UNIVERSITÄT BERN
Faculty of Medicine
CTU Bern

# Statistical Analysis Plan (SAP)

## Paroxetine-mediated GRK2 inhibition to reduce cardiac remodeling after acute myocardial infarction (CARE-AMI): a randomized controlled pilot study

## CARE-AMI

# Administrative Information

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|---|---|
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## Contributors

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## Revision history

| Revision | Justification | Timing |
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## Approved by

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# 1. Introduction

## 1.1 Background and rationale

Cardiac remodeling is characterized by a composite of structural, geometric, molecular, and functional changes of the myocardium, and is an important determinant of heart failure and cardiovascular outcome in survivors of acute myocardial infarction. Progression of heart failure secondary to the remodeling process results from dysregulation of the G protein-coupled receptor (GPCR). Excessive adrenergic drive in patients with heart failure results in an enhanced activation of GPCR kinases (GRKs) that is considered to have a central role in adverse cardiac remodeling after ischemic injury. The selective Serotonin reuptake inhibitor paroxetine specifically binds to the catalytic domain of GRK2 as an off-target effect, and has been shown to reverse cardiac remodeling and increase left ventricular ejection fraction in a mouse model. The effect was observed at serum levels achieved with standard dosages of paroxetine, and was robust in mice with and without concomitant heart failure treatment, respectively.

## 1.2 Objectives

The objective of this study is to evaluate whether paroxetine-mediated GRK2 inhibition reverses cardiac dysfunction and remodeling after acute anterior wall ST-segment elevation myocardial infarction.

The primary objective is to evaluate whether paroxetine-mediated GRK-2 inhibition following myocardial infarction improves left ventricular ejection fraction over a course of 3 months as assessed by cardiac MRI (cMRI).

# 2. Study methods

## 2.1 Trial design

This study is a prospective, randomized, placebo controlled, double-blinded, explorative single-center study.

A total of 50 patients presenting with acute myocardial infarction (<24 hours since symptom onset) for primary percutaneous coronary intervention will be randomized in a 1:1 ratio to treatment with paroxetine or placebo <7 days after primary PCI. Randomization will be performed by the use of sequentially numbered, sealed, opaque, tamper-proof security envelopes. Study participants will be blinded to the treatment allocation. Patients will be treated with paroxetine 20 mg QD or placebo QD for the duration of 12 weeks in addition to standard medical therapy for myocardial infarction (in particular including ACE-inhibitors/AT1-AT2-antagonists and beta-blocker therapy). LVEF will be assessed at baseline and at 12 weeks by the use of transthoracic echocardiography and cardiac MRI. Paroxetine serum levels will be measured at 12 weeks. In week 13, a paroxetine dose of 10mg QD or placebo QD will be given to avoid abrupt discontinuation. Telephone follow-up will be performed at 1 month; clinical follow-up will be performed at 12 weeks, and at 12 months.

## 2.2 Randomization

Randomization will be performed after primary percutaneous coronary intervention has been performed, all eligibility criteria have been checked, and written informed consent has been obtained. The allocation schedule is based on computer-generated random numbers and randomization will be performed using REDCap software. Patients are assigned on a 1:1 basis to treatment with a paroxetine 20 mg q.d. for 12 weeks(week 1-12)/10mg q.d. for 1 week (week 13) or placebo q.d. for 13 weeks, respectively.

## 2.3 Sample size

For each arm of the study the estimated number of participants will be 25. We assume a difference in delta LVEF of 10% in the treatment group compared to the control group with a standard deviation of 10% (increase of 5% in the control group and 15% in the treatment group) after 12 weeks. Dropout rate at 12 weeks was estimated to be 10% in both groups. We calculated a sample size of 50 patients to provide more than 90% power to detect superiority on the primary endpoint at a two-sided type I error of 0.05.

The difference in delta LVEF of 10% was assumed aligning with the study results of Schumacher et al. in which they found even an absolute increase in LVEF of 30% after the intake of Paroxetin (14).

## 2.4 Framework

We formulate the following Null Hypothesis: “There is no difference in LVEF recovery between patients with acute ST-segment elevation myocardial infarction with or without administration of Paroxetine, respectively”. Our Alternative Hypothesis is thus as follows: “The administration of

Paroxetine in patients with acute ST-segment elevation myocardial infarction increases LVEF by 10% compared to the control group". Using this hypothesis we will be able to evaluate the off-target effect of Paroxetine on cardiac remodeling.

## 2.5 Statistical interim analyses and stopping guidance

No interim analyses are planned.

## 2.6 Timing of final analysis

Final analysis will be performed after all data have been entered into the REDCap database and locked.

## 2.7 Timing of outcome assessments

The primary and secondary outcomes are measured during the 12 week visit. All primary and secondary outcomes will be analyzed collectively after study completion. After completion of data entry, data validation and cleaning will be performed. The investigators will receive first the analyses of all 50 patients together to check for plausibility. If these analyses are deemed plausible and correct, the database will be locked.

## 2.8 Blinding

Placebo tablets specifically prepared for this trial will be identical to the real drug in color, appearance, smell and taste, as well as packaging and labeling. Trial participants, care providers, outcome assessors, and data analysists will be blinded to the assignment of treatment.

# 3. Data management

## 3.1 Data export

Data from REDCap will be downloaded to Stata for statistical analysis. The data will be stored in REDCap for the duration of 10 years after completion of the study. MRI and echocardiographic data will be stored as usual in the clinical setting. Blood samples will be destroyed according to local standards.

## 3.2 Data validation

Before locking, the data will be checked for completeness using e.g. missing tables functions. The plausibility of the primary and secondary outcomes will be checked using outlier analyses and histogram, and will be queried if they are outside the expected range. The plausibility of IMP intake will be checked with the number of pills returned at the 12 week visit. The plausibility of the event dates will be checked compared to the date of randomization.

## 3.3 Data preparation

The primary and secondary outcomes are derived from the 12 weeks imaging (MRI and TTE) minus the baseline imaging (MRI and TTE) for the continuous variables.

## 3.4 Data sharing

The data will be shared anonymized according to our SOP anonymization on the BORIS portal.

# 4. Statistical principles

## 4.1 Confidence intervals and *P* values

Continuous variables will be summarised by means and standard deviations (SD) for normally distributed continuous variables or medians and interquartile ranges otherwise. Categorical variables will be summarised by frequencies and percentages. P-values will be computed using Chi-square or (in case of few events) Fisher's tests for categorical variables, Student's t-test for normally distributed continuous variables and Wilcoxon's Mann-Whitney U-test for non- symmetrically distributed continuous variables.

The primary and secondary outcomes will be reported using mean differences and two-sided 95% confidence intervals with two-sided p-values.

The p-values will refer to differences across groups at patient-level, except if lesion characteristics are reported, in which case appropriate mixed models will be used to account for the nesting of lesions within patients. All tests will be two-sided and a p-value <0.05 will be considered statistically significant.

## 4.2 Analysis populations

This is an exploratory trial with an intention-to-treat analysis design for the primary outcome, with no adjustment for covariates.

### 4.2.1 Full analysis set (FAS)

The full analysis set (FAS) will include all randomized subjects, which have the assessment of the respective outcome at both baseline and 12 weeks. Following the intent-to-treat principle, subjects will be analyzed according to the treatment they are assigned to at randomization.

### 4.2.2 Per-protocol (PP)

The PP set (PP) will include all randomized subjects, which have the assessment of the respective outcome at both baseline and 12 weeks; but excluding from the PP population patients who had the following major protocol deviations:

1. Breached one of the inclusion or exclusion criteria.
2. IMP was not started at all, or returned more than 20% of the 84 full-dosage IMP pills.

### 4.2.3 Safety population

The safety population consists of all subjects in the FAS who took at least one dose of study medication. Subjects will be analyzed according to the treatment actually taken, paroxetine or placebo.

### 4.3 Estimands

The primary and secondary outcomes will be reported using the mean differences of the change in value (week 12 minus baseline) comparing paroxetine vs placebo arm; with 95% confidence intervals and p-values (two-sided). The patient set will be the ITT FAS population with the value assessed by MRI (or TTE for some secondary outcomes) at both baseline and 12 weeks.

If there are more than 10% missing data (estimated lost-to-follow-up), then additional sensitivity analyses of the primary and secondary outcomes will be performed using multiple imputation with the chained equations methodology (using baseline risk factors to impute), creating 50 data-sets; and the mean differences of the change in value (week 12 minus baseline) comparing paroxetine vs placebo arm; with 95% confidence intervals and p-values will be computed from these 50 data-sets using Rubin's rule.

# 5. Trial Population

## 5.1 Screening data

A screening log of STEMI patients will be presented, with the number of patients excluded because of:

1. LVEF >45% (visual or MRI estimate).
2. refused consent.
3. already taking antidepressants.
4. included in different cardiovascular trial.

## 5.2 Eligibility

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Acute anterior wall ST-segment elevation myocardial infarction
- Informed Consent as documented by signature (Appendix Informed Consent Form)
- Age ≥18 years
- Primary PCI within 24 hours of symptom onset
- LVEF ≤ 45% within 48-96h after primary PCI (TTE)

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

• Contraindications to the SSRIs, e.g. known hypersensitivity or allergy to class of drugs or the investigational product
• Intolerance to Paroxetine
• Current medical therapy with MAO-blocker (during, 14 days before, and 14 days after treatment with MAO-blocker), lithium, thioridazide, or pimozide,
• Women at reproductive age (<50 years)
• Significant renal failure, hepatic dysfunction
• Known or suspected non-compliance, drug or alcohol abuse,
• Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant,
• Participation in another study with paroxetine within the 30 days preceding and during the present study,
• Previous enrolment into the current study,
• Enrolment of the investigator, his/her family members, employees and other dependent persons,
• Current Paroxetine treatment
• Previous myocardial infarction
• Previous revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting).
• Contraindications to CMR (metallic foreign bodies)
• Cardiac MRI

## 5.3 Baseline characteristics

A Table of baseline clinical and risk factors will be produced.

**Table 1. Baseline Clinical Characteristics**

| | Paroxetine (N=) | Placebo (N=) |
|---|---|---|
| **Demographics** | | |
| Age — years (SD) | xx.x ± x.x | xx.x ± x.x |
| Male gender — no. (%) | x (x.x%) | x (x.x%) |
| **Medical history** | | |
| Family history of CAD — no. (%) | x (x.x%) | x (x.x%) |
| Peripheral arterial disease — no. (%) | x (x.x%) | x (x.x%) |
| Diabetes mellitus — no. (%) | x (x.x%) | x (x.x%) |
| Current smoker — no. (%) | x (x.x%) | x (x.x%) |
| Hypertension* — no. (%) | x (x.x%) | x (x.x%) |
| Hypercholesterolemia — no. (%) | x (x.x%) | x (x.x%) |
| Previous MI — no. (%) | x (x.x%) | x (x.x%) |
| Previous PCI — no. (%) | x (x.x%) | x (x.x%) |
| Previous CABG — no. (%) | x (x.x%) | x (x.x%) |
| Renal insufficiency requiring dialysis — no. (%) | x (x.x%) | x (x.x%) |
| History of malignancy — no. (%) | x (x.x%) | x (x.x%) |
| Chronic obstructive lung disease — no. (%) | x (x.x%) | x (x.x%) |
| History of Cerebrovascular Accident (stroke/TIA) — no. (%) | x (x.x%) | x (x.x%) |
| History of atrial fibrillation/flutter — no. (%) | x (x.x%) | x (x.x%) |
| History of intracranial bleeding — no. (%) | x (x.x%) | x (x.x%) |
| History of systemic inflammatory disease — no. (%) | x (x.x%) | x (x.x%) |
| Pacemaker — no. (%) | x (x.x%) | x (x.x%) |
| ICD — no. (%) | x (x.x%) | x (x.x%) |
| CRT — no. (%) | x (x.x%) | x (x.x%) |

Data expressed as n (%) or means±standard deviations.
TIA: transient ischemic attack; ICD: implanted cardioverter defibrillator; CRT: cardial resynchronisation device
*blood pressure >140/90 in 3 repetitive measurements in flat position or requiring treatment

## 5.4 Angiographic and Procedural characteristics

A Table of angiographic and procedural PCI details will be produced, with the mean difference comparing paroxetine vs placebo.

**Table 2. Angiographic and Index Procedural Characteristics**

| Nr of patients | Paroxetine (N=) | Placebo (N=) |
|---|---|---|
| Killip III or IV — no. | x (x.x%) | x (x.x%) |
| LVEF by ventriculography — % (SD) | n = xx, xx.x ± x.x | n = xx, xx.x ± x.x |
| Time between symptom onset and first balloon-ing/stenting — minutes (SD) | n = xx, xx.x ± x.x | n = xx, xx.x ± x.x |
| Total contrast — ml (SD) | n = xx, xx.x ± x.x | n = xx, xx.x ± x.x |
| Hemodynamic support — no. (%) | x (x.x%) | x (x.x%) |
| IABP | x (x.x%) | x (x.x%) |
| Impella | x (x.x%) | x (x.x%) |
| ECMO | x (x.x%) | x (x.x%) |
| Vasopressors | x (x.x%) | x (x.x%) |
| Any evidence of thrombus — no. (%) | x (x.x%) | x (x.x%) |
| Any thrombus aspiration — no. (%) | x (x.x%) | x (x.x%) |
| **Details on coronaries — no. (%)** | | |
| Left main artery LM | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| Left circumflex LCX | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| 1st Marginal Branch | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |

| | | |
|---|---|---|
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| 2nd Marginal Branch | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| Left ascending artery LAD | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| 1st Diagnonal Branch | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| 2nd Diagnonal Branch | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| Ramus intermedius RIM | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| Right coronary artery RCA | n = xx , | n = xx , |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent DES | x (x.x%) | x (x.x%) |
| Ramus interventricularis posterior RIVPO | | |

| | | |
|---|---|---|
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent | x (x.x%) | x (x.x%) |
| Posterolateral artery PLA | | |
| Significant lesion | x (x.x%) | x (x.x%) |
| Target lesion | x (x.x%) | x (x.x%) |
| Treated with PCI | x (x.x%) | x (x.x%) |
| PTCA | x (x.x%) | x (x.x%) |
| Drug-eluting stent | x (x.x%) | x (x.x%) |
| Nr of DES implanted in target lesion | | |
| 1 | x (x.x%) | x (x.x%) |
| 2 | x (x.x%) | x (x.x%) |
| 3 or more | x (x.x%) | x (x.x%) |
| **Procedural medications (within 24h and up to end procedure) — no. (%)** | | |
| Loading with aspirin | x (x.x%) | x (x.x%) |
| Loading with clopidogrel | x (x.x%) | x (x.x%) |
| Loading with ticagrelor | x (x.x%) | x (x.x%) |
| Loading with prasugrel | x (x.x%) | x (x.x%) |
| Unfractionated heparin | x (x.x%) | x (x.x%) |
| Bivalirudin | x (x.x%) | x (x.x%) |
| GP IIb/IIIa | x (x.x%) | x (x.x%) |

Data expressed as n (%) or means±standard deviations.

IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; PTCA: percutaneous transluminal coronary angioplasty.

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## 5.5 Medication

A Table of medications at each visit will be produced, with the mean difference comparing paroxetine vs placebo.

**Table 3. Medication use**

| | Paroxetine (N=) | Placebo (N=) | p-value |
|---|---|---|---|
| **Baseline** — no. (%) | | | |
| Aspirin | x (x.x%) | x (x.x%) | |
| Clopidogrel | x (x.x%) | x (x.x%) | |
| Prasugrel | x (x.x%) | x (x.x%) | |
| Ticagrelor | x (x.x%) | x (x.x%) | |
| Marcoumar or Warfarin | x (x.x%) | x (x.x%) | |
| NOAC | x (x.x%) | x (x.x%) | |
| Dabigatran | x (x.x%) | x (x.x%) | |
| Rivaroxaban | x (x.x%) | x (x.x%) | |
| Apixaban | x (x.x%) | x (x.x%) | |
| Statin | x (x.x%) | x (x.x%) | |
| Other lipid lowering drug | x (x.x%) | x (x.x%) | |
| ACE inhibitor | x (x.x%) | x (x.x%) | |
| ATII antagonist | x (x.x%) | x (x.x%) | |
| Betablocker | x (x.x%) | x (x.x%) | |
| Ca-antagonist | x (x.x%) | x (x.x%) | |
| Amiodarone | x (x.x%) | x (x.x%) | |
| Digoxin | x (x.x%) | x (x.x%) | |
| Nitrates | x (x.x%) | x (x.x%) | |
| Diuretics | x (x.x%) | x (x.x%) | |
| Insulin | x (x.x%) | x (x.x%) | |
| Oral antidiabetic | x (x.x%) | x (x.x%) | |
| NSAID (Non Steroidal Anti Inflammatory Drugs) | x (x.x%) | x (x.x%) | |
| PPI | x (x.x%) | x (x.x%) | |
| Antidepressant drug | x (x.x%) | x (x.x%) | |

| | | | |
|---|---|---|---|
| Antiarrhythmic (other than B-Blocker/Amiodarone) | x (x.x%) | x (x.x%) | |
| **Discharge** — no. (%) | | | |
| Aspirin | x (x.x%) | x (x.x%) | x.xx |
| Clopidogrel | x (x.x%) | x (x.x%) | x.xx |
| Prasugrel | x (x.x%) | x (x.x%) | x.xx |
| Ticagrelor | x (x.x%) | x (x.x%) | x.xx |
| Marcoumar or Warfarin | x (x.x%) | x (x.x%) | x.xx |
| NOAC | x (x.x%) | x (x.x%) | x.xx |
| Dabigatran | x (x.x%) | x (x.x%) | x.xx |
| Rivaroxaban | x (x.x%) | x (x.x%) | x.xx |
| Apixaban | x (x.x%) | x (x.x%) | x.xx |
| Statin | x (x.x%) | x (x.x%) | x.xx |
| Other lipid lowering drug | x (x.x%) | x (x.x%) | x.xx |
| ACE inhibitor | x (x.x%) | x (x.x%) | x.xx |
| ATII antagonist | x (x.x%) | x (x.x%) | x.xx |
| Betablocker | x (x.x%) | x (x.x%) | x.xx |
| Ca-antagonist | x (x.x%) | x (x.x%) | x.xx |
| Amiodarone | x (x.x%) | x (x.x%) | x.xx |
| Digoxin | x (x.x%) | x (x.x%) | x.xx |
| Nitrates | x (x.x%) | x (x.x%) | x.xx |
| Diuretics | x (x.x%) | x (x.x%) | x.xx |
| Insulin | x (x.x%) | x (x.x%) | x.xx |
| Oral antidiabetic | x (x.x%) | x (x.x%) | x.xx |
| NSAID (Non Steroidal Anti Inflammatory Drugs) | x (x.x%) | x (x.x%) | x.xx |
| PPI | x (x.x%) | x (x.x%) | x.xx |
| Antidepressant drug | x (x.x%) | x (x.x%) | x.xx |
| Antiarrhythmic (other than B-Blocker/Amiodarone) | x (x.x%) | x (x.x%) | x.xx |
| **Week 4** — no. (%) | | | |
| Aspirin | x (x.x%) | x (x.x%) | x.xx |
| Clopidogrel | x (x.x%) | x (x.x%) | x.xx |
| Prasugrel | x (x.x%) | x (x.x%) | x.xx |
| Ticagrelor | x (x.x%) | x (x.x%) | x.xx |
| Marcoumar or Warfarin | x (x.x%) | x (x.x%) | x.xx |

| | | | |
|---|---|---|---|
| NOAC | x (x.x%) | x (x.x%) | x.xx |
| Dabigatran | x (x.x%) | x (x.x%) | x.xx |
| Rivaroxaban | x (x.x%) | x (x.x%) | x.xx |
| Apixaban | x (x.x%) | x (x.x%) | x.xx |
| Statin | x (x.x%) | x (x.x%) | x.xx |
| Other lipid lowering drug | x (x.x%) | x (x.x%) | x.xx |
| ACE inhibitor | x (x.x%) | x (x.x%) | x.xx |
| ATII antagonist | x (x.x%) | x (x.x%) | x.xx |
| Betablocker | x (x.x%) | x (x.x%) | x.xx |
| Ca-antagonist | x (x.x%) | x (x.x%) | x.xx |
| Amiodarone | x (x.x%) | x (x.x%) | x.xx |
| Digoxin | x (x.x%) | x (x.x%) | x.xx |
| Nitrates | x (x.x%) | x (x.x%) | x.xx |
| Diuretics | x (x.x%) | x (x.x%) | x.xx |
| Insulin | x (x.x%) | x (x.x%) | x.xx |
| Oral antidiabetic | x (x.x%) | x (x.x%) | x.xx |
| NSAID (Non Steroidal Anti Inflammatory Drugs) | x (x.x%) | x (x.x%) | x.xx |
| PPI | x (x.x%) | x (x.x%) | x.xx |
| Antidepressant drug | x (x.x%) | x (x.x%) | x.xx |
| Antiarrhythmic (other than B-Blocker/Amiodarone) | x (x.x%) | x (x.x%) | x.xx |
| **Week 12** — no. (%) | | | |
| Aspirin | x (x.x%) | x (x.x%) | x.xx |
| Clopidogrel | x (x.x%) | x (x.x%) | x.xx |
| Prasugrel | x (x.x%) | x (x.x%) | x.xx |
| Ticagrelor | x (x.x%) | x (x.x%) | x.xx |
| Marcoumar or Warfarin | x (x.x%) | x (x.x%) | x.xx |
| NOAC | x (x.x%) | x (x.x%) | x.xx |
| Dabigatran | x (x.x%) | x (x.x%) | x.xx |
| Rivaroxaban | x (x.x%) | x (x.x%) | x.xx |
| Apixaban | x (x.x%) | x (x.x%) | x.xx |
| Statin | x (x.x%) | x (x.x%) | x.xx |
| Other lipid lowering drug | x (x.x%) | x (x.x%) | x.xx |
| ACE inhibitor | x (x.x%) | x (x.x%) | x.xx |
| ATII antagonist | x (x.x%) | x (x.x%) | x.xx |

| | | | |
|---|---|---|---|
| Betablocker | x (x.x%) | x (x.x%) | x.xx |
| Ca-antagonist | x (x.x%) | x (x.x%) | x.xx |
| Amiodarone | x (x.x%) | x (x.x%) | x.xx |
| Digoxin | x (x.x%) | x (x.x%) | x.xx |
| Nitrates | x (x.x%) | x (x.x%) | x.xx |
| Diuretics | x (x.x%) | x (x.x%) | x.xx |
| Insulin | x (x.x%) | x (x.x%) | x.xx |
| Oral antidiabetic | x (x.x%) | x (x.x%) | x.xx |
| NSAID (Non Steroidal Anti Inflammatory Drugs) | x (x.x%) | x (x.x%) | x.xx |
| PPI | x (x.x%) | x (x.x%) | x.xx |
| Antidepressant drug | x (x.x%) | x (x.x%) | x.xx |
| Antiarrhythmic (other than B-Blocker/Amiodarone) | x (x.x%) | x (x.x%) | x.xx |

Data expressed as n (%) and p-values are from Fisher's tests.

## 5.6 Adherence

A Table of regular intake of IMPs up to Week 4, and from Week 4 to Week 12 will be reported, with details and potential side-effects of the IMPs.

At Week 12 descriptive statistics will be provided of how many pills out of the 84 pills (12 weeks x 7 pills) were returned (% of total provided), single listing if only a few missed can be reported also inside the flowchart. Serum paroxetine levels above or equal to the lower detection threshold of the assay (6 ng/ml) will be provided, together with actual mean levels (with standard deviation) comparing paroxetine vs placebo, if paroxetine was detected. Mean differences comparing paroxetine vs placebo will be provided.

**Table 4. Adherence to IMP intake**

| | Paroxetine (N=xx) | Placebo (N=xx) | p-value |
|---|---|---|---|
| **At Baseline** | | | |
| IMP distributed to patient? | x (x.x%) | x (x.x%) | x.xx |
| If not, specify | | | |
| **At Week 4** | | | |
| Regular intake of IMP | x (x.x%) | x (x.x%) | x.xx |
| If not, specify | | | |
| Side-effects of IMP | x (x.x%) | x (x.x%) | x.xx |
| Patient continues study and IMP intake | x (x.x%) | x (x.x%) | x.xx |
| **At Week 12** | | | |
| Regular intake of IMP — no. (%) | x (x.x%) | x (x.x%) | x.xx |
| If not, specify | | | |
| Side-effects of IMP — no. (%) | x (x.x%) | x (x.x%) | x.xx |
| Percentage of IMP pills returned unused* — no. (%) | x (x.x%) | x (x.x%) | x.xx |
| Number of IMP pills returned* — no. | x, x, x | x, x, x | |
| Serum paroxetine ≥6ng/ml** — no. (%) | x (x.x%) | x (x.x%) | x.xx |
| Serum paroxetine if ≥6ng/ml — ng/ml (SD) | n = xx, xx.x ± x.x | n = xx, xx.x ± x.x | x.xx |

Data expressed as n (%, p-value from Fisher's tests) or means±standard deviations (p-value from unpaired t-tests).

*Patients received 12 weeks x 7 IMP pills (which contained either paroxetine or placebo), equals 84 pills in total.

**Detection threshold of paroxetine assay.

## 5.7 Magnetic resonance imaging MRI

A Table of variables (which includes the primary outcome and some secondary outcomes) measured using CT MRI will be produced, measured at baseline and Week 12; and the change from baseline to Week 12; with the difference in mean change comparing paroxetine vs placebo.

**Table 5. MRI assessments**

| | Paroxetine | | | | Placebo | | | | Paroxetine vs Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (N=xx) | Week 12 (N=xx) | Change Week 12 vs Baseline | p-value | Baseline (N=xx) | Week 12 (N=xx) | Change Week 12 vs Baseline | p-value | Mean difference of the change | p-value |
| **Left ventricle — means (SD)** | | | | | | | | | | |
| IVSD | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| IVSS | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVEDD | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVESD | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| PWD | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| PWS | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVEDV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVEDV index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVESV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVESV index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVSV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVSV index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LV mass | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LV mass index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LV CO | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LV CO index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| Late enhancement | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVEF - left ventricle ejection fraction — %* | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| **Right ventricle — means (SD)** | | | | | | | | | | |
| RVEDV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| RVEDV index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| RVESV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| RVES index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| RVSV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| RVSV index | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| RV CO | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |

Data expressed as n (%, p-value from Fisher's tests) or means±standard deviations (p-value from unpaired t-tests).
*Primary endpoint

## 5.8 Transthoracic echocardiography TTE

A Table of variables (which includes the primary outcome and some secondary outcomes) measured using CT MRI will be produced, measured at baseline and Week 12; with the difference in mean change comparing paroxetine vs placebo.

**Table 6. Transthoracic echocardiography assessments**

| | Paroxetine | | | | Placebo | | | | Paroxetine vs Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (N=xx) | Week 12 (N=xx) | Change Week 12 vs Baseline | p-value | Baseline (N=xx) | Week 12 (N=xx) | Change Week 12 vs Baseline | p-value | Mean difference of the change | p-value |
| LVEF visual — % (SD) | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVEF Simpson biplan — % (SD) | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| Pericardial effusion — no. (%) | x (x.x%) | x (x.x%) | xx.x ± x.x | x.xx | x (x.x%) | x (x.x%) | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| sPAP — mmHg (SD) | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| Right ventricular dysfunction — no. (%) | x (x.x%) | x (x.x%) | xx.x ± x.x | x.xx | x (x.x%) | x (x.x%) | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVEDV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVESV | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| LVEDD | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| IVSD | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| PWD | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x | x.xx | x.xx (x.xx to x.xx) | x.xx |
| Aortic regurgitation — no. (%) | | | | x.xx | | | | x.xx | x.xx (x.xx to x.xx) | x.xx |
| none | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| trivial / trace | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| light | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| moderate | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| Aortic stenosis — no. (%) | | | | x.xx | | | | x.xx | x.xx (x.xx to x.xx) | x.xx |
| none | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| trivial / trace | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| light | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| moderate | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| Mitral regurgitation — no. (%) | | | | x.xx | | | | x.xx | x.xx (x.xx to x.xx) | x.xx |
| none | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| trivial / trace | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| light | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| moderate | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| Mitral stenosis — no. (%) | | | | x.xx | | | | x.xx | x.xx (x.xx to x.xx) | x.xx |
| none | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| trivial / trace | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| light | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| moderate | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| Tricuspid regurgitation — no. (%) | | | | x.xx | | | | x.xx | x.xx (x.xx to x.xx) | x.xx |
| none | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| trivial / trace | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| light | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |
| moderate | x (x.x%) | x (x.x%) | xx.x ± x.x | | x (x.x%) | x (x.x%) | xx.x ± x.x | | x.xx (x.xx to x.xx) | |

Data expressed as n (%, p-value from Fisher's tests) or means±standard deviations (p-value from unpaired t-tests
*Primary endpoint
sPAP = RV/RA + ZVD

## 5.9 Safety assessment in Safety Population

A Table of clinical events up to Week 12 will be produced. Due to the low patient number, a comparison with Fisher's exact test will be conducted, only counting one event of the same type within the same patient. For instance, if the patient had two Myocardial infarctions, then only the first Myocardial infarction will be considered for the Fisher's exact test. It is suggested to add details of some events in the subheader of the Table, as relevant and applicable (e.g. rare events, events leading to IMP stop).

**Table 7. Safety assessment in Safety Population (took at least one dosage of IMP)**

| | Paroxetine (N=xx) | Placebo (N=xx) | p-value |
|---|---|---|---|
| Death | x (x.x%) | x (x.x%) | x.xx |
| Myocardial infarction* | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Definite stent thrombosis | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Repeat unplanned PCI or CABG | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Cerebrovascular event | | | |
| Stroke | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| ischemic | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| hemorhagic | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| unclear etiology | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| TIA | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Amaurosis fugax | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Bleeding | | | |
| TIMI major or minor | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| GUSTO moderate or severe | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| BARC 2 | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| BARC 3abc | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| BARC 4 | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| BARC 5ab | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Acute renal failure** | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Major vascular complication | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Pacemaker implanted during PCI | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Resuscitation during PCI | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Potential serious adverse event other than any of the above | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Mild | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Moderate | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |
| Severe | x in x patients (x.x%) | x in x patients (x.x%) | x.xx |

p-values from Fisher's exact tests, not counting multiple events of the same type if occurred within the same patient.

* Type 1 in xx, Type 2 in xx, Type 3 in xx, Type 4a in xx, Type 4b in xx; and Type 5 in xx {replace xx with paroxetine or placebo}

** Rifle score y in xx, etc {replace xx with paroxetine or placebo}

## 5.10 Physical examination

A Table of physical examinations at Baseline and at Week 12 will be produced.

**Table 8 Physical examinations**

| | Baseline (48h to 96h after PCI) | | | Week 12 follow-up | | |
|---|---|---|---|---|---|---|
| | Paroxetine (N=xx) | Placebo (N=xx) | p-value | Paroxetine (N=xx) | Placebo (N=xx) | p-value |
| Heart rate — beats/minute (SD) | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | x.xx |
| RR systolic (1st measure) — mmHg (SD) | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | x.xx |
| RR diastolic (1st measure) — mmHg (SD) | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | x.xx |
| Temperature (°C) | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | x.xx |
| Oxygen saturation (%) | xx.x ± x.x | xx.x ± x.x | x.xx | xx.x ± x.x | xx.x ± x.x | x.xx |
| NYHA | x (x.x%) | x (x.x%) | x.xx | x (x.x%) | x (x.x%) | x.xx |
| I | x (x.x%) | x (x.x%) | x.xx | x (x.x%) | x (x.x%) | x.xx |
| II | x (x.x%) | x (x.x%) | x.xx | x (x.x%) | x (x.x%) | x.xx |
| III | x (x.x%) | x (x.x%) | x.xx | x (x.x%) | x (x.x%) | x.xx |
| IV | x (x.x%) | x (x.x%) | x.xx | x (x.x%) | x (x.x%) | x.xx |
| Weight — kg (SD) | xx.x ± x.x | xx.x ± x.x | x.xx | | | |
| Height — m (SD) | xx.x ± x.x | xx.x ± x.x | x.xx | | | |
| BMI — kg/m² (SD) | xx.x ± x.x | xx.x ± x.x | x.xx | | | |

Data expressed as n (%, p-value from Fisher's tests) or means±standard deviations (p-value from unpaired t-tests).

RR: Riva-Rocci

## 5.11 Withdrawal/follow-up

Withdrawal, lost-to-follow-up and missed assessments of the primary outcome will be reported in the flowchart.

# 6. Analysis

## 6.1 Outcome definitions

### 6.1.1 Primary outcomes

The primary endpoint will be the difference in the change (Δ) in LVEF at 12 weeks in subjects treated with paroxetine 20 mg QD or placebo QD as assessed by cMRI.

### 6.1.2 Secondary outcomes

Secondary outcomes of the MRI assessment are:

in left left-ventricular end-diastolic volume (LVEDV) between baseline and 12 weeks in subjects treated with paroxetine 20 mg QD or placebo QD as assessed by cardiac MRI.

- in left left-ventricular end-systolic volume (LVESV) between baseline and 12 weeks in subjects treated with paroxetine 20 mg QD or placebo QD as assessed by cardiac MRI.

- in late-enhancement between baseline and 12 weeks in subjects treated with paroxetine 20 mg QD or placebo QD as assessed by cardiac MRI.

Secondary outcomes using the TTE assessment are:

- in LVEF between baseline and 12 weeks, and 12 months, respectively in subjects treated with paroxetine 20 mg QD or placebo QD as assessed by transthoracic echocardiography.

Secondary outcomes of the event reporting and clinical assessments are:

- major adverse cardiac events (cardiac death, myocardial infarction, repeat hospitalization for heart failure) at 12 weeks and 12 months, respectively.

- clinical symptoms of heart failure as assessed by New York Heart Association (NYHA) at 12 weeks and 12 months, respectively.

### 6.1.3 Safety outcomes

Incidence and severity of side effects related to study drug intake throughout the entire study.

The safety outcomes (AE and SAEs) reporting will be performed as tables or single listing if only a few events occurred.

## 6.2 Analysis methods

### 6.2.1 Primary analysis

The primary outcome analysis will be conducted by calculating the change in the value week 12 – baseline ("change") and then calculating the mean difference of the change in paroxetine patients vs the change in the placebo patients.

### 6.2.2 Secondary analyses

The secondary outcome TTE analyses will be conducted by calculating the change in the value week 12 – baseline ("change") and then calculating the mean difference of the change in paroxetine patients vs the change in the placebo patients.

The secondary outcome NYHA can be analyzed as binary improvement in NYHA if requested (e.g. improved from IV to III, or III to II, or II to I).

### 6.2.3 Sensitivity analyses

The primary and secondary outcomes will be analyses in the multiple imputed data-sets if applicable (see 4.3).

### 6.2.4 Additional analyses

No additional analyses are planned currently.

### 6.2.5 Assessment of statistical assumptions

Proportional hazards tests will be performed on the time to event safety (secondary) outcomes, in case there are sufficient events of that type up to one year of follow-up.

## 6.3 Missing data

The primary and secondary outcomes will be analyses in the multiple imputed data-sets if applicable (see 4.3).

## 6.4 Safety evaluation

The safety outcomes, AE and SAEs will be summarized in tables at 12 weeks and separately at 12 months.

## 6.5 Statistical software

Stata version 16.1 or higher and R version 4.03 or higher will be used.

### 6.6 Quality control

The primary and secondary MRI and secondary TTE outcomes will be double-programmed.

## 7. References

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