Effect of methotrexate carried by a lipid nanoemulsion on left ventricular remodeling after ST-elevation myocardial infarction

NCT 03516903

October 13, 2020.

Statistical Analysis Plan

Study design: Prospective, double-blind, parallel arm, proof of concept, randomized controlled trial.

Study casuistic: 50 patients presenting with acute anterior wall STEMI, after proper reperfusion therapy and in stable clinical condition. Patients will be randomly assigned 1:1 to methotrexate carried by a lipid nanoemulsion (ddMTX-LDE) or matching placebo.

1. Study Population

The main population analysis of interest will be the *per protocol population*, that means, all patients who have been randomized and completed the 3 months follow-up with an adequate cardiac MRI with complete measurements of LV diastolic and systolic volumes and LVEF, and who have received at least one dose of the study drug. In an attempt to minimize bias for not doing an ITT analysis, baseline characteristics will compared between both randomized arms within ITT and per protocol populations. Additionally, sensitivity analysis will be done including only patients who received the complete planned study doses of the investigational product.

2. Primary Endpoint

The primary endpoint of the study will be LV end-diastolic volume (LVEDV) assessed by cardiac MRI at 3 months. Both groups will be compared with a Student´s t test or Wilcoxon rank sum test, as appropriate. Besides that, an analysis of variance (ANOVA) for repeated measures will be performed as sensitivity analysis in order to assess the serial measurements of LVEDV at baseline and at 3 months between both groups of interest, as well as comparison between groups regarding the difference between baseline and 3 months (delta). Mean difference between groups will be reported with corresponding 95% CI. If the variable does not follow a normal distribution, an alternative approach to estimate 95% CI will be used, like bootstrapping with 1,000 repetitions.

3. Safety endpoints

Both groups will be compared regarding the incidence of the following pre-specified adverse events of special interest: overall serious adverse events (SAE), as defined in the protocol; adverse events of special interest (AESI), namely, stomatitis, vomiting, diarrhea, cough with fever or dyspnea; and fatal or life threatening infections (defined as those ones needing vital organ support measurements, like mechanical ventilation or vasopressors, as a direct consequence of the infection, e.g., septic shock). In those outcomes, these variables will be compared as binary variables, with Chi square or exact test, as appropriate, with risk ratios (RR) and 95% CI reported according to Wald proportion tests.

Laboratory parameters will also be compared between groups, following same principles outlined for the primary endpoint. Parameters of interest will be: hemoglobin, white cell blood count, platelet count, liver transaminases (AST and ALT), total bilirubin, and creatinine. Since some of those tests are performed weekly, we will use a mixed linear model with study drug and week as fixed effect and patient as random effect. Least mean squares difference with corresponding 95% CI will be reported. Besides that, we also report percentage of patients with at least one change in security laboratory parameter as prespecified by study protocol.

4. Sample size calculation

Sample size was calculated considering an expected 20% decrease in LVEDV in the LDE-MTX group compared to placebo, based on cardiac MRI at 3 months. From a prior study (the METOCARD study[1,2]), the expected mean LVEDV in the placebo arm is 197.6 mL with a common SD of 45.7 mL. For a two-tailed alpha of 5% and 80% power, we estimate our sample size as 21 patients per group. In order to account for eventual losses, we planned to enroll a total of 50 patients.

5. Interim analyses

The study had two pre-specified safety analysis (it was deemed to be stopped should any important imbalance, regardless of significance level, be found between safety outcomes). However, due to difficulty in enrolment after COVID-19 pandemic, a new unplanned efficacy interim analyses will be performed aiming to decide whether the study should be interrupted for futility or efficacy. For this third interim analysis, study will be stopped for efficacy if the experimental therapy is superior to the placebo group at a two-sided alpha of 0.05, regarding the primary endpoint, or if there is any difference favoring MTX for LVEF at an alpha = 0.05. Additionally, the study will be interrupted for futility if the conditional completion is < 30% for the primary endpoint and for LVEF.