**Information required for submission**

**Protocol RVX222-CS-015 dated 29Jun2015**

**TITLE:** BETonMACE: A phase III multi-center, double-blind, randomized, parallel group, up to 104 weeks dosing, placebo-controlled clinical trial in high-risk type 2 diabetes mellitus (T2DM) subjects with coronary artery disease (CAD) to determine whether treatment with RVX000222 increases the time to major adverse cardiovascular events (MACE).

**MAIN OBJECTIVES:**

**Primary Objective:**

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

**Secondary Objectives:**

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

Broadly defined MACE is any of the following events:

* CV death
* Non-fatal Myocardial Infarction (MI)
* Hospitalization for CVD events including:
  + Unstable angina AND evidence of new or presumed new progressive obstructive coronary disease, OR
  + Emergency revascularization procedures at any time and urgent revascularization procedures ≥30 days after the index events prior to randomization
  + Stroke
* To evaluate treatment group difference in all-cause mortality
* To evaluate changes in lipoprotein concentrations including apoA-I, apolipoprotein B (apoB), low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglyceride (TG) over time within and between treatment groups
* To evaluate changes in diabetes mellitus variables including glycated hemoglobin (HbA1c), fasting glucose, and fasting insulin over time within and between treatment groups
* To evaluate changes in alkaline phosphatase (ALP) over time within and between treatment groups including isoforms for whole population and quartiles of ALP baseline concentration
* Assess changes in kidney function in population with baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.7m2
* To evaluate the safety and tolerability of RVX000222

**Exploratory Objectives:**

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

**RATIONALE:**

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

Bromodomains (BRDs) are a family of evolutionary conserved protein-interaction modules that play key functions in chromatin organization and regulation of gene transcription. One recognized family of bromodomain-containing proteins is the bromodomain and extra-terminal (BET) family. BET inhibition represents a novel, epigenetic approach to treat CVD. RVX000222 is the first oral agent in the BET inhibitor class that preferentially targets BET protein 4 (BRD4) thereby regulating gene activity. RVX000222 affects biological processes important in atherosclerosis and acute coronary events via selective inhibition of BET proteins. Current studies of RVX000222 show that it has effects on vascular inflammation, the complement and coagulation cascades, and acute phase response pathways all of which have known roles in cardiovascular disease and acute cardiac events. Gene expression regulation by BET proteins appears to be at the root of the pathogenesis of cardiac events. The effect of selective BET inhibition on all of the pathways outlined above underlies the potential benefit of using RVX000222 in treating CVD risk and for the prevention of recurrent acute events. RVX000222 is available as a capsule formulation with standard excipients and established stability.

**Number of Patients at site:**

**The recruitment process:**

The study will be explained to prospective subjects, and informed consent will be obtained. Candidates who meet the entry criteria will be invited to enroll in the study.

**Gender and age:**

Male and female subjects age 18 and over with T2DM and high risk CVD treated with high intensity statin therapy and with a low level of HDL-C of <40 mg/dL males or <45 mg/dL females.

**INCLUSION CRITERIA:**

1. Male and female subjects age 18 and over with documented diagnosed T2DM and a CAD event not less than 7 days and no more than 90 days prior to Visit 1 (one or more of the following three primary criteria must be satisfied):
   * Unstable angina with documented coronary disease by coronary angiography requiring hospital admission
   * History of percutaneous coronary intervention (PCI) and / or coronary stenting to treat acute coronary syndrome 7-90 days before Visit 1
   * Previous MI 7-90 days before screening. **Two of the following three criteria must be satisfied**:
   1. Characteristic ischemic chest pain or pain in associated referral areas,
   2. Elevation of troponin T or I (at least above the upper limit of normal for the laboratory),
   3. Development of new Q-waves in at least two adjacent electrocardiogram (ECG) leads or development of a new dominant R wave in V1.
2. Documented history of T2DM and/or taking diabetes medication and/or having HbA1c >6.5%.
3. For males HDL-C of <40 mg/dL (1.0 mmol/L) and for females HDL-C of <45 mg/dL (1.1 mmol/L) at Visit 1.
4. In the opinion of the Investigator subjects currently not on high intensity statin therapy will be able to start rosuvastatin according to the protocol at Visit 1.
5. In the opinion of the Investigator subjects currently on statin therapy other than atorvastatin or rosuvastatin can be switched to rosuvastatin according to the protocol at Visit 1. High intensity statin therapy doses should remain unchanged during the study period if at all possible.
6. Female subjects must meet one of the following:
   * If of childbearing potential, female subjects must have a negative urine pregnancy test and be willing and able to use medically acceptable non-hormonal method of birth control (non-hormonal intrauterine device, condom, or diaphragm) or remain abstinent from Screening until Follow-up Visit.
   * Be of non-child-bearing potential: post-surgical sterilization or post-menopausal.
7. Have given signed informed consent to participate in this study.

**Exclusion Criteria:**

1. Heart disease which, in the opinion of the investigator, will within 3 months of Visit 1 likely require coronary bypass, PCI, cardiac transplantation, surgical repair and/or replacement.
2. Previous or current diagnosis of severe heart failure (New York Heart Association Class IV) or a documented left ventricular ejection fraction (LVEF) of <25% as determined by contrast left ventriculography, radionuclide ventriculography or echocardiography. The absence of a LVEF measurement in a subject without a previous or current diagnosis of heart failure does not prohibit entry into the study.
3. Subjects with evidence of cardiac electrophysiologic instability including a history of uncontrolled ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardias with a ventricular response heart rate of >100 beats per minute at rest within 4 weeks prior to Visit 1.
4. Evidence of severe renal impairment as determined by any **one** of the following:
   * + an eGFR <30 mL/min/1.7m2 at Visit 1
     + a current need for dialysis
5. Uncontrolled hypertension defined as 2 consecutive measurements of sitting blood pressure of systolic >180 mm Hg or diastolic >100 mm Hg at Visit 1.
6. Current or recent (within 12 months prior to Visit 1) treatment with immunosuppressants (e.g., cyclosporine).
7. Use of fibrates at any dose or niacin/nicotinic acid 250 mg or more within 30 days prior to Visit 1.
8. A known allergy or sensitivity to any ingredient in the investigational medicinal product.
9. History of intolerance to atorvastatin or rosuvastatin.
10. Triglycerides >400 mg/dL at Visit 1.
11. Any medical or surgical condition which might significantly alter the absorption, distribution, metabolism or excretion of medication including, but not limited to any of the following: untreated or incompletely treated thyroid dysfunction, cholecystitis, Crohn’s disease, ulcerative colitis, or any gastric bypass alteration.
12. Evidence of cirrhosis from liver imaging or biopsy, a history of hepatic encephalopathy, esophageal or gastric varices, active hepatitis, or prior porta-caval shunt procedure, or a Child-Pugh score of at least 5 points.
    * Any one of the following liver enzymes that is >1.5x the upper limit of normal range (ULN) by central lab at Visit 1
      1. Alanine aminotransferase (ALT)
      2. Aspartate aminotransferase (AST)
13. A total bilirubin that is >ULN by central lab at Visit 1.
14. History of malignancy of any organ system, treated or untreated, within the past 2 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
15. History or evidence of drug or alcohol abuse within 12 months of Visit 1, in the opinion of the investigator.
16. Female subjects who are pregnant.
17. Any condition which, in the opinion of the investigator, may place the subject at higher risk from his/her participation in the study, or is likely to prevent the subject from complying with the requirements of the study or completing the study.
18. Use of other investigational drugs and devices within 30 days or 5 half-lives of Visit 1, whichever is longer.
19. History of noncompliance with medical regimens or unwillingness to comply with the study protocol.
20. Any condition that, in the opinion of the investigator, would confound the evaluation and interpretation of efficacy and/or safety data.
21. Persons directly involved in the execution of this protocol.

**Subject Withdrawal / Discontinuation from Study:**

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

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

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

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

**Reference to the inclusion of special populations:**

Pregnant women and legally incompetent participants will be excluded from this study.

Length of treatment for each participant and study duration:

Total subject participation: Up to 122 weeks

 Screening period of 1-2 weeks

 Treatment period of up to 104 weeks

 Follow-up period of 4-16 weeks

**STUDY DESIGN:**

This design is a double-blind, placebo-controlled, 2-arm parallel-group (allocation ratio 1:1), study of RVX000222 at a dose of 100 mg b.i.d. (total daily dose of 200 mg) or matching placebo in combination with high intensity statin therapy administered to T2DM subjects with history of recent CVD event and HDL-C level <40 mg/dL males or <45 mg/dL females. High intensity statin therapy shall consist of a daily dose of either atorvastatin 20-80 mg or rosuvastatin 10-40 mg. 20 mg atorvastatin or 10 mg rosuvastatin is acceptable in circumstances such as advanced age, low body mass, previous intolerance to higher doses or specific drug-drug interactions (e.g. anti-retrovirals). After an initial screening period of 1 to 2 weeks during which subjects will be treated with high intensity statin therapy, subjects will be randomized to either RVX000222 100 mg b.i.d. or matching placebo with continued statin treatment. This combination treatment period will continue for up to 104 weeks at which time blinded treatment with RVX000222 or matching placebo will be discontinued. Subjects will remain on high intensity statin therapy for 4-16 more weeks until the Follow-Up Visit.

The study is an event-based trial and will continue until 250 broadly defined MACE events have occurred. The study will be monitored by a Data Safety Monitoring Board (DSMB).

MACE will be adjudicated by an independent, treatment masked MACE Adjudication Committee (EAC) in an ongoing manner.

**Concomitant Statin Therapy**: Protocol-defined concomitant statin therapy in this study is a tolerable atorvastatin daily dose of 20-80 mg or rosuvastatin daily dose of 10-40 mg. Doses of 20 mg atorvastatin and 10 mg rosuvastatin are acceptable in circumstances such as advanced age, low body mass, previous intolerance to higher doses, or specific drug-drug interactions (e.g. anti-retrovirals).