**Statistical Analysis Plans**

**The benefits of continuous epidural infusion of ropivacaine in acute pancreatitis**

**Version: 16/10/2023**

## Sample Size Estimation

Assuming a mean ± standard deviation of VAS at day 1 after intervention will be 0.57 ± 1.51, we determined that a sample size of 72 patients would provide the trial with an 80% power and considering a two-side type-I error rate (alpha) of 0.05.

An interim analysis of the primary endpoints will be performed after 50% of the patients had completed 60 days of follow-up.

## General considerations

All analyses will be performed with the use of R software version 4.3.1 (the R foundation for Statistical Computing).

The analysis of the primary endpoints will be conducted in the modified intention-to-treat (ITT) population. A per-protocol analysis will also be conducted on the primary outcome. The criteria for including patients in the modified ITT and in the per-protocol populations, respectively, are provided below.

Baseline variables will be reported as numbers and percentages for categorical variables and median with interquartile ranges [IQRs] for continuous variables. According to the CONSORT 2010 statement, group differences in baseline variables will not be compared using significance testing unless specifically requested by peer reviewers.

Post hoc analysis will be performed to explore the potential influence of perspecified factors on primary outcomes.

A particular focus will be given to safety and patients who are lost to follow-up. A sensitivity analysis will be performed, and the nature of missing data will be studied (missing at random or not). According to this study, the most appropriate approach to the imputation of missing data will be proposed (maximum bias (eg, last observation carried forward vs. baseline observations carried forward forward) or estimation proposed by Verbeke and Molenberghs for repeated data.)

A two-sided P value of less than 0.05 will be considered for statistical significance of all analyses (except the interim analysis).

**Study populations**

Intention-to treat (ITT) population: All randomised patients (except those who had withdrawn consent for the use of their data or did not meet the inclusion criteria retrospectively), including those from the interventional group who did not receive epidural analgesia for at least 72 hours.

Per-protocol population: All randomised patients except patients having one or more major protocol violations, defined as patients who would not be eligible for randomisation according to inclusion/exclusion criteria or patient who would have withdrawn consent.

**Description of statistical analysis of primary and secondary endpoints.**

**Analysis of the primary endpoints**

The comparison between randomisation groups will be analysed using Student's t-test or the Mann-Whitney test if assumtion of the t-test are not met. Normality will be studied by the Shapiro-Wilk test. Homoscedasticity will be analysed using the Fisher-Snedecor test Effect-sizes will be estimated with 95% confidence intervals (CI).

**Analysis of the secondary endpoints**

Other continuous endpoints (such as age, intubation, abdominal compartment pressure, GFR, biochemic parameters, interleukin levels, air blood gas parameters, urine volume, vital signs, visual analogue scale, CT severity Index at 72h hourse, number of ventilator-free days measured at day 30) will be compared between randomisation groups using Student's t-test or the Mann-Whitney test if assumptions of the t-test are not met. Results will be expressed as effect-size and 95% CI.

Categorical parameters (such as death, intubation rate, gender, causes, clinical parameters) will be analysed using Chi-squared or Fisher's exact tests for univariate analysis. The results will be expressed as absolute differences and relative risks with 95% CI estimated using a generalised linear model (more precisely Poisson with robust variance).

Survival analyses will be performed with the Kaplan-Meier estimator and differences between groups will then be assessed using the log-rank test. The assumption of log-

linearity of risk and the proportional hazards will be checked beforehand. Resuls will be expressed as hazard ratios and 95% CI.

Longitudinal analyses of repeated measures (such as vital signs, BPS, VAS, intra-abdominal pressure, the levels of biological markers of systemic inflammation, chemicial parameters on day 1, 2, 3, 4, 5) will be expressed as descriptive results.

According to clinical relevance and to CONSORT recommendations, subgroup analyses depending on the presence or absence of analgesia will be proposed after the study of subgroup x randomisation group interaction in regression models. For unadjusted subgroup analysis of the primary endpoint, zero-inflated negative binomial regression will be performed.