Study title and code: RANOLAZINE IN PATIENTS WITH SYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY: A PILOT STUDY ASSESSING THE EFFECTS ON EXERCISE CAPACITY, DIASTOLIC FUNCTION AND SYMPTOMATIC STATUS (RESTYLE – HCM STUDY)

Study type and design: Randomized, Double blind, Placebo controlled, Parallel Group, Pilot Study, in patients with SHCM.

Study phase: II

Number of Centres and Countries: 13 sites in 3 countries

Study aim: to demonstrate the efficacy and safety of ranolazine in improving exercise capacity, diastolic function and symptomatic status in patients affected by SHCM.

Study treatment:
Ranolazine, prolonged release tablets of 500, 750 and 1000 mg
Maintenance dose 1000 mg / bid or maximum tolerated/advisable dose.
The initial dose should be 500 mg/bid; after 1 week the dose should be up-titrated to 750 mg/bid in all patients and further titration up to 1000 mg/bid after another week if the drug is well tolerated. If the up titration to 750 or 1000 mg is not advisable, patients will continue with 500 or 750 mg respectively, throughout of the study.
Placebo tablets, 1 tablet/bid in the same conditions as ranolazine treatment.

Duration of treatment: 2 weeks up-titration + 5 months double-blind treatment.

Concomitant medication: symptomatic standard therapy (e.g. β-blockers or non dihydropiridine calcium channel blockers) will be maintained at stable doses during the study.

Study duration: 24 months enrolment and 2 weeks up-titration + 5 months study treatment.

Number and characteristics of patients: 100 patients with SHCM, defined as the presence of LV wall thickness ≥ 1.5 cm in the absence of other conditions potentially responsible for the same degree of hypertrophy.

Inclusion criteria:

• Male and female genders;
• Females of childbearing potential or within two years from the menopause must have a negative urine pregnancy test (females of childbearing potential must be using adequate contraceptive precautions such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence or vasectomised partner);
• Patients who fulfil conventional echocardiographic criteria for the diagnosis of SHCM: Maximum LV wall thickness ≥ 1.5 cm;
• Patients aged > 18 years;
• Patients with exertion symptoms and functional limitation (angina and or HF NYHA II–III);
• Presence of sinus rhythm;
• Peak VO2 < 75% of predicted for age and gender;
• Absence of resting LV outflow tract obstruction (peak gradient < 30 mmHg);
• Written informed consent prior to enrolment into the study;
• Persons capable to understand the nature, significance and implications of the clinical trial.

Exclusion criteria:

• Females of childbearing potential not using adequate contraceptive precautions;
• Females who are pregnant or lactating;
• Presence of known coronary artery disease (CAD);
• Presence of Chronic Obstructive Airways Disease;
• Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazol, posaconazol, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone)
• Concomitant administration of dronedarone Class Ia (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antiarrhythmics other than amiodarone, or other QT-prolonging drugs;
• Concomitant use of CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John’s Wort)
• Concomitant use of > 1000 mg daily dose of metformin during the study
• Concomitant use of >20 mg daily dose of Simvastatin during the study (in case of patients taking simvastatin >20 mg daily, the switch to other statins not metabolized by the CYP3A4 could be considered).
• Patients with QTc at baseline ≥ 500 ms; QTc values will be calculated using the standard Bazett formula
• Any clinically relevant haematological or biochemical abnormality on routine screening, according to Investigator’s judgment;
• Severe concurrent pathology, including terminal illness (cancer, AIDS, etc.);
• Severe renal impairment defined as GFR < 29 mL/min or creatinine level > 2.5 mg/dL; GFR must always be calculated;
• Moderate or severe hepatic impairment or hepatic insufficiency defined as SGOT or SGPT > 2 times greater than normal upper limit or total serum bilirubin > 1.5 times greater than normal upper limit;
• Dementia, psychosis, alcoholism (>280 g ethanol/week for male or >140 g ethanol/week for female patients) or chronic abuse of medicines, drugs or psychoactive substances;
• Conditions which in the Investigator’s opinion may interfere with the study’s execution or due to which the patient should not participate for safety reasons;
• Risk of low patient cooperation;
• Inability or unwillingness to issue the informed consent;
• Inability to perform a cardiopulmonary test;
• Lactose intolerance;
• Hypersensitivity to ranolazine or one of the excipients.

Objectives: the primary study objective will be to demonstrate the efficacy of ranolazine in improving exercise capacity in patients affected by SHCM using the Peak Oxygen Consumption (V02 peak) Technique.
Secondary objectives will be to demonstrate the efficacy of ranolazine on diastolic function, symptomatic status and natriuretic peptide biomarker proBNP, in patients affected by SHCM. The safety of ranolazine will be also checked in the same population.

Primary end-point:
Evaluation of Exercise Capacity with V02 peak technique in patients with SHCM after 5 months of treatment with ranolazine at the maximum reached dosage, or placebo.

Secondary end-points:
- Evaluation of E/E’ ratio changes with treatment using the Tissue Doppler (TD) Technique
- Evaluation of proBNP
- Evaluation of the symptomatic status using the Minnesota Living With Heart Failure Questionnaire (MLWHFQ).
- Safety Evaluation with:
  - Physical Examination
  - the routine laboratory tests
  - standard 12-lead ECG
  - Detection of 24-hour arrhythmic burden by Holter ECG monitoring.
  - Detection of AE in study population.

**Efficacy assessment**

**Primary assessment**
- V02 peak evaluation: a Cardiorespiratory test will be performed at visits 1, 4 and 6 in order to evaluate the exercise capacity from visit 1 (baseline) to visit 6 (endstudy visit) in the two treatment study groups.

**Secondary assessment**
- E/E’ ratio evaluation: a TD will be performed at visits 1, 4 and 6 in order to evaluate the possible changes in E/E’ ratio from visit 1 (baseline) to visit 6 (end-study visit) in the two treatment study groups;
- Natriuretic peptide biomarker evaluation: proBNP will be performed at visits 1, 4 and 6 in order to evaluate the possible changes in its value from visit 1 (baseline) to visit 6 (end-study visit) in the two treatment study groups;
- Symptomatic Status Evaluation: the Minnesota Living With Heart Failure Questionnaire will be used at visit 1, 4, 5 and 6, in order to evaluate possible changes in MLWHFQ score from visit 1 (baseline) to visit 6 (end-study visit) in the two treatment study groups.

**Safety assessment**
Physical examination, the rest standard 12-lead ECG and the vital signs (BP and HR detection) will be checked at each study visit from visit 1 to 6; the routinely lab tests, the detection of 24-hour arrhythmic burden by Holter ECG monitoring will be performed at visits 1, 4, 5 and 6; the detection of AEs will be performed from visit 2 to visit 6 in order to evaluate the patients safety status in the two treatment study groups. Routinely Laboratory Tests: the following laboratory parameters will be checked at visits 1, 4, 5 and 6:
- Haematology
- Na+, K+, Ca++
- Bilirubin (total and direct)
- Fasting blood glucose
- Triglycerides
- Total cholesterol
- HDL cholesterol
- Creatinine level
- SGOT
- SGPT
- GFR
- BUN
- ALP
- γGT
- Urine (Colour, pH, specific gravity, glucose, protein, blood)

**Sponsor statement**
The study will be conducted according to this protocol, the Good Clinical Practice (GCP), the ICH guidelines, local laws and obligations and the World Medical Association Declaration of Helsinki (Appendix 1).