transient ischaemic attack (TIA) that was severe in intensity. The patient experienced blurred vision, light feeling in his head, strength loss in the right arm, and difficulty speaking (considered as dysarthria by the neurologist). On the day of admission, the patient suffered from three attacks. A scan revealed recurrent TIAs, a small infarct in the left cerebellar and right occipital with severe stenosis at the transition arteria vertebralis and arteria basilaris caused by atherosclerosis. Laboratory data showed no abnormalities. On 20 NOV 2012 (Day 142), the event was considered resolved and the patient was discharged from the hospital on the same day. The patient started treatment with clopidogrel 75 mg on 21 NOV 2012 (Day 143). No action was taken with the study drug.

On 07 JAN 2013 (Day 190), the patient experienced moderate presyncope. Corrective therapy included unspecified drug therapy. On 11 JAN 2013 (Day 194), the event was considered resolved and the patient was discharged from the hospital on the same date. On 13 JAN 2013 (Day 196), the patient stopped taking the study drug as he had no more capsules (it was the last drug kit required per the protocol, all capsules were taken).

The investigator considered the events to be unrelated to study drug. At the time of discontinuation, the patient had received 196 days of study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 601/027
Age: 63	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Acute myocardial infarction

Narrative:

Patient 601-027, a 63-year-old female with a history of percutaneous coronary intervention (PCI), hypertension, stable angina, dyslipidemia, Type 2 diabetes mellitus, asthma, VIIth nerve paralysis, and varicose vein operation enrolled in the study on 20 SEP 2012. She was randomized to RVX000222 200 mg on 01 OCT 2012; the first dose of study drug was administered on the same date. Concomitant medications included irbesartan 300 mg QD, metoprolol 200 mg QD, rosuvastatin 20 mg QD, Ascal® (acetylsalicylate calcium) 100 mg QD, and ticagrelor 90 mg BID (coronary artery disease), paracetamol 1 g TID (toothache), metformin hydrochloride 500 mg BID and insulin 100 IU/mL PRN (diabetes), Singulair® (montelukast sodium) 10 mg QD (allergic asthma), and Pantozol® (pantoprazole sodium sesquihydrate) 40 mg QD (esophageal reflux).

On 14 NOV 2012 (Day 45), the patient experienced the non-serious event of angina pectoris. Treatment for the event included Promocard® (isosorbide mononitrate) 30 mg QD from 14 NOV 2012 to 27 NOV 2012. On 27 NOV 2012 (Day 58), the non-serious event of angina pectoris was considered resolved.

On 27 NOV 2012 (Day 58), the patient attended the outpatient clinic and described angina complaints. She was admitted the same day with non-ST-segment myocardial infarction that was moderate in severity, and signs and symptoms of angina pectoris. Relevant laboratory data included CK-MB 5.3 ug/L at 9:35 am and 5.2 ug/L at 12:55 pm (normal range: 0 - 4.7) and 4.3 ug/L at 8:00 am on 28 NOV 2012 (Day 59). On 29 NOV 2012 (Day 60), the patient underwent PCI to the right coronary artery by an intravascular ultrasound. Concomitant medications given for the PCI included Valium® (diazepam) 5 mg, heparin 1000 IU, glyceryl trinitrate 0.2 mg, and Isoptin® (verapamil hydrochloride) 5 mg. The patient was also treated with Arixta® (fondaparinux sodium) 2.5 mg QD and furosemide 40 mg QD from 27 NOV 2012 to 30 NOV 2012, hydrochlorothiazide 12.5 mg QD from 28 NOV 2012 to ongoing, and Promocard® (isosorbide mononitrate) 30 mg QD from 30 NOV 2012 to ongoing. On 30 NOV 2012 (Day 61), the event of acute myocardial infarction was considered resolved, and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 608/001
Age: 49	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event:	Angina pectoris

Narrative:

Patient 608-001, a 49-year-old male with a history of hypertension, stable angina, dyslipidemia, and obesity enrolled in the study on 20 AUG 2012. He was randomized to RVX000222 200 mg on 30 AUG 2012; the first dose of study drug was administered on the same date. Concomitant medications included lisinopril 5 mg Q24H (hypertension), metoprolol 50 mg Q24H (angina), rosuvastatin 10 mg Q24H (hypercholesterolemia), and aspirin (acetylsalicylic acid) 80 mg Q24H and clopidogrel 75 mg Q24H (thrombosis prophylaxis).

On 05 NOV 2012 (Day 68), the patient was admitted to the hospital due to worsening angina. The event was considered moderate in intensity. The patient had a history of ongoing angina since study start but had not experienced any adverse event. Intravascular ultrasound was performed in a non-angiographically significant lesion/vessel. Ergometry was positive and a single-photon emission computerized tomography scan showed ischemia in the left anterior descending artery region. Fractional flow reserve was performed, which showed significant flow limitation and consequently the IVUS vessel was stented. Per the CIOMS, relevant laboratory results included urea 3.7 mmol/L (normal range 3.0-7.0), creatine 102 µmol (normal range 60-110), glomerular filtration rate >60 mL/min (normal value >60), blood potassium 4.4 mmol/L (normal range 3.3-4.7) and sodium 143 mmol/L (normal range 135-145). The patient discontinued from the study on 05 Nov 2012 in response to the event of worsening angina. The last dose of study medication was taken on 04 NOV 2012 (Day 67).

On 06 NOV 2012 (Day 69), the event of worsening angina was considered resolved and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 608-003
Age: 60	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 608-003, a 60-year-old male with a history of stable angina, Type 2 diabetes mellitus, and cholecystectomy enrolled in the study on 24 AUG 2012. He was randomized to RVX000222 200 mg on 03 SEP 2012; the first dose of study drug was administered on the same date. Concomitant medications included lidocaine 100 mg, heparin 1000 IU, and glyceryl trinitrate 0.6 mg (procedure related), metformin 500 mg Q12H, Apidra® (insulin glulisine) 14 IU Q8H, and Lantus® (insulin glargine) 50 IU Q24H (diabetes), rosuvastatin 10 mg Q24H (hypercholesterolemia), isosorbide mononitrate 45 mg Q24H (angina pectoris), and acetylsalicylic acid 80 mg Q24H (coronary ischemia).

On 20 NOV 2012 (Day 79), at Visit 7, laboratory tests revealed hepatic enzyme increases with ALT >5x the upper limit of normal (ULN), AST =3x ULN, and slight elevations of GGT and direct and total bilirubin (see table below). The study drug was temporarily discontinued on 22 NOV 2012 (Day 81). On 10 DEC 2012 (Day 99), ALT and AST returned to within normal limits; the study drug was restarted on 12 DEC 2012 (Day 101). On 20 Feb 2013, ALT was elevated again but despite continuous dosing with study drug, gradually improved, such that by all visits thereafter, ALT was within normal limits. After discontinuation of study drug on 22 NOV 2012, AST gradually improved. However, at the follow-up visit on 16 APR 2013, ALT was slightly elevated again. GGT and direct bilirubin remained slightly elevated through the follow-up visit.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	27AUG2012	34	35	72	0.4 (H)	1.2	
Week 0	03SEP2012	36	25	71	0.4 (H)	1.2 (H)	
Week 2	17SEP2012	41	31	72	0.4 (H)	1.6 (H)	
Week 4	04OCT2012	37	25	85 (H)	0.4 (H)	1.4 (H)	
Week 6	15OCT2012	27	22	72	0.3	0.8	
Week 8	30OCT2012	33	29	77 (H)	0.4 (H)	1.5 (H)	
Week 11	20NOV2012	258 (H)	117 (H)	128 (H)	0.5 (H)	1.4 (H)	
Unscheduled 1	26NOV2012	178 (H)	76 (H)			1.5 (H)	1.00
Unscheduled 2	29NOV2012	118 (H)	42 (H)			0.7	
Unscheduled 3	03DEC2012	65 (H)	33			0.6	
Unscheduled 5	06DEC2012	55 (H)	29			0.9	
Unscheduled 6	10DEC2012	47	33			1.2 (H)	
Week 14	12DEC2012	43	27	84 (H)	0.3	0.8	
Unscheduled 7	21DEC2012	49	30			0.8	

Week 17	11JAN2013	43	32	77 (H)	0.3 (H)	1.1
Week 20	01FEB2013	47	32	81 (H)	0.4 (H)	1.3 (H)
Week 23	20FEB2013	51 (H)	33	81 (H)	0.3 (H)	0.9
Week 26	18MAR2013	47	35	87 (H)	0.5 (H)	1.3 (H)
Follow-Up	16APR2013	40	46 (H)	76 (H)	0.4 (H)	1.2

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 608-014
Age: 59	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 608-014, a 59-year-old male with a history of stable angina, dyslipidemia, and transient ischemic attack enrolled in the study on 20 SEP 2012. He was randomized to RVX000222 200 mg on 25 SEP 2012; the first dose of study drug was administered on the same date. Concomitant medications included lidocaine 100 mg, heparin 10,000 IU, and glyceryl trinitrate 100 mg (procedure related), rosuvastatin 10 mg Q24H (hyperlipidemia), isosorbide mononitrate 30 mg Q24H (angina pectoris), Topamax® (topiramate) 50 mg Q12H (migraine), and Ascal® (acetylsalicylate calcium) 100 mg Q24H (ischemia prophylaxis).

On 21 NOV 2012 (Day 58), at Visit 6, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal (ULN), and elevations of AST and GGT (see table below). Treatment with the study drug was not changed. Despite continuous dosing with study drug, hepatic enzyme levels gradually improved, such that by 02 JAN 2013 (Day 100), all values had returned to within normal limits and remained normal through the follow-up visits.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	21SEP2012	23	38	28	<0.0	0.3	
Week 0	25SEP2012	22	19	30	0.2	0.5	
Week 2	10OCT2012	24	24	35	0.2	0.5	
Week 4	24OCT2012	25	22	33	0.2	0.6	
Week 6	07NOV2012	30	36	34	0.1	0.7	
Week 8	21NOV2012	221 (H)	114 (H)	76 (H)	0.2	0.6	
Unscheduled 1	27NOV2012	168 (H)	73 (H)			0.9	
Unscheduled 2	05DEC2012	104 (H)	59 (H)			0.8	
Unscheduled 3	10DEC2012	69 (H)	50 (H)			1.1	
Week 11	12DEC2012	62 (H)	40 (H)	62	0.3 (H)	0.8	
Week 14	02JAN2013	34	23	49	0.3	0.7	
Week 17	23JAN2013	27	29	46	0.2	0.6	
Week 20	14FEB2013	33	31	44	0.2	0.6	
Week 23	06MAR2013	29	30	39	0.3	0.8	
Week 26	08APR2013	29	37	37	0.3 (H)	0.7	
Follow-Up	25APR2013	23	26	30	0.3	0.5	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 608/016
Age: 54	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Vascular pseudoaneurysm

Narrative:

Patient 608-016, a 54-year-old male with a history of myocardial infarction, stable angina, dyslipidemia, and chronic obstructive pulmonary disease enrolled in the study on 20 SEP 2012. He was randomized to RVX000222 200 mg on 03 OCT 2012; the first dose of study drug was administered on the same date. Concomitant medications included lisinopril 20 mg Q24H (post-infarction prophylaxis), lidocaine 100 mg, Nitro-Pohl® (glyceryl trinitrate) 0.3 mg, and heparin 9000 IU (procedure-related), metoprolol 200 mg Q24H (ischemia), Voluven® (hetastarch) 300 mg (hypotension during procedure), prasugrel 10 mg Q24H (thrombosis prophylaxis), Pantozol® (pantoprazole sodium sesquihydrate) 40 mg Q24H (gastritis prevention), acenocoumarol 1 mg PRN (arterial cardiac disease and thrombosis prophylaxis), and rosuvastatin 10 mg Q24H (hypercholesterolemia).

On 29 OCT 2012 (Day 27), the patient experienced a painful groin at outpatient clinical visit and was admitted to the hospital. An echocardiogram of the groin revealed a vascular pseudoaneurysm that was moderate in severity. Treatment for the event included compression of the groin and Tissucol® (dose not provided); treatment with study drug was not changed. Another echocardiogram was performed on 31 OCT 2012 (Day 29), however no information was available. On 31 OCT 2012, the event of vascular pseudoaneurysm was considered resolved, and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug. The investigator also considered that the event could be caused by catheterization for coronary angiography.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 608/018
Age: 48	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Angina unstable Acute coronary syndrome

Narrative:

Patient 608-018, a 48-year-old male with a history of unstable angina, dyslipidemia, aneurysm, and lumbar hernia enrolled in the study on 24 SEP 2012. He was randomized to RVX000222 200 mg on 04 OCT 2012; the first dose of study drug was administered on the same date. Concomitant medications included lidocaine 100 mg, adenosine 7 cc, heparin 2500 IU and 8500 IU, Nitro-Pohl® (glyceryl trinitrate) 0.8 mg, verapamil 5 mg, and Brilique® (ticagrelor) 180 mg (procedure-related), diclofenac 50 mg Q24H, paracetamol 500 mg Q6H, Oxycontin® (oxycodone hydrochloride) 20 mg Q12H, and tramadol 100 mg Q24H (hernia), diltiazem 120 mg Q24H and isosorbide mononitrate 60 and 90 mg Q24H (angina pectoris), rosuvastatin 10 mg Q24H and simvastatin 40 mg Q24H (hypercholesterolemia), metoprolol 50 mg Q24H (ischemia), acetylsalicylic acid 80 mg Q24H and ticagrelor 90 mg Q24H (prophylaxis of thrombosis), Pantozol® (pantoprazole sodium sesquihydrate) 40 mg Q24H (prophylaxis of gastritis), and sertraline 50 mg Q24H (stress).

On 06 NOV 2012 (Day 34), the patient was admitted to the hospital due to progressive angina pectoris that was moderate in intensity and had initially been reported during an outpatient clinic visit; however it became more severe during a physiotherapy session. Relevant laboratory data included high-sensitivity troponin T (hs-troponin T) of 5 ng/L (normal range: 0 - 14). An electrocardiogram was unchanged and no cardiac enzymes were present. Treatment for the event included increased dosage of diltiazem from 120 mg to 240 mg Q24H from 06 NOV 2012 to ongoing; treatment with the study drug was not changed. On 07 NOV 2012 (Day 35), the event of unstable angina was considered resolved, and the patient was discharged from the hospital on the same day.

On 15 NOV 2012 (Day 43), the patient was admitted to hospital due to acute coronary syndrome (ACS) that was moderate in severity. The patient had been experiencing chest pain when exercising which radiated to the left arm and was accompanied by a feeling of nausea. Relevant laboratory data included CK 90 U/L (normal range: 0 - 170) and hs-troponin T of 7 ng/L (normal range: 0 – 14). On 16 NOV 2012 (Day 44), fractional flow reserve (FFR) of RCA was noted to be 0.88. On 17 NOV 2012 (Day 45), the patient was discharged from the hospital after FFR confirmed ongoing stable angina. Treatment for the event included isosorbide mononitrate 30 mg Q24H from

15 NOV 2012 to 21 NOV 2012, 60 mg Q24H from 21 NOV 2012 to 30 NOV 2012, and 90 mg Q24H from 30 NOV 2012 to ongoing. Treatment with the study drug was not changed. On 30 NOV 2012 (Day 58), the event of ACS was considered resolved with sequelae (continued complaints of angina). It was reported that complaints of angina stopped after the dose of isosorbide mononitrate was increased to 90 mg. However, on 09 Jan 2013 (Day 98), the patient experienced a non-serious event of angina pectoris; the event resolved without treatment on 04 APR 2013 (Day 183).

The investigator considered all of the events to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 703-004
Age: 44	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 703-004, a 44-year-old male with a history of hypertension, angina, metabolic syndrome, dyslipidemia, benign prostatic hyperplasia, and hypothyroidism enrolled in the study on 13 FEB 2012. He was randomized to RVX000222 200 mg on 21 FEB 2012; the first dose of study drug was administered on the same date. Concomitant medications included carvedilol 3.125 mg BID, acetylsalicylic acid 75 mg QD, and clopidogrel 75 mg QD - BID (coronary artery disease), tamulosin 0.4 mg QD (benign prostatic hyperplasia), valsartan 40 mg QD (arterial hypertension), natamycin 1% BID, hydrocortisone 1% BID, and neomycin 0.5% BID (rash on right hand), co-trimoxazole 960 mg BID (orchitis), sodium chloride 0.9% solution 500 mL QD (prevention of dehydration), heparin 5000 IU QD, glyceryl trinitrate 200 µg QD, and Ultravist® 370 (iopromide) 250 mL QD (for diagnostic procedure), Crestor® (rosuvastatin) 10 mg QD (dyslipidemia), and levothyroxine 75 µg QD (hypothyroidism).

On 03 APR 2012 (Day 43), at Visit 5, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal (ULN), and slightly elevated AST (see table below). On 17 APR 2012 (Day 57) at Visit 6, ALT was >8x ULN, AST was >5X ULN, and GGT was elevated; treatment with study drug was permanently discontinued. Hepatic enzymes started to decrease on 23 APR 2013. On 28 MAY 2012 (Day 98), all liver enzymes returned to within normal limits and remained normal through the follow-up visits.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	14FEB2012	39	27	41	0.3	0.8	
Week 0	21FEB2012	46	27	40	0.2	0.6	
Week 2	06MAR2012	36	26	40	0.1	0.4	
Week 4	20MAR2012	32	23	36	0.1	0.3 (L)	
Week 6	03APR2012	184 (H)	94 (H)	44	0.2	0.6	
Week 8	17APR2012	525 (H)	217 (H)	132 (H)	0.3 (H)	0.8	
Unscheduled 3	23APR2012	175 (H)	58 (H)			0.4	1.09
Unscheduled 5	30APR2012	82 (H)	39			0.5	
Week 11	07MAY2012	60 (H)	39	84 (H)	0.2	0.5	
Week 14	28MAY2012	46	29	54	0.2	0.5	
Week 17	18JUN2012	49	31	46	0.1	0.5	
Week 20	11JUL2012	44	28	46	0.1	0.3	
Week 23	14AUG2012	49	27	48	0.1	0.3	
Week 26	10SEP2012	40	30	45	0.2	0.5	
Follow-Up	10OCT2012	48	31	43	0.2	0.5	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 703/012
Age: 54	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event:	Coronary artery disease

Narrative:

Patient 703-012, a 54-year-old male with a history of percutaneous coronary intervention, stable angina, and dyslipidemia enrolled in the study on 26 MAR 2012. He was randomized to RVX000222 200 mg on 30 MAR 2012; the first dose of study drug was administered on the same date. Concomitant medications included bisoprolol 1.25 mg QD, aspirin (acetylsalicylic acid) 75 mg QD and clopidogrel 75 mg QD (coronary artery disease), and atorvastatin 20 mg QD (dyslipidemia).

On 08 OCT 2012 (Day 193), the patient presented for Visit 12 and follow-up intravascular ultrasound revealed progression of coronary artery disease. The patient was given diazepam 5 mg, sodium chloride 0.9% solution 500 mL, heparin 5000 IU, glyceryl trinitrate 200 µg, and Ultavist® 370 (iopromide) 80 mL for the angiography. The patient was scheduled for coronary artery bypass grafting surgery. On 04 NOV 2012 (Day 220), the patient was admitted to the hospital due to progression of coronary artery disease. The event was considered moderate in intensity. On 09 NOV 2012 (Day 225), coronary artery bypass grafting surgery was performed. On 16 NOV 2012 (Day 232), the event of progression of coronary artery disease was considered resolved with sequelae of stable coronary artery disease and the patient was discharged from the hospital on the same date. The last dose of study drug was taken on 07 OCT 2012 (Day 192), prior to the onset of the SAE.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 705/007
Age: 55	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Coronary artery disease

Narrative:

Patient 705-007, a 55-year-old male with a history of percutaneous coronary intervention, hypertension, stable angina, metabolic syndrome, dyslipidemia, Type 2 diabetes mellitus, peripheral vascular disease, carotid artery disease, inguinal hernia repair, carotid endarterectomy, and nephrolithiasis enrolled in the study on 17 FEB 2012. He was randomized to placebo on 24 FEB 2012; the first dose of placebo was administered on the same date. Concomitant medications included ramipril 5 and 7.5 mg BID and indapamide 1.5 mg QD (arterial hypertension), diltiazem 60 mg BID and acetylsalicylic acid 75 mg QD (coronary artery disease), metformin 850 mg TID, insulin 40 IU QD, and glimepiride 4 mg QD (diabetes), amlodipine 5 and 10 mg QD (coronary artery disease, arterial hypertension), heparin 10,000 IU QD (prophylaxis of coronary/radial artery thrombosis), atorvastatin 40 mg QD (hyperlipidemia), Limus drug eluting stent (prophylaxis of stent restenosis), glyceryl trinitrate (nitroglycerin) 0.2 mg QD (prophylaxis of coronary spasm and radial artery), clopidogrel 75 mg QD (prophylaxis of stent thrombosis), potassium chloride 391 mg QD (prophylaxis of hypokalemia), omeprazole 20 mg QD (prophylaxis of gastrointestinal bleeding), and pentoxifylline 600 mg QD (peripheral vascular disease).

On 08 Mar 2012 (Day 14), during study Visit 3, the patient reported atypical chest pain, and was subsequently hospitalized due to the chest pain on 21 MAR 2013 (Day 27). A single photon emission computed tomography was performed to assess for inducible ischemia with the following findings: fixed perfusion defect of inferior and inferolateral wall; insignificant reversible perfusion defect of apical and antero-septal walls. There were no other relevant laboratory or diagnostic test results. On 21 MAR 2012 (Day 27), the event of coronary artery disease, which was moderate in severity, was considered resolved with sequelae (recurrent chest pain of lesser severity) and the patient was discharged from the hospital on the same day. Treatment for the event included amlodipine 5 mg QD from 02 APR 2012 to 16 APR 2012 and 10 mg QD from 17 APR 2012 to ongoing; treatment with study drug was not changed.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 705/011
Age: 61	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Peripheral vascular disorder

Narrative:

Patient 705-011, a 61-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, stable angina, dyslipidemia, and peripheral vascular disease enrolled in the study on 15 MAR 2012. He was randomized to RVX000222 200 mg on 22 MAR 2012; the first dose of study drug was administered on the same date. Concomitant medications included ramipril 2.5 mg QD and BID (arterial hypertension), metoprolol 25 mg QD (post-myocardial infarction and arterial hypertension), heparin 10,000 IU QD (prophylaxis of coronary thrombosis), rosuvastatin 20 mg QD (hyperlipidemia), glyceryl trinitrate 0.2 mg QD (prophylaxis of coronary and arterial spasm), acetylsalicylic acid 75 mg QD (coronary artery disease), clopidogrel 75 mg QD (coronary artery disease and post-myocardial infarction), pantoprazole 40 mg QD (prophylaxis of bleeding complications), and zotarolimus 10 µg/mm (prophylaxis of stent restenosis).

On 24 May 2012 (Day 64), the patient was hospitalized for worsening of peripheral vascular disease that was moderate in severity. Relevant laboratory test results included activated partial thromboplastin time of 27.9 sec (normal range 23-35), thrombin time 14.8 sec (normal range 10.3-16.6), INR 0.94, hematocrit 34% (normal range 35-55), total bilirubin 0.4 (normal range 0.0-1.1mg/dL), glucose 113 mg/dL (normal range 74-106), aspartate aminotransferase 43 U/L (normal range < 37) and alanine aminotransferase 52 U/l (normal range < 41). On 25 MAY 2012 (Day 65), the patient underwent arteriography with balloon angioplasty of the common external iliac artery without complications. Treatment for the event included Fraxipine® (nadroparin) 0.6 mL QD from 25 MAY 2012 to 28 JUN 2012; treatment with the study drug was not changed. On 28 MAY 2012 (Day 68), the event of peripheral vascular disease was considered resolved, and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 705/013
Age: 62	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Benign neoplasm of bladder

Narrative:

Patient 705-013, a 62-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, stable angina, dyslipidemia, atrial fibrillation, and peptic ulcer enrolled in the study on 22 MAR 2012. He was randomized to RVX000222 200 mg on 29 MAR 2012; the first dose of study drug was administered on the same date. Concomitant medications included Co-Diovan® (valsartan/hydrochlorothiazide) 80/12.5 mg BID (arterial hypertension), propafenone 150 mg TID (atrial fibrillation), metoprolol 100 mg QD (coronary artery disease and post-myocardial infarction), enoxaparin 80 mg QD (prophylaxis of stent thrombosis), atorvastatin 40 mg QD, acetylsalicylic acid 75 mg QD, and clopidogrel 75 mg QD (coronary artery disease), potassium chloride 391 mg TID (prophylaxis of hypokalemia), pantoprazole 40 mg QD (prophylaxis of bleeding complications), and everolimus 100 $\mu g/m^2$ (prophylaxis of restenosis).

On 19-JUL-2012 (Day 113), the patient was admitted to the urology ward with severe haematuria with blood clots. Urinalysis showed severe haematuria and an ultrasonogram revealed a benign tumor of the urinary bladder, that was severe in intensity. The patient underwent transurethral resection of the bladder tumor on 20 JUL 2012 (Day 114) and transurethral coagulation of the bladder on 21 JUL 2012 (Day 115). On 24 JUL 2012 (Day 118), the event was considered resolved with sequelae (not specified), and the patient was discharged from the hospital on the same day. Discharge medications included nettle leaf (cefaclor monohydrate) 100 mg BID and cranberry leaf (vaccinium macrocarpon) 300 mg QD for prophylaxis of bladder haematuria from 25 JUL 2012 to ongoing.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 705/021
Age: 64	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason(s) for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Event(s):	Alanine aminotransferase increased Aspartate aminotransferase increased

Narrative:

Patient 705-021, a 64-year-old male with a history of hypertension, congestive heart failure, stable angina, dyslipidemia, Type 1 diabetes mellitus, cataracts, glaucoma, polyneuropathy, and psoriasis enrolled in the study on 05 JUN 2012. He was randomized to RVX000222 200 mg on 13 JUN 2012; the first dose of study drug was administered on the same date. Concomitant medications included perindopril 5 mg QD, spironolactone 25 mg QD, carvedilol 25 mg BID, furosemide 40 mg BID, and torasemide 10 mg QD, (arterial hypertension), ascorbic acid 200 mg TID (polyneuropathy, glaucoma), rutoside 50 mg TID and calcium dobesilate 250 mg TID (polyneuropathy), heparin 7500 IU QD (prophylaxis of coronary thrombosis), rosuvastatin 20 mg QD (hyperlipidemia), humalog mix (insulin lispro and protamine) 12 U and 22 U QD (Type 1 diabetes mellitus), Nitroglycerin (glyceryl trinitrate) 0.2 mg QD (prophylaxis of radial artery and coronary spasm), Aspirin (acetylsalicylic acid) 75 mg QD (prophylaxis of coronary artery disease), and potassium chloride 391 mg BID and 600 mg QD (prophylaxis of hypokalemia).

On 31 JUL 2012 (Day 49), the patient was hospitalized due to elevated alanine aminotransferase (ALT), considered mild in intensity. An increase in aspartate aminotransferase (AST), considered mild in severity, also occurred at this time (see Table). No symptoms were present except for dysgeusia, which was reported as a non-serious event on 15 JUL 2012 (Day 33). Treatment with study drug was permanently discontinued on 02 AUG 2012 (Day 51) due to the ALT elevation; spironolactone was also discontinued. The investigator reported that hepatitis B might be the cause of the event, and on 02 AUG 2012 (Day 51), positive antibodies against HBc confirmed the diagnosis. HBs antigen was negative. A mild increase in blood creatinine also occurred the same day. On 03 AUG 2012 (Day 52), ultrasonography examination showed no significant liver pathology, and no kidney or urinary tract pathology was found. On 04 AUG 2012 (Day 53), urinalysis was normal. However the gradual decrease of ALT and AST between 02 AUG 2012 (Day 51) and 07 AUG 2012 (Day 56), after drug withdrawal, suggested that the ALT increase may also be related to study drug. On 07 AUG 2012 (Day 56), elevation of ALT was considered resolved with sequelae (liver enzymes were still mildly elevated), and the patient was discharged from the

hospital on the same day. The event of AST increased was considered resolved on 04 SEP 2012 (Day 84) while the event of an increase in blood creatinine was considered resolved on 07 AUG 2012.

The investigator considered the events of elevated ALT and AST to be possibly related to study drug, while the event of an increase in blood creatinine was considered not related to study drug. At the time of discontinuation, the patient had received 50 days of study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	06JUN2012	23	18	18	0.3 (H)	1.0	
Week 0	13JUN2012	27	21	18	0.2	0.5	
Week 2	29JUN2012	32	25	19	0.2	0.6	
Week 4	16JUL2012	25	20	17	0.2	0.5	
Week 6	31JUL2012	595 (H)	263 (H)	30	0.4 (H)	0.9	
Unscheduled 2	03AUG2012	603 (H)	242 (H)			1.0	1.09
Unscheduled 3	07AUG2012	304 (H)	92 (H)			1.3 (H)	
Week 8	13AUG2012	140 (H)	52 (H)	43	0.3 (H)	0.7	
Unscheduled 4	13AUG2012	139 (H)	52 (H)			0.7	
Unscheduled 5	17AUG2012	82 (H)	37			0.6	
Week 11	04SEP2012	26	23	34	0.3	0.7	
Week 14	26SEP2012	23	21	30	0.3	0.5	
Week 17	17OCT2012	22	23	28	0.2	0.5	
Week 20	08NOV2012	24	22	23	0.2	0.3	
Week 23	26NOV2012	27	25	19	0.1	0.4	
Week 26	17DEC2012	30	29	28	0.3	0.7	
Follow-Up	14JAN2013	27	25	20	0.2	0.5	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 705/023
Age: 65	**Sex:** Female
Race: White	**Study Drug:** RVX000222
Reason(s) for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Event(s):	Coronary artery disease Cardiac failure Rhabdomyolysis

Narrative:

Patient 705-023, a 65-year-old female with a history of hypertension, stable angina, Type 2 diabetes mellitus, arrhythmia, atrial fibrillation, and cholecystectomy enrolled in the study on 18 JUN 2012. She was randomized to RVX000222 200 mg on 26 JUN 2012; the first dose of study drug was administered on the same date. Concomitant medications included ramipril 2.5 mg and 5 mg BID, doxazosin 4 mg QD and 4 mg BID, amlodipine 5 mg QD and 10 mg QD, and indapamide 1.5 mg QD (arterial hypertension), metoprolol 75 mg QD and 100 mg QD (atrial fibrillation, coronary artery disease, arterial hypertension), metformin 850 mg TID and glipizide 3 mg and 4 mg QD (diabetes mellitus), enoxaparin 80 mg QD (prophylaxis of thromboembolic event), heparin 7000 IU QD (prophylaxis of coronary thrombosis), rosuvastatin 20 mg QD (hyperlipidemia), glyceryl trinitrate 0.2 mg QD (prophylaxis of coronary spasm), acetylsalicylic acid 75 mg QD (prophylaxis of stent thrombosis and coronary artery disease), clopidogrel 75 mg QD (prophylaxis of stent thrombosis), potassium chloride 391 mg QD and 782 mg TID (prophylaxis of hypokalemia), pantoprazole 20 mg QD and 40 mg QD (prophylaxis of peptic ulcer and bleeding complications), and acenocoumarol QD (atrial fibrillation).

On 04 OCT 2012 (Day 101), the patient was admitted to the hospital with angina due to worsening of coronary artery disease (CAD), which was moderate in severity. This episode lasted for about 20 minutes at rest. On admission the troponin level was negative and stated as within normal limit. The patient was treated with isosorbide mononitrate 50 mg QD (12 OCT 2012 to 12 NOV 2012). No action was taken with the study drug. On 11 OCT 2012 (Day 108), the event was considered resolved and the patient was discharged from hospital with a diagnosis of worsening of CAD with associated symptom of chest pain.

On 01 NOV 2012 (Day 129), the patient experienced recurrent episodes of dyspnoea and chest pain on exertion due to cardiac failure that was moderate in severity. On 11 NOV 2012 (Day 139), the patient was admitted to hospital. The recurrent episodes of dyspnoea and chest pain were regarded as worsening of heart failure due to persistent atrial fibrillation. On

15 NOV 2012 (Day 143), cardioversion was performed with successful return of sinus rhythm, which resulted in complete symptom resolution. No action was taken with the study drug. On 19 NOV 2012 (Day 147), the event was considered resolved and the patient was discharged from the hospital with a final diagnosis of worsening of heart failure.

On 16 DEC 2012 (Day 174), the patient was admitted to the hospital due to severe rhabdomyolysis. Relevant laboratory data are presented in the tables below. Ultrasound doppler examination revealed enlarged renal pyramids and tiny renal calculus located in the renal calyx. A non-contrast computed tomography scan excluded neoplasia; intravascular ultrasound was not performed due to excessive calcium. On an unknown date, coronary angiography was performed with the following results: left main coronary artery had no significant lesions, left anterior descending artery had 60% lesions in the mid-segment diagonal branch with 80% stenosis, left circumflex artery had lesions of less than 60% and right coronary artery had mild coronary lesions in the posterolateral branch with 70% stenosis. Myoglobin analysis was not performed. After nephrologist consultation, the patient was treated with intravenous fluids (0.9% sodium chloride, dose not specified) and furosemide 20 mg BID (16 DEC 2012 to 21 DEC 2012). Treatment with the study drug was permanently discontinued on 17 DEC 2012 (Day 175); concomitant medication rosuvastatin was temporarily interrupted starting on the same date.

On 27 DEC 2012 (Day 185), the investigator reported that the patient's renal function and liver enzymes returned to baseline values. On 28 DEC 2012 (Day 186) the patient recovered with complete resolution of clinical symptoms and steady decrease in laboratory tests (normalization of AST and creatine phosphokinase with slightly elevated ALT and creatinine levels), and the event was considered resolved. The patient was discharged from the hospital on the same day.

The investigator considered the events of coronary artery disease and cardiac failure to be unrelated to study drug; the rhabdomyolysis was considered to be possibly related to study drug. The most probable cause of her condition was rosuvastatin-related rhabdomyolysis (the dose of 20 mg was required to achieve optimal low density level in high-risk diabetic patient). However, the investigator could not exclude that the study drug alone or in interaction with rosuvastatin (or other drug) could be responsible for this event. The investigator also reported that probability of rosuvastatin-related rhabdomyolysis should not be estimated as the most probable cause of the patient's condition. At the time of discontinuation, the patient had received 175 days of study drug.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR

Screening	20JUN2012	27	27	11	0.3	0.7
Week 0	26JUN2012	63 (H)	54 (H)	13	0.1	0.3
Week 2	11JUL2012	20	17	9	0.2	0.5
Week 4	25JUL2012	19	17	10	0.2	0.5
Week 6	13AUG2012	174 (H)	90 (H)	20	0.2	0.7
Unscheduled 1	17AUG2012	118 (H)	58 (H)			0.6
Week 8	24AUG2012	76 (H)	51 (H)	24	0.2	0.5
Week 11	14SEP2012	38	31	27	0.3	0.7
Week 14	04OCT2012	26	26	19	0.3	0.6
Week 17	25OCT2012	18	19	18	0.3 (H)	0.7
Week 20	12NOV2012	17	22	15	0.4 (H)	0.7
Week 23	27NOV2012	24	26	10	0.3	0.6
Week 26	19DEC2012	337 (H)	294 (H)	12	0.2	0.5
Follow-Up	21JAN2013	14	22	10	0.1	0.3

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Date Collected	**Creatinine (µmol/L)**	**eGFR (mL/min/m^2)**	**Urea (µmol/L)**	**ALT (U/L)**	**AST (U/L)**	**Creatine phosphokinase (U/L)**
16DEC2012	433 (H)	8.9	18.9 (H)			
17DEC2012	442 (H)					
18DEC2012	400 (H)			330 (H)	296 (H)	5911 (H)
19DEC2012	335 (H)					
20DEC2012	240 (H)					
21DEC2012	239 (H)			245 (H)	136 (H)	2608 (H)
22DEC2012	199 (H)					
24DEC2012	171 (H)					
27DEC2012	142 (H)			557 (H)	18	73

ALT=alanine aminotransferase; AST=aspartate aminotransferase; eGFR=estimated glomerular filtration rate; H=high.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 705/028
Age: 61	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Epistaxis

Narrative:

Patient 705-028, a 61-year-old female with a history of hypertension, stable angina, dyslipidemia, asthma, and hypothyroidism enrolled in the study on 29 AUG 2012. She was randomized to RVX000222 200 mg on 05 SEP 2012; the first dose of study drug was administered on the same date. Concomitant medications included valsartan 80 and 160 mg BID, nebivolol 2.5 mg QD, and hydrochlorothiazide 12.5 mg BID (arterial hypertension), beclometasone dipropionate 250 µg QD, budenoside 0.2 mg PRN, and certirizine 10 mg QD (asthma), heparin 7000 IU QD (prophylaxis of thrombosis), atorvastatin 40 mg QD (hyperlipidemia), Biolimus (drug-eluting stent) 10 µg/mm (prophylaxis of stent restenosis), glyceryl trinitrate 200 µg QD (spasm prophylaxis), acetylsalicylic acid 75 mg QD and clopidogrel 75 mg QD (prophylaxis of coronary artery disease), potassium chloride 391 mg QD (prophylaxis of hypokalemia), pantoprazole 20 mg QD (prophylaxis of gastrointestinal bleeding), and levothyroxine 0.125 mg QD (hypothyroidism).

On 07 SEP 2012 (Day 3), the patient was admitted to the hospital due to epistaxis that was moderate in severity. Treatment for the event included anterior nasal packing and cyclonamine (etamsilate) 250 mg BID from 07 SEP 2012 to 10 SEP 2012; treatment with the study drug was not changed. On 10 SEP 2013 (Day 6), the event was considered resolved and the patient was discharged from the hospital on the same day. Discharge medications included Ascorutical (calcium carbonate, rutin, ascorbic acid) 2 tablets TID from 10 SEP 2012 to 14 SEP 2012, sesame oil (tocopheryl acetate) 2 inhalations TID from 10 SEP 2012 to 09 OCT 2012, and hemostatic ointment (herbal drug) 30 g TID from 10 SEP 2012 to 16 SEP 2012.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 802/017
Age: 62	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Acute myocardial infarction

Narrative:

Patient 802-017, a 62-year-old female with a history of hypertension, congestive heart failure, stable angina, dyslipidemia, chronic obstructive pulmonary disease, and obesity enrolled in the study on 26 APR 2012. She was randomized to RVX000222 200 mg on 10 MAY 2012; the first dose of study drug was administered on the same date. Concomitant medications included rosuvastatin 10 mg QD (dyslipidemia), isosorbide mononitrate 40 mg QD and cardiomagnyl 75 mg QD (angina), and verapamil 240 mg QD (arterial hypertension).

On 07 JUN 2012 (Day 29), the patient experienced acute retrosternal pain lasting 30 minutes in duration and was admitted to the hospital. An echocardiogram revealed akinesia of apex and intraventricular septum in the middle and apex area, hypokinesia in the apex area of the anterior-lateral wall of the left ventricle and reduced global contractivity. A chest X-ray revealed signs of alveolar pulmonary edema, which was reported as a non-serious adverse event. The patient was diagnosed with acute myocardial infarction (without Q-wave) of the anterior-lateral wall of the left ventricle (Killip class IV), that was severe in intensity. Treatment for the event included glyceryl trinitrate 0.8 mg QD on 07 JUN 2012, and perindopril 2.5 mg QD, bisoprolol 7.5 mg QD, and clopidogrel 75 mg QD from 07 JUN 2012 to ongoing. Treatment with the study drug was not changed. On 18 JUN 2012 (Day 40), a chest X-ray showed that the non-serious event of pulmonary edema had resolved and no other clinically significant abnormalities were revealed (no infiltration). An echocardiogram performed on 25 JUN 2012 (Day 47) showed left ventricular hypertrophy and an ECG performed on the same day revealed sinus rhythm, heart rate of 86 beats per minute, left ventricular hypertrophy, repolarization abnormality, and negative T-wave. On 26 JUN 2012 (Day 48), the event of acute myocardial infarction was considered resolved, and the patient was discharged from the hospital on the same day.

The investigator considered the events to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 804/003
Age: 55	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event:	Arteriosclerosis

Narrative:

Patient 804-003, a 55-year-old male with a history of hypertension, congestive heart failure, stable angina, dyslipidemia, peripheral vascular disease, duodenitis, gastritis, jaw cyst, encephalopathy, hypertrophic rhinitis, and obesity enrolled in the study on 22 MAR 2012. He was randomized to placebo on 18 APR 2012; the first dose of placebo was administered on the same date. Concomitant medications included valsartan 160 mg QD, amlodipine 5 mg QD, and indapamide 1.5 mg QD (hypertension), metoprolol 25 mg BID, acetylsalicylic acid 100 mg QD, and clopidogrel 75 mg QD (ischemic heart disease), atorvastatin 20 mg QD (dyslipidemia), and molsidomine 2 mg QD (angina).

On 30 OCT 2012 (Day 196), the patient presented for Visit 12 and follow-up intravascular ultrasound revealed atherosclerosis progression with 74% stenosis of the left anterior descending artery. This hospitalization was pre-planned for Study Visit 12 and the patient had no complaints. The event was considered mild in intensity. The patient was given heparin 10,000 IU, glyceryl trinitrate 250 µg, diazepam solution 0.5% 2 mL, and Omnipaque® (iohexol) 200 mL for the angiography. On 02 NOV 2012 (Day 199), the patient underwent percutaneous coronary intervention (PCI). The patient received Novocaine® solution 0.5% (procaine HCl) 20 mL, Promedoli® solution 2% (trimeperidine HCl) 1 mL, heparin 10,000 IU, glyceryl trinitrate 250 µg, and Omnipaque® (iohexol) 100 mL for the percutaneous coronary intervention. On the same date, the event of atherosclerosis progression led to PCI was reported to be recovered with sequelae of stent in left anterior descending artery. The patient was discharged from the hospital on 08 NOV 2012 (Day 205). The last dose of study drug was taken on 29 OCT 2012 (Day 195), prior to the onset of the SAE, when the patient completed study drug treatment.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 804/007
Age: 64	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Angina unstable

Narrative:

Patient 804-007, a 64-year-old male with a history of myocardial infarction, percutaneous coronary intervention (PCI), hypertension, congestive heart failure, stable angina, metabolic syndrome, dyslipidemia, Type 2 diabetes mellitus, stroke, peripheral vascular disease, arachnoiditis, prostatitis, encephalopathy, gastroduodenitis, left endarterectomy, nephroptosis, and thyroiditis enrolled in the study on 25 APR 2012. He was randomized to RVX000222 200 mg on 10 MAY 2012; the first dose of study drug was administered on the same date. Concomitant medications included perindopril 5 mg QD and bisoprolol 3.75 mg BID (hypertension), atorvastatin 20 mg QD (dyslipidemia), trimetazidine 70 mg QD, acetylsalicylic acid 100 mg QD, and clopidogrel 75 mg QD (ischemic heart disease), and gliclazide 15 and 30 mg QD (diabetes).

On 30 OCT 2012 (Day 174) the patient returned to the site for study Visit 12 and was admitted to hospital due to unstable angina that was moderate in intensity. The patient presented with acute coronary syndrome without ST-segment elevation and troponin test performed on 30 OCT 2012 or 31 OCT 2012 (Day 175) was noted to be negative. An electrocardiogram on 30 OCT 2012 and 31 OCT 2012 showed negative changes. On 31 OCT 2012, a coronary angiography and PCI were performed followed by intravascular ultrasound of the target vessel not involved in the event. Treatment for the event included heparin 5000 IU on 30 OCT 2012 and 10,000 IU on 31 OCT 2012; enalapril 5 mg BID, glyceryl trinitrate 50 mL, and zolpidem 10 mg QD from 30 OCT 2012 to 31 OCT 2012; metoprolol 50 mg QD from 30 OCT 2012 to 01 NOV 2012; omeprazole 20 mg BID from 30 OCT 2012 to 09 NOV 2012; Novocaine solution 0.5% (procaine hydrochloride) 20 mL, glyceryl trinitrate 250 µg, isosorbide mononitrate 40 mg QD, and enoxaparin sodium 0.4 mL BID on 31 OCT 2012; atorvastatin 40 mg QD from 31 OCT 2012 to ongoing; perindopril 4 mg on 01 NOV 2012; and bisoprolol 5 mg QD and amlodipine 2.5 mg BID from 02 NOV 2012 to ongoing. Treatment with the study drug was not changed due to the event; however, study drug was discontinued on 31 OCT 2012 per the protocol. On 09 NOV 2012 (Day 184), the event of angina unstable was considered resolved with sequelae (stent in left anterior descending artery), and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 806/010
Age: 60	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Events:	Hypersensitivity Myocardial infarction

Narrative:

Patient 806/010, a 60-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, dyslipidemia, duodenal ulcer, Meniere's Disease, and hypoacusis enrolled in the study on 22 MAR 2012. He was randomized to RVX000222 200 mg on 26 MAR 2012; the first dose of study drug was administered on the same date. Concomitant medications included enalapril 5 mg BID, metoprolol 50 mg BID, atorvastatin 20 mg QD, aspirin (acetylsalicylic acid) 75 mg QD, clopidogrel 75 mg QD (myocardial infarction), and Betaserc® (betahistine) 24 mg TID (Meniere's Disease).

On 31 AUG 2012 (Day 159), the patient experienced a non-serious adverse event of allergic reaction that was moderate in severity. The patient was treated with intramuscular 1 mL betamethasone on 03 SEP 2012 (Day 162). Concomitant medications metoprolol and atorvastatin were temporarily discontinued on 31 AUG 2012 and 01 SEP 2012 (Day 160), respectively, and restarted on 05 SEP 2012 (Day 163) and 10 SEP 2012 (Day 168), respectively. Study drug was also temporarily discontinued on 01 SEP 2012 and restarted on 17 SEP 2010 (Day 176). The event was considered resolved on 11 SEP 2012 (Day 170). On 18 SEP 2012 (Day 177), the day after the patient restarted study drug, he experienced another non-serious adverse event of allergic reaction that was mild in intensity. The study drug was permanently discontinued due to the event of hypersensitivity. The event was considered resolved on 29 SEP 2012 (Day 188).

On 04 OCT 2012 (Day 193), the patient presented for Visit 12 and follow up intravascular ultrasound. The patient received lidocaine solution 2% 20 mL, glyceryl trinitrate 250 µg, and Optiray® (ioversol) 200 mL for the intravascular ultrasound. Immediately after the intravascular ultrasound, in the surgery room, the patient complained of pain, ECG changes occurred, and he was hospitalized for myocardial infarction. The event was considered mild in intensity. Mural thrombosis of diagonal artery was revealed during control angiography. The patient received an antiplatelet agent Monafram® (monoclonal antibodies) 25 mg, and the thrombosis was reduced but still present. The patient was treated with intra-arterial heparin 10,000 IU. Per the CIOMS report, troponin level was 3.7 ug/L (normal range <0.08) on

05 OCT 2012 (Day 194). Thrombus aspiration was performed and the patient also received morphine 1% solution 1 mL intravenously. The pain was arrested and did not return. During the last control angiography, no thrombus was revealed in left coronary artery circulation and vascular permeability was observed with TIMI 3 flow. On 11 OCT 2012 (Day 200), the event of myocardial infarction was considered resolved and the patient was discharged from the hospital on the same date.

The investigator considered the initial event of hypersensitivity to be possibly related to study drug, and the subsequent event of hypersensitivity to be definitely related to study drug. The event of myocardial infarction was considered to be unrelated to study drug but rather due to thrombosis during invasive procedure.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 806/019
Age: 63	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Chest pain

Narrative:

Patient 806-019, a 63-year-old male with a history of myocardial infarction, hypertension, stable angina, prostatitis, duodenitis, erosive gastritis, and malignant tumor excision enrolled in the study on 04 SEP 2012. He was randomized to RVX000222 200 mg on 10 SEP 2012; the first dose of study drug was administered on the same date. Concomitant medications included enalapril 3.75 mg BID, bisoprolol 2.5 mg QD, atorvastatin 20 mg QD, acetylsalicylic acid 75 mg QD, and clopidogrel 75 mg QD (myocardial infarction), and omeprazole 20 mg QD (gastritis).

On 30 JAN 2013 (Day 143), the patient experienced strong pain behind the sternum similar to angina, which was moderate in intensity, and was admitted to the hospital. On 31 JAN 2013 (Day 144), relevant laboratory data included creatine kinase MB 1.7 ng/mL (normal range: 0.0-10.4). On 01 FEB 2013 (Day 145), angiography was performed with no findings. Lidocaine 200 mg, heparin 2000 IU, glyceryl trinitrate 250 µg, and Ultravist® (iopromide) 100 mL were given for the angiography. On the same day, a follow-up study intravascular ultrasound was performed in the left coronary artery that revealed excentric heterogenous plaque 47.5% in the middle segment and concentric heterogenous plaque 65.1% in the proximal segment. Relevant laboratory data included troponin I 0.014 ng/mL (normal range 0.000-0.300). The investigator noted that vasospasm could not be excluded; however there was no confirmation and treatment with amlodipine 5 mg QD was started on 04 FEB 2012 to ongoing. Treatment with the study drug was not changed. On 04 FEB 2013 (Day 148), the event of chest pain of was considered resolved, and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 807/005
Age: 71	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Discontinuation Due to Adverse Event Serious Adverse Event
Events:	Pancreatitis Acute

Narrative:

Patient 807/005, a 71-year-old male with a history of percutaneous coronary intervention, hypertension, stable angina, dyslipidemia, benign tumor excision, gastritis, gastroesophageal reflux disease, duodenogastric reflux, encephalopathy, partial lung resection, chronic pancreatic disease, and urinary calculus enrolled in the study on 28 MAR 2012. He was randomized to RVX000222 200 mg on 09 APR 2012; the first dose of study drug was administered on the same date. Concomitant medications included Diovan Triple® (amlodipine 10 mg/valsartan 160 mg/hydrochlorothiazide 12.5 mg) 1 tablet QD and bisoprolol 2.5 mg QD (hypertension), atorvastatin 20 mg QD (dyslipidemia), and acetylsalicylic acid 100 mg QD and clopidogrel 75 mg QD (ischemic heart disease).

On 17 APR 2012 (Day 9), the patient was admitted to the hospital for the serious adverse event of acute pancreatitis. The event was moderate in intensity. The non-serious adverse event of hepatomegaly was also reported on the same date. Corrective treatment for hepatomegaly included ademetionine 400 mg BID intravenously from 17 APR 2012 to 22 APR 2012. Treatment for acute pancreatitis included Trisol® (potassium chloride 5 mg/mL, sodium chloride 4 mg/mL, sodium bicarbonate 1 mg/mL) solution 200 mL and metamizole sodium 500 mg once on 17 APR 2012; sulpiride 100 mg QD from 17 APR 2012 to 20 APR 2012 and 100 mg BID from 21 APR 2012 to 22 APR 2012; and omeprazole 20 mg BID, mebeverine 200 mg TID, hydrochlorothiazide 20 mg QD, and Milgamma® (vitamin B1 100 mg, vitamin B6 100 mg, vitamin B12 1 mg, lidocaine 20 mg) 2 mL QD intramuscular from 17 APR 2012 to 22 APR 2012. Per the CIOMS report, relevant laboratory data on 22 APR 2012 (Day 14) included ALT 57.7 U/L (normal range: 0-50), total bilirubin 11.3 mcmol/L (normal range: 5.1-17.0), direct bilirubin 2.9 mcmol/L (normal range: 1.0-5.1), and AST 36 U/L (normal range: 0-37). On an unknown date, ALT was 51 u/mL. All other tests (biochemistry, blood count, and urinalysis) were normal. The patient considered this SAE related to the study drug and withdrew consent. The study drug was permanently discontinued on 17 APR 2012 due to the acute pancreatitis. The investigator confirmed that treatment with atorvastatin had not been permanently discontinued, as patient had lipid disorders following percutaneous coronary intervention. On 23 APR 2012 (Day 15), the events of acute pancreatitis and hepatomegaly were considered resolved.

The investigator considered the serious adverse event of acute pancreatitis to be unrelated to study drug, as the pancreatitis was an exacerbation of chronic pancreatic disease. The investigator also confirmed that the event was not related to statin therapy (atorvastatin). The non-serious adverse event of hepatomegaly was considered to be unrelated to the study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 809/011
Age: 64	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Angioedema Angina pectoris

Narrative:

Patient 809-011, a 64-year-old male with a history of hypertension, stable angina, and dyslipidemia enrolled in the study on 10 AUG 2012. He was randomized to RVX000222 200 mg on 16 AUG 2012; the first dose of study drug was administered on the same date. Concomitant medications included lidocaine solution 2% 1 mL (anesthetic for catheterization), bisoprolol 2.5 mg QD, acetylsalicylic acid 100 mg QD, and clopidogrel 75 mg QD (ischemic heart disease), heparin 5000 U (prophylaxis of thrombosis), rosuvastatin 20 mg QD (atherosclerosis), glyceryl trinitrate 250 µg (prophylaxis of angiospasm), Nolpaza® (pantoprazole sodium sesquihydrate) 40 mg QD (prophylaxis of gastritis), and iopromide 120 mL (contrasting agent for angiogram).

On 19 AUG 2012 (Day 4), the patient felt throat edema and contacted the investigator, who instructed him to stop taking the study drug and go to the hospital. On the same day, the patient was hospitalized for Quincke's edema. Temperature was normal (36.6°C) and had no pain in his throat. The patient reported that on 18 AUG 2012 (Day 3) he had eaten nearly 3 tablespoons of caviar and drank some orange juice. Treatment for the event included dexamethasone 8 mg, antihistamine therapy, tavegil, and potassium chloride (dose and duration not provided). On 19 AUG 2012, the event of angioedema, which was moderate in severity, was considered resolved, and the patient was discharged from the hospital on the same day. Treatment with the study drug was restarted 20 AUG 2012 (Day 5).

On 06 NOV 2012 (Day 83) the patient complained of chest pain at Visit 7 and was admitted to the hospital due to angina progression that was mild in intensity. Stress test was positive and on 08 NOV 2012 (Day 85), an angioplasty with stenting of diagonal artery was performed. Lidocaine solution 2% 2 mL, heparin 7000 IU, and Optiray® (ioversol) 160 mL were given for the angioplasty; treatment with the study drug was not changed. On 12 NOV 2012 (Day 89), the event of angina pectoris was considered resolved with sequelae (stent in coronary artery), and the patient was discharged from the hospital on the same day.

The investigator considered the events to be unrelated to study drug. The investigator provided the alternative causality of caviar for the event of angioedema.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 810/013
Age: 53	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Cholecystitis acute Cholecystitis acute

Narrative:

Patient 810-013, a 53-year-old male with a history of myocardial infarction, congestive heart failure, stable angina, dyslipidemia, arrhythmia, atrial fibrillation, gastritis, hand fracture, and gastroesophageal sphincter insufficiency enrolled in the study on 18 SEP 2012. He was randomized to RVX000222 200 mg on 27 SEP 2012; the first dose of study drug was administered on the same date. Concomitant medications included valsartan 80 mg HS, metoprolol succinate 75 mg QD, rosuvastatin 10 mg HS, acetylsalicylic acid 300 mg QD, and clopidogrel 75 mg QD (coronary artery disease), omeprazole 20 mg BID (gastritis), and iopromide 50 mL (percutaneous coronary intervention and intravascular ultrasound).

On 30 SEP 2012 (Day 4), the patient was hospitalized for severe pain in the right subcostal region after having fatty meals and was diagnosed with acute cholecystitis that was moderate in severity. An electrocardiogram (ECG) showed sinus rhythm and signs of an old antero-septal myocardial infarction. On 01 OCT 2012 (Day 5), urine test revealed: SG 1015, trace of protein, and white blood cell (WBC) 0-2-4 (units and normal ranges not provided). On an unknown date, blood chemistry test revealed: total bilirubin 26.8 µmol/L (normal range: 7.5 - 21.5), potassium 4.3 mmol/L (normal range: 3.5 - 5.1), conjugated bilirubin 9.9 µmol/L, alanine aminotransferase (ALT) 23 IU/L, aspartate aminotransferase (AST) 38 IU/L, sodium 141 mmol/L, creatine phosphokinase 154 IU/L (normal ranges not provided), international normalized ratio 1.12, and amylase 43 (units and normal ranges not provided). Abdominal ultrasound revealed the following: liver, homogenous fine-grained structure; gallbladder, 8.5 x 3.5 x 3.0 cm, no stones, thickening of the wall up to 0.8 cm, layered structure of the walls; and pancreas, homogenous structure with smooth contours. Gastroduodenoscopy showed moderate atrophy of the upper gastrointestinal tract. On 09 OCT 2012 (Day 13), relevant laboratory results included: hemoglobin (HgB) 121 g/L, red blood cell (RBC) count 3.93 x 10^{12}/L, WBC 7.7 x 10^{9}/L, eosinophil 10%, neutrophil 68%, lymphocyte 18%, monocyte 4%, and erythrocyte sedimentation rate (ESR) 46 mm/h (normal ranges not provided). Treatment for the event included diet, antibiotics, and spasmolytics (drug names and dosages not reported); treatment with the study drug was not changed. The pain stopped quickly after injection of spasmolytic and no recurrence of pain followed. On 09 OCT 2012 (Day 13), the event of acute cholecystitis was considered resolved, and the patient was discharged from the hospital on the

same day.

On 10 NOV 2012 (Day 45), the patient was hospitalized with a diagnosis of acute cholecystitis that was moderate in severity. A chest X-ray was normal. Treatment with the study drug and concomitant oral medications was interrupted between 12 NOV 2012 and 13 NOV 2013 (Day 48); study drug was restarted on 14 NOV 2012 (Day 49). On 15 NOV 2012 (Day 50), an ultrasound scan showed gallbladder 10 x 3 x 4 cm, wall 0.6 cm, local separation of the wall, and choledoch 0.3 cm. On 22 NOV 2012 (Day 57), an ultrasound scan showed normal-sized gallbladder and wall 0.4 cm with no separation. On an unknown date, an ECG showed sinus rhythm and non-specific ST changes, and urine test was normal. On 24 NOV 2012 (Day 59), relevant laboratory data included HgB 128 g/L (normal range: 130 - 160), RBC count 4.36 x 10^{12}/L (normal range: 4.0 - 5.0), WBC count 8.4 x 10^{9}/L (normal range: 4.0 - 9.0) and ESR 48 mm/h (normal range: 2 - 10). On an unknown date relevant laboratory data included: creatinine 80 µmol/L (normal range: 64 - 111), total bilirubin 19.0 µmol/L (normal range: 3.4 - 20.5), glucose 5.3 mmol/L (normal range: 3.89 - 5.5), AST 20 IU/L (normal range: 5.0 - 34) and amylase 22 U/L (normal range not provided). Corrective treatment included diet, antibiotics, and spasmolytics (drug names and dosages not reported). On 24 NOV 2012 (Day 59), the event of acute cholecystitis was considered resolved, and the patient was discharged from the hospital on the same day. Discharge medication included ursodeoxycholic acid 500 mg HS from 25 NOV 2012 to ongoing.

The investigator considered the events to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 811-004
Age: 52	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 811-004, a 52-year-old male with a history of myocardial infarction, percutaneous coronary intervention, hypertension, stable angina, and dyslipidemia enrolled in the study on 06 AUG 2012. He was randomized to RVX000222 200 mg on 13 AUG 2012; the first dose of study drug was administered on the same date. Concomitant medications included perindopril 2.5 mg QD and bisoprolol 5 mg QD (hypertension), atorvastatin 40 mg QD (dyslipidemia), glyceryl trinitrate 0.5 mg PRN and isosorbide dinitrate 20 mg BID (angina), and acetylsalicylic acid 100 mg QD and clopidogrel 75 mg QD (ischemic heart disease).

On 08 OCT 2012 (Day 57), at Visit 6, laboratory tests revealed hepatic enzyme increases with ALT and AST >3x the upper limit of normal, and GGT elevation (see table below). Treatment with the study drug was not changed. Despite continuous dosing with study drug, hepatic enzyme levels gradually improved, such that by the follow-up visit on 13 MAR 2013 (Day 213), all enzyme values had returned to within normal limits.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	08AUG2012	26	19	37	0.2	0.7	
Week 0	13AUG2012	31	22	34	0.2	0.7	
Week 2	27AUG2012	24	25	32	0.3	0.7	
Week 4	10SEP2012	28	27	29	0.1	0.4	
Week 6	24SEP2012	68 (H)	46 (H)	45	0.1	0.1 (L)	
Week 8	08OCT2012	242 (H)	146 (H)	98 (H)	0.1	0.3 (L)	
Unscheduled 2	15OCT2012	186 (H)	89 (H)			0.3	
Unscheduled 5	23OCT2012	179 (H)	102 (H)			0.8	
Week 11	29OCT2012	148 (H)	74 (H)	61	0.2	0.8	
Week 14	19NOV2012	88 (H)	58 (H)	66	0.1	0.3	
Week 17	10DEC2012	74 (H)	52 (H)	43	0.2	0.7	
Week 20	26DEC2012	50 (H)	41 (H)	45	0.3 (H)	0.9	
Week 23	21JAN2013	68 (H)	48 (H)	91 (H)	0.3	0.9	
Week 26	13FEB2013	55 (H)	44 (H)	95 (H)	0.2	0.8	
Follow-Up	13MAR2013	39	33	60	0.2	0.4	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 901/003
Age: 44	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Chest pain

Narrative:

Patient 901-003, a 44-year-old male with a history of myocardial infarction, percutaneous coronary intervention, and dyslipidemia enrolled in the study on 20 SEP 2012. He was randomized to RVX000222 200 mg on 15 OCT 2012; the first dose of study drug was administered on the same date. Concomitant medications included mepivicaine 1% 2 cc (local anesthetic), bisoprolol 10 mg QD (angina and hypertension), fenofibrate 160 mg QD (treatment of high cholesterol), ciprofloxacin 500 mg QD BID (urinary infection), heparin 10,000 IU (anticoagulant), atorvastatin 20 and 40 mg BID (dyslipidemia), glyceryl trinitrate 300 µg (vasodilation), verapamil 2.5 mg (vasospasm), Adiro® (acetylsalicylic acid) 100 mg QD (prevention, inhibition of platelet aggregation), clopidogrel 75 mg QD (inhibition of blood clots in coronary artery), and pantoprazole sodium sesquihydrate 40 mg QD (prevention of gastroesophageal reflux disease).

On 17 OCT 2012 (Day 3), the patient was hospitalized complaining of thoracic pain, mild in severity, which started while he was doing physical activity. The patient stopped the activity, however the pain continued. An electrocardiogram on 17 OCT 2012 showed increased levels of troponin I 1,332 ng/mL (normal range: 0 - 0.056 ng/mL) with no deterioration of cardiac function or other vital organ function. Treatment for the event included nitrates (dose not reported) and morphine (dose not reported) on 17 OCT 2012, captopril 6.25 mg TID from 17 OCT 2012 to 18 OCT 2012, alprazolam 0.25 mg BID from 17 OCT 2012 to 20 OCT 2012, glyceryl trinitrate 10 mg QD from 17 OCT 2012 to 20 OCT 2012, enalapril 5 mg BID and bisoprolol 10 mg BID from 18 OCT 2012 to 20 OCT 2012, Adiro® (acetylsalicylic acid) 300 mg on 18 OCT 2012; treatment with the study drug was not changed. The pain disappeared gradually, and the event of chest pain was considered resolved on 17 OCT 2012.

On 18 OCT 2012 (Day 4), an angiography showed coronary arteries with no lesions and evidence of stents placed in the left anterior descending artery with no restenosis. A systolic milking in the left anterior descending artery was noted. Mepivicaine hydrochloirde 2 cc, heparin 5000 IU, glyceryl trinitrate 100 µg, and verapamil 2.5 cc were given for the angiography. On 20 OCT 2012 (Day 6), the patient was discharged from the hospital on amlodipine 5 mg QD from 20 OCT 2012 to ongoing.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 902/001
Age: 59	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Head injury

Narrative:

Patient 902-001, a 59-year-old male with a history of stable angina, dyslipidemia, and Type 2 diabetes mellitus enrolled in the study on 27 MAR 2012. He was randomized to RVX000222 200 mg on 09 APR 2012; the first dose of study drug was administered on the same date. Concomitant medications included bisoprolol 2.5 and 5 mg QD (hypertension and stable angina), metformin 850 mg TID (diabetes), heparin 5000 IU (angiography and IVUS), rosuvastatin 5 mg QD (dyslipidemia), glyceryl trinitrate 5 mg QD (stable angina), acetylsalicylic acid 100 mg QD (cardiovascular disease risk), clopidogrel 75 mg QD (stenting), omeprazole 20 µg QD (gastric prophylaxis), cefuroxime 500 mg BID (fever), and citalopram 20 µg QD (anxiety).

On 29 JUN 2012 (Day 82), the patient fell down and suffered a cranial trauma, moderate in severity, and was hospitalized. He reported having had a failure of strength in legs without loss of consciousness. A computed tomography (CT) scan showed intraparenchymal hematoma temperoparietal right, parietal left; posterior CT scan showed hemorrhagic contusion primary resorption phase. Treatment for the event included Clexane® (enoxaparin sodium) 40 mg QD from 01 JUL 2012 to 22 JUL 2012, and discontinuation of clopidogrel on 30 JUN 2012; treatment with the study drug was temporarily interrupted for an unknown number of days. On 19 JUL 2012 (Day 102), the event of head injury was considered resolved, and the patient was discharged from the hospital on the same day.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 903/007
Age: 68	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Acute myocardial infarction Gastritis erosive Haemorrhoidal haemorrhage

Narrative:

Patient 903-007, a 68-year-old male with a history of myocardial infarction, percutaneous coronary intervention (PCI), hypertension, stable angina, dyslipidemia, Type 2 diabetes mellitus, peripheral vascular disease, atrial fibrillation, chronic obstructive pulmonary disease, diplopia, and sleep apnea syndrome enrolled in the study on 21 AUG 2012. He was randomized to RVX000222 200 mg on 28 AUG 2012; the first dose of study drug was administered on the same date. Concomitant medications included Sevikar® HCT (Azor) 40/10/25 mg Q24H, Olmetec Plus® (benicar HCT) 40/25 mg Q24H, Futuran® (eprosartan mesilate) 600 mg Q24H, and diltiazem hydrochloride 120 mg Q24H (hypertension), digoxin 0.5 mg Q24H, Clexane® (enoxaparin sodium) 80 mg Q24H, and Sintrom® (acenocoumarol) 4 mg PRN and unknown Q24H (atrial fibrillation), heparin 6000 IU and glyceryl trinitrate 1 mg (IVUS), Crestor® (rosuvastatin calcium) 5 mg Q24H (dyslipidemia), Cafinitrina® 25 mg and 1/25 mg PRN (angina), Uniket® (isosorbide mononitrate) 40 mg Q12H, Ranexa® (ranolazine) 375 and 500 mg Q12H, Adiro® (acetylsalicylic acid) 100 mg Q24H, and clopidogrel 75 mg Q24H (coronary disease), Zaldiar® (ultracet) 37.5/325 mg (lumbar pain), Praxilene® (naftidrofuryl oxalate) 100 mg QD and Q24H (peripheral vascular disease), Zyloric® (allopurinol) 100 mg Q24H (hyperuricemia), omeprazole 20 mg Q24H (gastric protection), Ventolin® (salbutamol) 2 inhalations PRN (chronic obstructive pulmonary disease), clorazepate dipotassium 5 mg PRN (insomnia), and Seguril® (furosemide) 40 mg intermittent and Q24H (heart failure and lower extremities).

On 07 NOV 2012 (Day 72) the patient was admitted to the hospital due to non-ST-segment elevation myocardial infarction, severe in intensity, and minimal troponin elevation. The patient was noted to have chronic ischemic heart disease. He underwent PCI of left anterior descending artery responsible for acute coronary syndrome with placement of two drug eluting stents (DES) and achieved good results. Heparin 5000 IU and glyceryl trinitrate 1.2 mg were given for the PCI. On 08 NOV 2012 (Day 73), relevant laboratory data included creatinine 2.19 mg/dL (normal range: 0.55 - 1.40) and troponin I 0.41 mg/dL (normal range: 0 - 0.1). The patient experienced numerous recurrences of chest pain and on 13 NOV 2012 (Day 78), PCI of the right coronary artery with one DES placement was performed with good

results. Heparin 7000 IU and glyceryl trinitrate 1 mg were given for the PCI. Treatment for the event included atenolol 12.5 mg Q12H and amplodipine 5 mg Q12H from 07 NOV 2012 to 09 NOV 2012, Traxilium® (clorazepate dipotassium) 5 mg Q24H PRN from 07 NOV 2012 to 11 NOV 2012, paracetamol 1 g PRN and Adiro® (acetylsalicylic acid) 100 mg Q24H from 07 NOV 2012 to 19 NOV 2012, Seguril® (furosemide) 20 mg on 07 NOV 2012,10 mg Q8H from 11 NOV 2012 to 14 NOV 2012, 20 mg on 17 NOV 2012, 40 mg Q12H from 18 NOV 2012 to 19 NOV 2012, carvedilol 3.125 mg, 6.25 mg, and 12.5 mg Q12H and 9.375 mg Q24H from 09 NOV 2012 to 20 NOV 2012, glyceryl trinitrate (dose not provided) from 11 NOV 2012 to 13 NOV 2012, Uniket® (isosorbide mononitrate) 20 mg on 11 NOV 2012 and 40 mg Q12H from 14 NOV 2012 to ongoing, Orfidal® (lorazepam) 1 mg Q24H from 12 NOV 2012 to 13 NOV 2012, morphine 3 mg Q24H from 12 NOV 2012 to 13 NOV 2012, 2.5 mg on 17 NOV 2012, and 3 mg on 19 NOV 2012, Flumil® (acetylcysteine) 600 mg Q12H from 12 NOV 2012 to 14 NOV 2012, enoxaparin sodium 40 and 60 mg Q12H from 12 NOV 2012 to 20 NOV 2012, and ramipril 1.25 mg Q12H from 16 NOV 2012 to 20 NOV 2012. Treatment with the study drug was not changed. On 20 NOV 2012 (Day 85), the event of acute myocardial infarction was considered resolved, and the patient was discharged on the same day. Discharge medications included: amlodipine 5 mg Q12H, Seguril® (furosemide) 40 mg BID, and Duoplavin® (clopidogrel and acetylsalicylic acid) 100/75 mg Q24H.

On 02 FEB 2013 (Day 159), the patient began experiencing hematemesis, rectorrhagia, and melena. On 05 FEB 2013 (Day 162), the patient was admitted to the hospital; there was no bleeding during hospitalization. Gastroscopy revealed erosive gastritis and hemorrhoids were found on colonoscopy. Both events were moderate in severity. An abdominal CT was normal. The patient was taking Sintrom® (acenocoumarol) and Duoplavin® (clopidogrel and acetylsalicylic acid) and the investigator suspected intestinal subocclusion and digestive hemorrhage. Treatment with both therapies was discontinued. On 15 FEB 2013 (Day 172), the events of erosive gastritis and haemorrhoidal haemorrhage were considered resolved, and the patient was discharged on the same day.

The investigator considered all of the events to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 908/004
Age: 57	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	Colon cancer

Narrative:

Patient 908-004, a 57-year-old male with a history of hypertension, dyslipidemia, and bladder neoplasm surgery enrolled in the study on 08 MAY 2012. He was randomized to placebo on 17 MAY 2012; the first dose of placebo was administered on the same date. Concomitant medications included captopril 25 mg PRN (hypertension), ramipril 5 mg QD (hypertension and ischemic heart disease), tamulosin hydrochloride 0.4 mg QD (benign prostatic hyperplasia), lorazepam 1 mg QD (insomnia), bisoprolol 5 mg QD, acetylsalicylic acid 100 mg QD, and clopidogrel 75 mg QD (ischemic heart disease), norfloxacin 400 mg QD and cefuroxime 250 mg Q12H (urine infection), atorvastatin 40 mg QD (dyslipidemia and ischemic heart disease), glyceryl trinitrate 10 mg QD (atypical chest pain and ischemic heart disease), magnesium hydroxide 1 Tbsp Q12H (constipation), and pantoprazole sodium sesquihydrate 20 mg QD (stomach protection).

From 01 JUL 2012 (Day 46) through 18 AUG 2012 (Day 94), the patient experienced the non-serious event of mild diarrhea. The patient went to the emergency room several times (specific dates not reported) for diarrheal stool, vomiting, and weight loss. Treatment for the event of diarrhea included ciprofloxacin 500 mg Q12H from 03 JUL 2012 to 06 JUL 2012 and from 14 JUL 2012 to 21 JUL 2012, acetorphan 100 mg Q12H from 14 JUL 2012 to 17 JUL 2012, loperamide hydrochloride 2 mg PRN from 23 JUL 2012 to 26 JUL 2012 and rifaximin 200 mg Q8H from 26 JUL 2012 to 05 AUG 2012. On 14 AUG 2012 (Day XX), a colonoscopy was performed that showed hemorrhoids, colonic polyps, and sigmoid tumor, and a biopsy performed the same day showed tubular adenoma. On 18 AUG 2012 (Day 94), the patient experienced a non-serious event of lower gastrointestinal haemorrhage that resolved on the same date. On 10 SEP 2012 (Day 117), the patient was hospitalized and a colonoscopy (sigmoidoscopy) was performed. On the same day, a biopsy showed colonic mucosa with high grade dysplasia and focus of adenocarcinoma and the patient was diagnosed with sigmoid colon tumor. The event of colon cancer, severe in intensity, was considered resolved with sequelae (left hemicolectomy) on 22 OCT 2012 (Day 159). Treatment for the event included paracetamol 1 g Q8H from 22 OCT 2012 to 24 OCT 2012 and 1 g PRN from 25 OCT 2012 to ongoing, morphine 100 mg PRN from 22 OCT 2012 to 24 OCT 2012 and 5 mg PRN from 24 OCT 2012 to 25 OCT 2012, metamizole magnesium 2 g Q8H from 22 OCT 2012 to 25 OCT 2012 and 575 mg Q12H from 25 OCT 2012 to 28 OCT 2012 for pain post-hemicolectomy; Atrovent® (ipratropium bromide)

500 µg Q6H and Mucofluid® (mesna) 600 mg Q6H from 22 OCT 2012 to 24 OCT 2012 for respiratory distress; potassium chloride 10 mEq PRN for prevention of hypokalemia from 22 OCT 2012 to 24 OCT 2012; heparin 3500 IU QD post-hemicolectomy from 22 OCT 2012 to 07 NOV 2012; ondansetron 4 mg Q8H from 23 OCT 2012 to 24 OCT 2012 and metoclopramide hydrochloride 10 mg PRN from 24 OCT 2012 to 25 OCT 2012 for nausea and vomiting; omeprazole 40 mg QD from 22 OCT 2012 to 25 OCT 2012 and 20 mg QD from 25 OCT 2012 to 26OCT 2012 for stomach protection; and phytomenadione 10 mg QD from 24 OCT 2012 to 25 OCT 2012 for bleeding prevention.

The investigator considered all of the events to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 911/002
Age: 49	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Coronary artery disease

Narrative:

Patient 911-002, a 49-year-old female with a history of hypertension, stable angina, metabolic syndrome, dyslipidemia, Type 2 diabetes mellitus, radical hysterectomy, osteoarthritis, and migraine enrolled in the study on 07 FEB 2012. She was randomized to RVX000222 200 mg on 13 FEB 2012; the first dose of study drug was administered on the same date. Concomitant medications included enalapril 20 mg QD, valsartan 160 mg QD, and hydrochlorothiazide 12.5 mg QD (hypertension), mepivicaine 2% 1 mL (local anesthesia), diazepam 10 mg (anxiety prevention), lorazepam 1 mg PRN (insomnia), midazolam 2 mg, morphine 2 mg, and verapamil 2.5 mg (radial spasm prevention), bisoprolol 2.5 and 5 mg QD (angina pectoris), metformin hydrochloride 1000 mg BID, sitagliptim 100 mg BID, insulin aspart PRN, and insulin glargine 40 and 70 IU QD (diabetes mellitus), almagate 500 mg TID (epigastric pain), heparin 9,000 IU (catheter thrombosis prevention), atorvastatin 40 mg QD, rosuvastatin 10 mg QD, and simvastatin 40 mg QD (coronary atherosclerosis), Tryptizol® (amitriptyline hydrochloride) 75 mg PRN (diabetic neuropathy), glyceryl trinitrate 400 µg (coronary spasm prevention) and 5 and 10 mg QD (chest pain), acetylsalicylic acid 100 mg QD (ischemic heart disease) and 300 mg (unstable angina), clopidogrel 75 mg QD (acute coronary syndrome), naproxen 250 mg BID (poliarticular pain), and omeprazole 20 mg QD (peptic ulcer prophylaxis).

On 28 MAR 2012 (Day 45), the patient experienced chest pain and was hospitalized. Treatment for the event included bisoprolol 2.5 mg QD from 28 MAR 2012 to ongoing and glyceryl trinitrate 500 µg; however, due to persistence of symptoms, the patient underwent coronary angiography that revealed a de novo lesion on the distal LAD with 90% stenosis by visual parameters. Successful percutaneous coronary intervention (PCI) with drug-eluting stent placement was performed on the same day. Mepivicaine 2% 1 mL, diazepam 5 mg, midazolam 2 mg, heparin 10,000 IU, morphine 2 mg, verapamil 2.5 mg, and clopidogrel 300 mg were given for the PCI; treatment with the study drug was not changed. On 28 MAR 2012, the event of coronary artery disease, which was moderate in severity, was considered resolved.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 911/004
Age: 52	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event(s):	In-stent coronary artery restenosis

Narrative:

Patient 911-004, a 52-year-old male with a history of percutaneous coronary intervention, hypertension, stable angina, metabolic syndrome, dyslipidemia, depression, sleep apnoea syndrome, duodenal ulcer, and hyperuricaemia enrolled in the study on 10 FEB 2012. He was randomized to placebo on 23 FEB 2012; the first dose of placebo was administered on the same date. Concomitant medications included carvedilol 25 mg QD and BID, rosuvastatin 10 mg QD, glyceryl trinitrate 10 and 15 mg QD, and acetylsalicylic acid 100 mg QD (angina pectoris), mepivicaine 2% 1 mL (local anesthesia), losartan 100 mg QD, amlodipine 10 mg QD, and hydrochlorothiazide 50 mg QD (hypertension), diazepam 5 and 10 mg (anxiety), metformin hydrochloride 850 mg QD, insulin lispro 98 IU TID, and pioglitazone 15 mg QD (diabetes mellitus), heparin 10,000 IU and 11,000 IU (catheter thrombosis prevention), glyceryl trinitrate 400 and 600 µg (coronary spasm prevention), pregabalin 75 mg QD (diabetic neuropathy), verapamil 2.5 mg (radial spasm prevention), clopidogrel 75 mg QD (stent deployment), allopurinol 300 mg QD (hyperuricemia), omeprazole 20 mg QD (peptic ulcer), and sertraline 100 mg QD (depression).

On 19 MAR 2012 (Day 26), the patient experienced exertional angina and complained of chest pain two times. The exertional angina and effort-related symptoms including dyspnea were related to restenosis of the stents previously implanted in the LAD and RCA, which was mild in severity. Treatment included a second percutaneous coronary intervention on both arteries, including implantation of sirolimus eluting stents, with good angiographic and clinical result. Action taken with study drug was noted as not applicable for the event; however, study drug was stopped on 23 AUG 2012 as the patient had completed the end of study visit (Visit 12). On 10 May 2012 (Day 78), the event was considered resolved.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 911/008
Age: 56	**Sex:** Female
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event(s):	Fibula fracture

Narrative:

Patient 911-008, a 56-year-old female with a history of myocardial infarction, percutaneous coronary intervention, hypertension, unstable angina, dyslipidemia, duodenal ulcer, glaucoma, helicobacter test positive, and hysterectomy enrolled in the study on 12 MAR 2012. She was randomized to RVX000222 200 mg on 23 MAR 2012; the first dose of study drug was administered on the same date. Concomitant medications included enalapril 20 mg QD (hypertension), bisoprolol 5 mg QD, rosuvastatin 10 mg QD, and acetylsalicylic acid 100 mg QD (myocardial infarction), dimemorfan phosphate 20 mg TID (superior airway infection), clopidogrel 75 mg QD (stent deployment), and latanoprost 1 gtt QD (glaucoma).

On 31 AUG 2012 (Day 162), the patient was hospitalized for a fibula fracture, moderate in severity, from a casual fall. On 01 SEP 2012 (Day 163), surgery was performed without complications. Action taken with study drug was noted as not applicable. On 03 SEP 2012 (Day 165), the serious adverse event of fibula fracture was considered resolved with sequelae (on the same date, the event of fibula fracture was reported as a non-serious adverse event). The investigator reported that at the end of study follow-up visit on 19 NOV 2012 (Day 242) the patient was starting to put her foot on the ground with the support of an aircast and a crutch. On 30 JAN 2013 (Day 314), the patient visited a traumatologist and he determined that the patient continued to improve, and only needed crutches to walk on the street (not at home). An X-ray taken on the same date showed good evolution and the patient was advised to stop the crutch and aircast 1 month later. It was reported that the event would be considered completely resolved when the patient stops using the crutches; however, at the time of this report, the non-serious event of fibula fracture was reported as ongoing.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 911/009
Age: 61	**Sex:** Male
Race: White	**Study Drug:** Placebo
Reason for Narrative:	Serious Adverse Event
Event:	In-stent coronary artery restenosis

Narrative:

Patient 911-009, a 61-year-old male with a history of myocardial infarction, hypertension, unstable angina, and dyslipidemia enrolled in the study on 19 MAR 2012. He was randomized to placebo on 26 MAR 2012; the first dose of placebo was administered on the same date. Concomitant medications included enalapril 10 mg BID (hypertension), atenolol 25 mg BID (angina pectoris), rosuvastatin 10 mg QD (dyslipidemia), milk of magnesia 8.5% 2 mL once (constipation), aspirin (acetylsalicylic acid) 100 mg QD, clopidogrel 75 mg QD (acute coronary syndrome), and omeprazole 20 mg QD (peptic ulcer prophylaxis).

On 02 OCT 2012 (Day 191), the patient presented for Visit 12 and follow up intravascular ultrasound revealed severe restenosis in the left circumflex stent (in-stent). The event was considered moderate in intensity. A dobutamine stress echocardiography showed no ischemia and the patient remained asymptomatic. Corrective treatment involved a new angioplasty and drug-eluting stent deployment. The patient received mepivicaine 2% 1 mL, diazepam 5 mg, midazolam 1 mg, unfractionated heparin 9000 IU, morphine 1 mg, glyceryl trinitrate 900 µg, and verapamil 2.5 mg for the percutaneous coronary intervention. On 02 OCT 2012, the event was considered resolved. Study drug had been discontinued on 01 OCT 2012 (Day 190), prior to the onset of the SAE, when the patient completed study drug treatment.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 911/012
Age: 66	**Sex:** Male
Race: White	**Study Drug:** RVX000222 200 mg
Reason for Narrative:	Serious Adverse Event
Event:	Coronary artery disease

Narrative:

Patient 911-012, a 66-year-old male with a history of hypertension, unstable angina, abdominal hernia repair, spinal osteoarthritis, peptic ulcer, benign prostatic hyperplasia, and procedural hypotension enrolled in the study on 20 APR 2012. He was randomized to RVX000222 200 mg on 21 MAY 2012; the first dose of study drug was administered on the same date. Concomitant medications included enalapril 20 mg QD and hydrochlorothiazide 12.5 mg QD (hypertension), tamsulosin 0.5 mg QD and dutasteride 0.4 mg QD (prostatic hypertrophy), rosuvastatin 10 mg QD (ischemic heart disease), Flumil® (acetylcysteine) 200 mg QD (upper airway infection), aspirin (acetylsalicylic acid) 100 mg QD and clopidogrel 75 mg QD (unstable angina), and omeprazole 20 mg QD (stomach protector).

The patient was diagnosed with angina pectoris which was a non-serious adverse event reported on 20 SEP 2012 and the event is ongoing. Treatment for the event included bisoprolol 2.5 mg QD and glyceryl trinitrate 5 mg QD from 05 OCT 2012 to 08 OCT 2012 with a good response. Bisoprolol dose was increased to 5 mg QD and glyceryl trinitrate to 10 mg QD on 08 OCT 2012; both treatments are ongoing.

On 19 NOV 2012 (Day 183), the patient presented for Visit 12 and follow up intravascular ultrasound and angiography showed a severe "de novo" lesion in the left anterior descending artery. The event was considered moderate in intensity. The patient was hospitalized on the same day and corrective treatment involved a new angioplasty and drug-eluting stent deployment, without any complications. The patient received mepivicaine 2% 1 mL, diazepam 5 mg, unfractionated heparin 11,500 IU, glyceryl trinitrate 500 µg, and verapamil 2.5 mg for the percutaneous coronary intervention. On 19 NOV 2012, the event was considered resolved, and the patient was discharged from the hospital on the same date. Study drug had been discontinued on 18 NOV 2012 (Day 182), prior to the onset of the SAE, when the patient completed study drug treatment.

The investigator considered the event to be unrelated to study drug.

Protocol No.: RVX222-CS-007	**Center No./Patient No.:** 911-015
Age: 50	**Sex:** Male
Race: White	**Study Drug:** RVX000222
Reason for Narrative: Clinically Significant Event	
Event(s): Elevated liver enzymes	

Narrative:

Patient 911-015, a 50-year-old male with a history of myocardial infarction, hypertension, angina, metabolic syndrome, dyslipidemia, asthma, and tinnitus enrolled in the study on 29 MAY 2012. He was randomized to RVX000222 200 mg on 04 JUN 2012; the first dose of study drug was administered on 12 JUN 2012. Concomitant medications included mepivicaine 1 mL (local anesthesia), losartan 100 mg QD and hydrochlorothiazide 25 mg QD (hypertension), paracetamol 1 g QD and ibuprofen 600 mg TID (ankle sprain), diazepam 10 mg (anxiety prophylaxis), midazolam 1 mg once, morphine 1 mg once, and verapamil 2.5 mg once (radial spasm prevention), enoxaparin 40 mg QD (deep vein thrombosis), heparin 7000 IU once (catheter thrombosis prevention), atorvastatin 40 mg QD (dyslipidemia), rosuvastatin 10 mg QD and Adiro® (acetylsalicylic acid) 100 mg QD (ischemic heart disease), and glyceryl trinitrate 100 µg once (coronary spasm prevention).

On 23 JUL 2012 (Day 42), at Visit 5, laboratory tests revealed hepatic enzyme increases with ALT >3x the upper limit of normal, and AST and GGT elevations (see table below). Treatment with the study drug was not changed. Despite continuous dosing with study drug, hepatic enzyme levels gradually improved, such that by 17 SEP 2012 (Day 98), all values had returned to within normal limits and remained normal through the follow-up visits.

Visit	Date Collected	ALT (U/L)	AST (U/L)	GGT (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	INR
Screening	07JUN2012	35	28	74 (H)	0.1	0.3 (L)	
Week 0	15JUN2012	30	24	84 (H)	0.1	0.4	
Week 2	25JUN2012	30	25	65	0.0	0.3	
Week 4	09JUL2012	37	44 (H)	78 (H)	<0.0	0.1 (L)	
Week 6	23JUL2012	172 (H)	95 (H)	86 (H)	0.1	0.2 (L)	
Week 8	06AUG2012	118 (H)	61 (H)	110 (H)	0.1	0.3 (L)	
Week 11	27AUG2012	46	55 (H)	65	<0.0	0.3	
Week 14	17SEP2012	32	26	51	0.1	0.5	
Week 17	08OCT2012	19	20	40	0.1	0.2 (L)	
Week 20	29OCT2012	29	26	45	0.1	0.3 (L)	
Week 23	22NOV2012	22	18	70	0.1	0.4	
Week 26	17DEC2012	23	23	61	0.1	0.2 (L)	
Follow-Up	14JAN2013	24	29	50	0.1	0.2 (L)	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; H=high; INR=prothrombin international normalized ratio.

15 REFERENCE LIST

1. Missel E, Mintz GS, Carlier SG, Sano K, Qian J, Kaple RK, Castellanos C, Dangas G, Mehran R, Moses JW, Stone GW, and Leon MB. Necrotic core and its ratio to dense calcium are predictors of high-risk non-ST-elevation acute coronary syndrome. Am J Cardiol. 2008; 101(5): 573-578.

16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form (unique pages only)

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) – Representative Written Information for Patient and Sample Consent Forms

16.1.4 List and Description of Investigators and Other Important Participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer Depending on the Regulatory Authority's Requirement

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