# ***Ranolazine Mediated PVC Reduction in Ischemic Heart Disease***

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## ***Background and Rationale***

Ischemic heart disease is a heterogeneous condition with multiple etiologies that may contribute to an imbalance in myocardial oxygen supply and demand, resulting in depletion of myocardial cellular energy stores. Management of this disease state is aimed primarily at improving myocardial oxygen supply through revascularization of underlying obstructive atherosclerosis, in conjunction with interventions to reduce myocardial oxygen demand. Chronic treatment is directed at reducing recurrent ischemic symptoms. Despite advances in anti-thrombotic therapy, coronary revascularization, and other preventive therapies, the risk of recurrent events in this population remains substantial, in particular among those patients with indicators of higher risk (e.g. ST-segment depression, or arrhythmias).

Ranolazine is a piperazine derivative that exerts anti-ischemic actions without a clinically significant effect on heart rate or blood pressure. At clinically relevant concentrations, ranolazine is an inhibitor of the slowly inactivating component of the cardiac sodium current (late INa), which may reduce the deleterious effects associated with the intracellular sodium and calcium overload that accompany and may promote myocardial ischemia. Ranolazine is available as an anti-anginal agent for patients with chronic angina. The Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial demonstrated the safety of ranolazine in patients after ACS and also showed it's anti-arrhythmic properties. In addition to the safety properties of ranolazine, the study showed that ranolazine had a significant anti-ischemic effect and patient's on therapeutic dosing.

In an analysis of the 6560 patients in MERLIN-TIMI 36, using a digital continuous electrocardiographic Holter monitor for ischemia (Lifecard CF, Delmar Reynolds was applied to patients at the time of randomization and remained in place for 7 days, including after hospital discharge). Findings showed that patients treated with ranolazine had significantly lower incidences of arrhythmias. Specifically, fewer patients had an episode of ventricular tachycardia lasting ≥8 beats, supraventricular tachycardia or new-

onset atrial fibrillation. In addition, pauses ≥3 seconds were less frequent with ranolazine. Based on this report, further studies of the antiarrhythmic effects of ranolazine were warranted.

Premature ventricular complexes (PVCs) are a frequent occurrence in the presence of ischemic heart disease. A very high PVC burden can be symptomatic or occasionally result in a cardiomyopathy. The mechanism by which PVCs cause cardiomyopathies or symptoms is not well understood, but may be related to an increase in myocardial strain or demand. Reduction in PVC burden has been associated with both improvement in ejection fraction and symptoms. Ranolazine has also been shown to reduce PVC burden in patients already on optimal medical therapy. The estimate of the minimal number of PVCs required to be associated with a cardiomyopathy is around 10%. In fact, subjects that had evidence for PVCs on baseline 12 lead electrocardiogram were found to have a significantly higher risk of cardiovascular events.

Current strategies for managing complex cardiomyopathies driven by arrhythmias have been complicated by intolerance to medical therapy as well as the requirement for frequent titration and the development of tolerance. Patients with ischemic heart disease have limited options for antiarrhythmic medical therapy. Prior trials of flecainide and eicainide in patients with ischemic heart disease for control of ventricular arrhythmias resulted in a significant and deleterious proarrhythmic effect current options for management line on amiodarone which has significant liver, thyroid, and lung toxicities or sotalol which can have significant bronchospastic effects as well as QT prolongation or tedious and which has to be carefully dose in the setting of renal insufficiency to avoid significant QT prolongation and the risk for proarrhythmia.

While ICD therapy has been appropriate for patients with reduced ejection fraction and evidence for unstable ventricular arrhythmias/sudden cardiac death, frequent or low level ventricular arrhythmias such as nonsustained VT or frequent PVCs would not be treated by ICD therapy. Escalation of traditional nodal therapies such as beta blockers or calcium channel blockers is his often limited by marginal systolic blood pressures and/or symptoms.

With the increasing prevalence of ischemic heart disease, it is critically important to identify therapies that have a neutral response to heart rate and blood pressure, good safety profile, and can reduce ischemia and the burden ventricular arrhythmias. Ultimately, the hope is that they will reduce strain induced ischemic heart changes. To that end, investigation of the effects of ranolazine in patients with ischemic heart disease and an elevated burden of PVCs is of great interest.

## ***Hypothesis***

We propose that one mechanism by which ranolazine may manifest its beneficial effects on ischemia is through a reduction in PVC burden. It would be expected that the administration of ranolazine in patients an elevated PVC burden would significantly reduce PVCs and associated strain related ischemia on continuous ECG. These findings may support a potentially novel role for ranolazine in the management of arrhythmia based cardiomyopathies.

## ***Specific Aims/Endpoints***

*Primary Outcome Measures:*

- The effect of ranolazine on pre-ventricular contraction burden (PVC) over treatment period.
- The effect of ranolazine on ischemia as measured by ST segment deviation on Holter monitoring and quality of life survey measurements.

*Secondary Outcome Measures:*

- PVC burden for each visit period (Weeks 1,after run-in Holter and week 5, after final Holter and end of treatment)
- Quantification of non-sustained ventricular tachycardia >8 beats, supra-ventricular tachycardia and sustained ventricular arrhythmia episodes on Holter monitoring.
- Ventricular rate over monitoring period of treatment and for each visit period (Weeks 1 and 5)
- Incidence of symptomatic episodes
- The percentage of subjects who have $\geq 30\%$ ($\geq 50\%$) reduction from baseline in symptoms as measured by arrhythmia quality of life (QOL) survey

## ***Study Group***

| | |
|---|---|
| Ages Eligible for Study: | 18 Years and older |
| Genders Eligible for Study: | Both |
| Accepts Healthy Volunteers: | No |

**Criteria**

Inclusion Criteria:

- Males and females aged 18 years and older
- Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
- History of ischemic heart disease (prior bypass or coronary stenting, documentation on cardiac catheterization, nuclear SPECT imaging, cardiac MR, stress echocardiography, or exercise stress testing) *or* a history of chronic angina without evidence of ischemic heart disease.

~~Subjects are not required to have chronic angina to be enrolled in the study~~

- Elevated PVC burden determined by one of the following:
    - At least 1% PVC burden on prior Holter/event monitor in previous 12 months
    - evidence for PVC(s) on baseline ECG within prior 12 months
    - $\geq$ 10,000 PVC's on a device check (pacemaker, ICD) since the last interrogation of the device
- Sexually active females of childbearing potential must agree to utilize effective methods of contraception during heterosexual intercourse throughout the treatment period and for 14 days following discontinuation of the study medication

Exclusion Criteria:

Disease - specific:

- Hospitalization for hyperthyroidism, pericarditis, myocarditis, or pulmonary embolism within 4 weeks prior to screening
- Implantation of ICD or permanent pacemaker within 1 month of screening

- New York Heart Association (NYHA) Class III and IV heart failure or NYHA Class II heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic within 4 weeks prior to Screening.
- Myocardial infarction, unstable angina, or coronary artery bypass graft (CABG) surgery within three months prior to Screening or percutaneous coronary intervention (PCI) within 4 weeks prior to Screening
- Clinically significant valvular disease in the opinion of the Investigator
- Stroke within 1 months prior to Screening
- History of serious ventricular arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation) within 4 weeks prior to Screening
- Family history of long QT syndrome
- QTc ≥ 500 msec (Bazett) at Screening ECG if in sinus rhythm (SR). If in AF, evidence of QTc ≥ 500 msec (Bazett) within 4 weeks prior to Screening
- Prior heart transplant
- Cardiac ablation within 3 months prior to Screening, or planned ablation during the course of the study
- Need for concomitant treatment during the trial, with drugs or products that are strong inhibitors of CYP3A, or inducers of CYP3A

  — Such medications should be discontinued 5-half- lives prior to the Run-in period
- Use of grapefruit juice or Seville orange juice during the study
- Use of drugs that prolong the QT interval
- Previous use of ranolazine within 2 months prior to screening
- Prior use of ranolazine which was discontinued for safety or tolerability
- Use of dabigatran during the study
- Use of a greater than 1000 mg total daily dose of metformin during the study

Laboratory tests:

- Hypokalemia (serum potassium < 3.5 mEq/L) at Screening that cannot be corrected to a level of potassium ≥ 3.5 mEq/L prior to randomization
- Moderate and severe hepatic impairment (ie, Child-Pugh Class B and C), abnormal liver function test defined as ALT, AST, or bilirubin > 2 x ULN at Screening

- Severe renal impairment defined as creatinine clearance ≤ 30 mL/min at Screening

Others:

- Females who are pregnant or are breastfeeding
- Exclusion of patients with Contraindications to use of RANEXA, including patients on CYP3A4 inducers/potent inhibitors, and patients with liver cirrhosis
- Exclusion of Patients with CrCl < 30 mL/min
- Limit dose of RANEXA to 500mg BID in patients on concurrent diltiazem/verapamil
- Limit concurrent simvastatin to 20 mg/day
- Please also see Interactions, Warnings and Precautions noted in the Prescribing Information for RANEXA
- In the judgment of the Investigator, any clinically-significant ongoing medical condition that might jeopardize the subject's safety or interfere with the study, including participation in another clinical trial within the previous 30 days using a therapeutic modality which could have potential residual effects that might confound the results of this study
- Any technical issue (device related) which in the judgment of the investigator would disrupt adequate data collection or interpretation

## ***Study Design***

*Patient recruitment*

Patients will be recruited from Kent Hospital and the hospital affiliated cardiology practices in this non-randomized study. Brigham and Women's Cardiovascular Associates at Kent hospital has an outpatient volume of 400-500 patients per month. Kent Hospital is a 360 acute care bed hospital and the second largest hospital in Rhode Island. The Kent Hospital emergency room has approximately 70,000 visits per year. Enrollment of 10-20 patients within a twelve-month timeframe would be expected.

The clinical trial program and Kent Hospital and Brigham and Women's Cardiovascular Associates has two on-site research coordinators who would be primarily charged with patient recruitment in both the inpatient and outpatient settings. Those coordinators and an additional data entry specialist would be involved with screening potential study patients, obtaining informed consent, enrolling patients, and performing all follow-up on trial patients. Both research coordinators are experienced in the execution of cardiovascular clinical trials and have extensive clinical trial experience. The five general cardiologists in the practice (Brigham and Women's Cardiovascular Associates at Kent hospital) will also assist with patient identification and recruitment.

*Informed Consent*

The study will be reviewed with the prospective study participant by the investigator or his/her designee. The prospective study participant will be given adequate time to read the written consent form. The investigator or his/her designee will be available to answer questions about the study including procedures, risks, and alternatives. The informed consent form will be signed and dated by the patient as per local regulation. In addition, prospective study participants will be requested to consent to appropriate laboratory testing. A copy of the signed consent form will be given to the participant and the original(s) will be kept securely with each participant's research records.

*Treatment Assignment*

Gilead Sciences will provide Ranolazine extended/prolong released tablets containing thousand milligrams of active ingredient. The investigational pharmacy will dispense the study drug to subjects per the study protocol. Upon initial receipt of the study drug investigator and/or investigative site staff will acknowledge receipt of the material, indicating Shipman contact and condition. The study site must maintain a dated inventory record of all study drug supplies received and dispensed to subjects. A copy of the inventory log for study drug will be sent to the sponsor after the study is complete.

The study pharmacist will dispense study drugs. Each subjective will be instructed to take one tablet of the study drug with food twice daily in the morning and evening approximately 12 hours apart. There is no dose modification in the study. The subject experiences intolerable adverse events during treatment. The study drugs will be discontinued in the subject will be terminated from that study.

*Study Procedures*

Please see attached the flow chart for details of timing of screening and enrollment. After extensive review of the patient's medical history and identification of a history of ischemic heart disease as well as history of elevated burden of pre-ventricular contractions (PVCs), patients will be consented for the study. Patients will wear a screening, continuous Holter monitor for seven days to assess underlying burdenning of PVCs and ventricular arrhythmias as well as for ischemic ST changes. Patients who have greater then 5% PVC burden (roughly 5000 PVCs for an avg 100000 beats/day) at the end of the Holter evaluation will be brought back to the office where they will be formally enrolled and started on the study drug. Screening Holter failures (e.g. less than 5% PVC on monitor) could be rescreened with an additional seven day monitor.

At the time, physical exam, baseline EKG, medication and history review, will be performed and documented. Patients will then be started on ranolazine thousand milligrams by mouth twice a day for a thirty-day treatment period. On day 23 (one week prior to end of treatment), the patient will return to the office and have another seven-day Holter monitor placed. At the end of that seven day Holter monitor, the patients will return to the office where they will return the Holter, complete the quality of life survey, end the study and receive further follow-up instructions.

The study drug could be terminated at the end of the study or could be continued per patient preference. Holter monitor analysis will then be undertaken and further reports generated.

Holter monitors will be evaluated for the presence of ischemia using standard techniques. A continuous ECG (cECG, Holter) recording (Lifecard CF, DelMar Reynolds/Spacelabs, Issaqua, Washington or equivalent) will be performed to assess for ischemia. Cardiologists will perform ischemia analyses of all cECG recordings in the TIMI ECG Core Laboratory to detect any ischemic episode with ≥0.5 mm ST-segment depression lasting at least 1 min.

The primary ischemic end point of the cECG assessment was the incidence of ischemia defined as ≥1 mm ST-segment depression lasting at least 1 min with a heart rate at the onset of the episode <100 beats/min. Ischemic burden will be calculated from the sum of the area under the ST-segment trend curves for each ischemic episode.

Quality of life surveys will be performed at enrollment and at treatment/study end. SF-36v2 (or equivalent) will assess baseline quality of life and assess for qualitative treatment improvements.

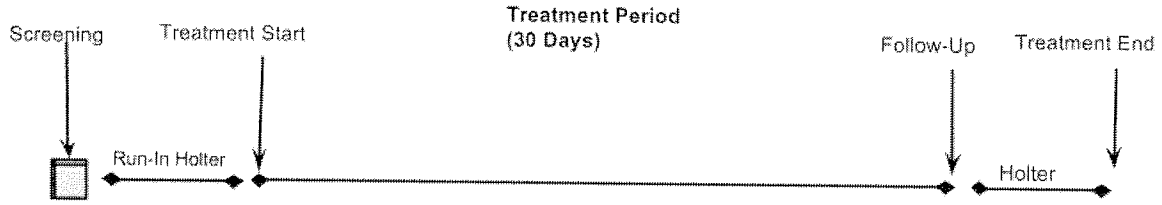


Figure 1: Study Procedure Schematic

## ***Statistical Methods***

All analyses are based on patients with evaluable cECG ischemic and arrhythmia data. Continuous data will be compared with a t test.

## *Budget*

Please see attached.

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