SUPPLEMENTAL MATERIAL

Title: The Chemical Optimization of Cerebral Embolectomy (CHOICE) Trial: Study protocol

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STATISTICAL ANALYSIS PLAN

## 1. TITLE PAGE

# Statistical Analysis Plan

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| | |
|---|---|
| **Project** | **TITLE**: **Che**mical **O**pt**I**mization of **C**erebral **E**mbolectomy in patients with acute stroke treated with mechanical thrombectomy (CHOICE TRIAL) |
| **EudraCT Number** | 2018-002195-40 |
| **Protocol** | Version 2.0, Date: 08-Mar-2019 |
| **Sponsor** | Fundació Clínic per a la Recerca Biomèdica (FCRB) |
| **Principal Investigator/s** | Dr. Ángel Chamorro |
| **Institution** | Medical Statistics Core Facility<br>IDIBAPS - Hospital Clínic de Barcelona |
| **SAP Version and Date** | Final, Date: 15-Jul-2019 |

# 1 SIGNATURES' PAGE

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# 3 STUDY PERSONNEL

## *3.1 Sponsor and Principal Investigators*

**Sponsor:** Fundació Clínic per a la Recerca Biomèdica *

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# 4 LIST OF ABBREVIATIONS

| | |
|---|---|
| ADO | Available Data Only |
| AE | Adverse Event |
| AR(1) | Auto-Regressive first order |
| CRF | Case Report Form |
| CS | Compound Symmetry |
| CT | Computerized Axial Tomography |
| CTA | Computerized Axial Tomography Angiography |
| CTP | Computerized Tomography Perfusion |
| CRO | Contract Research Organization |
| DBR | Data Blind Review |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| HR | Hazard Ratio |
| IER | Infarct Expansion Ratio |
| ICH | Intra-cerebral Haemorrhage |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |
| IQR | Interquartile range |
| LSMeans | Least Square Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mFAS | Modified Full Analysis Set |
| MMRM | Mixed Effect Model Repeat Measurements |
| MRA | Magnetic Resonance Angiography |
| mRS | Modified Rankin Scale |
| MT | Mechanical thrombectomy |
| mTICI | Modified Treatment In Cerebral Infarction scale |
| NIHSS | National Institute of Health Stroke Scale |
| OR | Odds Ratio |
| PP | Per Protocol |
| RR | Rate Ratio or Relative Risk |
| rt-PA | Recombinant tissue Plasminogen Activator |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SEM | Standard Error of Means |
| SICH | Symptomatic Intra-Cerebral Haemorrhage |

# 5 SCOPE OF ANALYSIS PLAN

The statistical analysis will be carried out in accordance with the principles specified in the International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/ 363/96)[1]. This SAP will follow the general regulatory recommendations given in the ICHE9[1] guidance, as well as other specific guidance on methodological and statistical issues[2]. Also, it will stick to the recommendations given by the consensus documents of the scientific journals[3,4,5] to improve reliability and value of medical research literature by promoting transparent and accurate reporting of clinical research studies.

The SAS System[6] (Release 9.4, or an upgraded version), or equivalent validated statistical software, will be the statistical software used to analyse the data sets.

A summary of the overall approach to statistical analysis is presented hereafter.

# 6 STUDY OBJECTIVES

The study objective is to evaluate whether rt-PA is safe and efficient as an add-on to mechanical thrombectomy (MT) in patients with acute ischemic stroke and complete or near-complete recanalization of a proximal vessel occlusion but partial brain reperfusion on cerebral angiography (corresponding to mTICI score 2b).

# 7 TRIAL CHARACTERISTICS

## *7.1 TRIAL DESIGN*

Multicentre, randomized, placebo-controlled, double blind, phase 2b trial of acute stroke patients treated with MT, in which two therapies are compared: rt-PA or placebo. Allocation at each centre will account for 1 stratum: use of alteplase (yes vs. no) before MT. Subjects will be followed up to 90 days post-randomization.

## *7.2 RANDOMIZATION PROCEDURE*

Randomization codes will be produced by means of the PROC PLAN of the SAS system, with a 1:1 ratio of assignment between both arms, stratifying by centre, and use of IV alteplase (no or yes), in blocks multiple of 2 elements. The codes will release to the manufacturer site, which is independent from the study sponsor and be managed from the eCRF in a blinded manner.

## *7.3 JUSTIFICATION OF SAMPLE SIZE*

A sample size of 100 patients per treatment arm in a 1:1 allocation will have >95% statistical power for the primary outcome (5% of improved TICI score control vs 60% in experimental) for a two-sided 5% alpha, taken into account a 5% of the sample lost to follow up. This sample size will also guarantee around 80% power for most of the secondary outcomes with at least 90 valid patients per arm, as shown in the table below:

**Table 1**: Sample size estimations for the primary and for those secondary endpoints with ≥ 80% statistical power.

| | | Control | Experimental | OR / $P_{(Noether)}$ | Differences: % or Median | Power[3] |
|---|---|---|---|---|---|---|
| **Primary Outcome** | | | | | | |
| Proportion of patients with a mTICI improvement | % | 5% | 60% | OR: 0.04<br>RR: 0.08 | % diff: 55% | >>95% |
| **Secondary Outcomes with at least 80% statistical power** | | | | | | |
| Infarct Expansion Ratio on DWI-MRI | Median (IQR) | 1.5 (0.5 - 4.4) | 0.8 (0.3 - 1.5) | $P_{(Noether)}$[1]: 0.622 | Median diff: 0.7 | 92% |
| | | | | $P_{(Noether)}$[2]: 0.645 | | 80% |
| Categorical shift in mRS, at day 90 | Median (IQR) | 2 (1 - 3) | 1 (0 - 3) | $P_{(Noether)}$[1]: 0.622 | Median diff: 1.00 | 80% |
| % of patients with excellent outcome (mRS 0-1) | % | 31% | 54% | OR: 0.38<br>RR: 0.57 | % diff: 23% | 88% |
| Proportion of patients with no infarct expansion | % | 45% | 66% | OR: 0.42<br>RR: 0.68 | % diff: 21% | 81% |

*OR: Odds ratio; RR: Rate Ratio; IQR. Interquartile range (P25-P75)*
*$P_{(Noether)}$: Probability that an observation in the Experimental arm has a better value than an observation in the Control arm*

*1: Estimated from data of Chamorro et al. 2017*[7]

*2: Estimated the work of the MR Stroke Collaborative Group 2006*[8]

*3: Sample sizes estimated using nQuery v7.0 softwarwe*[9]*, relying on Noether*[10] *for the Wilcoxon-Mann-Whitney approach for ordinal and non-parametric continuous data, and on Machin & Cambell*[11] *and Fleis*[12] *for binary endpoints*

## *7.4 STATISTICAL INTERIM ANALYSIS AND MULTIPLICITY ADJUSTMENTS*

The analysis will follow the principles specified in the ICHE91 and the CPMP/EWP/908/99[13] Points to Consider on Multiplicity issues in Clinical Trials guidelines.

No interim analysis is planned for this study. For this reason, there is no statistical criterion for early termination of the trial. Since this is a study with only two treatment groups and a single primary endpoint, no multiplicity adjustments are needed.All statistical tests will be applied with 0.05 two-sided significance level.

# 8 STATISTICAL ANALYSIS

## *8.1 Analysis Populations*

There will the following analysis populations for this study:

1) Modified Full Analysis Set (mFAS): All patients who are randomized into the study and who have received the investigational medicinal product (IMP) will be included in the mFAS population.
2) Per Protocol Population: Per protocol (PP) patient sets will be defined as those patients included in the mFAS set without major protocol deviations that might impact the study's main assessments. These deviations will be assessed during the data review prior to database lock.
3) The Safety population (SP) is defined as all randomized participants who received the investigational drug (any of the two arm treatment). In this study the SP will have the same definition than the mFAS subset and thus, all safety analyses will be conducted on the mFAS population.

The precise reasons for excluding participants from each population will be fully defined and documented independently of the randomization codes during the Data Blind Review and before the database lock (see section 9).

## *8.2 Study Estimand and Handling of Missing Data*

The handling of missing data will follow the principles specified in the ICH-E91 and the CPMP/EWP/1776/99 Rev1. Guideline on Missing Data in confirmatory trials Guidelines[14].

As per the ICH E9(R1) (*draft addendum on estimands and sensitivity analysis in clinical trials EMA/CHMP/ICH/436221/2017*)[15], the plan for the assessment of the Primary endpoint (PEP) is described here after using the 4 attributes of the estimand:

1. Population: as described in protocol, see section 3.2
2. Primary endpoint (PEP): The proportion of patients with an improved mTICI score 10 minutes after the end of study treatment (see section 8.6.4.1)
3. Intercurrent events: The relevant intercurrent events expected to occur in this study include the following situations and methods for handling them:
    a. No treatment initiation with the IMP: exclusion from the main analysis with the mFAS population
    b. Treatment discontinuation: "Treatment Policy" strategy, i.e., the efficacy observed assessment will be used regardless of this intercurrent event.
    c. Death before the time of the image assessment: it will be handled as the "Composite" strategy, and the PEP will be considered as failure
    d. Other reasons for not assessing the PEP:
        - Treatment related reasons (i.e. due to efficacy or safety issues):they will be handled as in 3.c using the "Composite" strategy.
        - Non treatment-related reasons: the "Hypothetical" strategy will be used. Multiple imputation techniques with implemented using the observed rate of improvement in the control arm.
    e. Rescue medication and other reasons for study discontinuation. These are not expected for the PEP due to the very early time of assessment for the PEP.

4. Population-level summary: Estimation of the Rate Ratio (RR) for the PEP will be used as the population-level summary. The log-binomial model adjusted by the randomisation strata will be used for the inferential analysis (p-value, RR and 95% Confidence Intervals).

A number of sensitivity analyses are proposed:

- Analysis using multiple imputation with the observed rates in the placebo group in all cases
- A responder analysis imputing to failure all causes of missingness
- Analysis using the above described strategies with the PP population

Missing data for other binary efficacy secondary outcomes will be considered as failures, irrespectively to the reason for missingness. For mRS, the worst case imputation will be used (i.e. imputing the worst category of the scale). With regards to the continuous variables, mixed models[16,17,18]are robust to the presence of missing at random (MAR) and conducts the analysis with all participants despite the presence of missingness. Of note, this method calculates the estimations based on the variance-covariance structure but without any formal imputations.

No formal imputations will be performed for the rest of variables and the analyses will be based on the Available Data Only (ADO) approach.

## *8.3 Flow Diagram*

A flow diagram will be performed according to ICHE3 and the consort statement in order to summarize the number of patients at study losses by time at each stage. Patients screened, eligible, consented, randomized, receiving their allocated treatment, withdrawing/lost to follow up, and included in the different populations sets defined in the section 8.1.

## *8.4 Endpoints Definition*

### 8.4.1 Primary endpoint

The primary outcome will be the proportion of patients with an improved mTICI score ten (10) minutes after the end of study treatment. Improvement refers to eTICI 2b67 (67–89% reperfusion) in patients with eTICI 2b50 (50–66% reperfusion) at baseline, eTICI 2c (90–99% reperfusion) in patients with eTICI 2b50 or eTICI 2b67 at baseline, and eTICI 3 (100% reperfusion) in patients with eTICI 2b50, eTICI 2b67 or eTICI 2c at baseline, as judged by central readers.

### 8.4.2 Secondary endpoints

- The shift analysis of the modified Rankin Scale (mRS), at day 90. The mRS at 90 days will be analysed using a proportional odds model (POM) that combine into single worst rank the last two categories (5: severe incapacity and 6: death).
- Infarct Expansion Ratio on DWI-MRI (continuous variable), at 48h (+/- 24h) of stroke
- Proportion of patients with excellent outcome (mRS 0-1) at day 90
- Proportion of patients with/without infarct expansion (dichotomous variable)
- Infarction Volume on DWI-MRI, at 48h (+/- 24h) of stroke onset

### 8.4.3 Tertiary endpoints

- mRS of 0 to 2, at day 90
- Barthel Scale score of 95 to 100, at day 90
- Ischemic worsening (> 4 points in the NIHSS score) within 72 hours of stroke onset not attributable to stroke recurrence
- Quality of life measured with the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D-3L) at 90 days

### 8.4.4 Safety endpoints

- Mortality at 90 days
- sICH rates at 24h (defined as deterioration in NIHSS score ≥ 4 and intracranial haemorrhage)

## *8.5 Variables*

### 8.5.1 Demographic characteristics, pre-randomization and baseline variables

The following pre-treatment characteristics will be analysed:

- Informed consent
- Inclusion and exclusion criteria
- Randomization
- Demographic data including age, sex, race and weight
- Substance use (toxic and alcohol habits)
- Medical history
- Previous Medication
- Pregnancy test
- Procedure clinically general information
- Previous IV r-TPA
- Stroke etiology

### 8.5.2 Efficacy variables

The efficacy variables are listed below:

- TICI
  - Radiological eTICI at arteriography procedure pre-choice and post-choice (main evaluation)
  - Clinical mTICI
- NIHSS score
- mRS
- Barthel index
- Euroqol survey Questionnaire
- Clinically Control Neuroimage
- Radiological evaluation:
  - Neuroimage: type of image, ASPECTS, infarct volume, infarct location, infarct laterality, infarct type, hyperdense vessel sign, white matter disease Fazekas Scale and volume of haemorrhage.
  - TAN score at CTA evaluation
  - Perfusion and DWI-MRI evaluation: infarct volume, hypoperfusion volume, mismatch percentage and profile, infarct growth, infarct expansion rate and
- Arteriography: vessels occluded (including location and laterality), cervical carotid occlusions and grade, complications, vasospasm, emboli to the new and same territory.

### 8.5.3 Safety variables

The safety outcomes will include the following items:

- Laboratory parameters: haematology
- Laboratory parameters: biochemistry
- Vital signs (HR, SBP, DBP and Body temperature)
- Adverse events

- Concomitant medication
- Study drug compliance
- End of the study

## *8.6 Statistical Methods*

### 8.6.1 Descriptive Analysis

Results will be presented by study product with descriptive statistics appropriate to the nature of the variables:

- Continuous variables: Mean, 95% CI of Mean (95% mean confidence interval), SD (standard deviation), minimum, P25 (percentile 25), Median, P75 (percentile 75), maximum and N. Per group and globally.
- Categorical variables: total column %, each category N. Per group and globally.
- Ordinal variables with few categories (less than 10) will be described using two tables: one including continuous variables descriptive parameters (as long as the interpretation is reasonable) and the other including categorical variables descriptive parameters. For ordinal variables with >10 categories, the same approximation used for continuous variables will be applied.

All statistics results will be presented tabulated by treatment group, and where applicable, these summaries will be provided by time point including the absolute differences between visit and baseline results.

All text variables will be listed.

### 8.6.2 Inferential Analysis

All statistical tests will be applied with 0.05 two-sided significance level. Please refer to section 7.4 for details on the handling of multiplicity.

#### *8.6.2.1 Primary endpoint*

The main efficacy variable, the proportion of patients with an improved mTICI score ten (10) minutes after the end of study treatment will be estimated using a binomial regression model including the stratification variables, except centre. For rates-ratios the link function will be set to log (log-binomial model). In the unexpected event that the model does not fit, the Poisson regression model with log-link and robust variance estimator will be used instead[19,20,21,22,23].

#### *8.6.2.2 Binary outcomes*

Binary efficacy and safety (mortality at 90 days and sICH rates at 24 hours) outcomes will be analysed as described for the primary endpoint.

#### *8.6.2.3 Continuous outcomes. Parametric analysis*

Longitudinal continuous variables will be analysed using Mixed Models[24] using a restricted maximum likelihood (REML)-based repeated measures approach in combination with the Newton Raphson Algorithm. Analyses will include the fixed, categorical effects of treatment, the stratification variables except centre, time, and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-time interaction. Acommon unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested in a subsequent order until model-convergence is achieved: AR(1) (Auto-Regressive first order), Toeplitz and CS (Compound Symmetry). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Significance tests will be based on least-squares means using a two-sided α = .05 (two-sided 95% confidence intervals).

For those variables without repeated measurements, the model will be equivalent but without the term time and their interactions.

#### *8.6.2.4 Ordinal outcomes and non-gaussian continuous variables*

##### *8.6.2.4.1 Shift analysis*

The shift analysis of the modified Rankin Scale (mRS) will be analysed using the proportional odds model[25], combining into single worst rank the last two categories (5: severe incapacity and 6: death) and the stratification variables except centre. The common odds ratio can also be interpreted as the average shift over the total ordinal outcome scale caused by the treatment under study[26,27,28]. The stratified non-parametric van Elteren test[29], using modified ridit scores which is as a direct extension of the extension of the Wilcoxon's rank-sum test for 2-samples, will be calculated as a sensitivity analysis to compare the modified Rankin scale as an ordinal rather than a binary outcome, without assuming proportional odds[30,31].

Other ordinal variables such as the TAN score will be analysed using the same principal approach for the mRS.

##### *8.6.2.4.2 Quantile regression*

The median and 95% confidence interval (95%CI) will be calculated using the quantile regression method[32,33,34], including the stratification variables except centre, the treatment and the baseline value when appropriate.

#### *8.6.2.5 Others*

The rest of variables will be analysed according to the following strategy: the Fisher's exact test to compare categorical variables, the dependent or independent t-test for continuous Gaussian-distributed variables and the Mann-Whitney for ordinal and non-Gaussian continuous data. The survival function for death as well as the median [95% confidence interval -95%CI-] will be estimated by means of the Kaplan-Meier method. Group comparisons will be conducted using the stratified the log-rank test and, hazard ratios -HR- (95%CI) were taken from the Cox model[35], in both cases using the randomisation strata, except centre.

### 8.6.3 Demographic and Baseline Characteristics

Descriptive statistics and listings for each baseline characteristic per treatment will be performed. This analysis will be performed using the mFAS population on ADO approach

Results are presented by means of individual tables and listings for each of the variables described in section 8.5.1.

No inferential analysis will be performed for the baseline comparability.

### 8.6.4 Efficacy variables

#### *8.6.4.1 Primary efficacy analysis*

The primary efficacy variable will be conducted to evaluate the proportion of patients with an improved mTICI score ten (10) minutes after the end of study treatment.

This analysis will be performed by a log-binomial regression model specified in section 8.6.2 using the imputed data on mFAS population.

The primary efficacy variables will be also analysed using the PP population to test the robustness of the results with the same approximation (imputed data according to the strategy indicated in section 8.6.2).

#### *8.6.4.2 Secondary analysis*

Binary efficacy and safety (mortality at 90 days and sICH rates at 24 hours) outcomes will be analysed as described for the primary endpoint described in section 8.6.2.

The shift analysis of the modified Rankin Scale (mRS) will be analysed using the proportional odds model described in section 8.6.2.

The rest of variables will be analysed according to the following strategy: the Fisher's exact test to compare categorical variables, the dependent or independent t-test for continuous Gaussian-distributed variables and the Mann-Whitney for ordinal and non-Gaussian continuous data.

The survival function for death as well as the median [95% confidence interval -95%CI-] will be estimated by means of the Kaplan-Meier method. Group comparisons will be conducted using the stratified the log-rank test and, hazard ratios -HR- (95%CI) were taken from the Cox model[35].

Finally, the rest of continuous variables (measurements at different times) will be analysed using MMRM models see section 8.6.2 for more details.

All secondary analysis will be performed using mFAS data. Binary efficacy variables will be performed using imputed data and the rest of variables will be performed using ADO data.

#### *8.6.4.3 EuroQoL-5D*

The items of EuroQoL-5D questionnaire (mobility, self care, usual activities, pain discomfort and anxiety depression) will be analysed according to the EQ-5D-3L user guide[36]. All items responses will be transformed in responses of three levels and two levels, as a follow:

- Three levels: no problems, some problems and extreme problems
- Two levels: no problems and problems.

Descriptive statistical analyses will be performed for three levels response and for two levels response (as a continuous and as a categorical).

### 8.6.5 Safety outcomes

The statistical analysis will consider listings and descriptive statistics (continuous or categorical as appropriate, see section 8.6.1). The continuous safety variables will be described with the absolute values and with the absolute difference from baseline (when applicable).

No inferential analysis for safety variables will be performed, except for the comparison between treatments of the number (%) of subjects reporting one or more treatment-emergent adverse events (in general and by System Organ Class), mortality and sICH rates.

The safety analysis will be performed on Safety set.

#### *8.6.5.1 Laboratory parameters*

Laboratory parameters (haematology and biochemistry) will be described and listed by visit and treatment group.

#### *8.6.5.2 Vital signs*

Vital signs will be described and listing by visit and treatment group.

#### *8.6.5.3 Adverse events*

Inferential tests (see section 8.6.2) will be performed only for comparison between treatments by means of Fisher exact test:

- The number (%) of subjects reporting one or more treatment-emergent AES (in general and by System Organ Class).

A summary of AES by means of the number and percentage of patients reporting at least one event of each of the following:

- Any AE
- Any severe AE
- Any treatment-related AE
- Any severe treatment-related AE
- Any AE with outcome of death
- Any serious AE (SAE)
- Any treatment-related serious AE
- Any AE leading to discontinuation of the study
- Any treatment-related AE leading to discontinuation of the study

The number and percentage of patients who experience one or more AES as well as the number of TEAE episodes will be tabulated by, body system, preferred term (according to MedDRA v20.0), severity, intensity, action taken with the study treatment, other action taken, causality, pattern and outcome.

#### *8.6.5.4 Concomitant medication*

The number and percentage of patients with at least one concomitant medication will be described and listed by treatment arm.

The complete information about concomitant medication will be listed.

#### *8.6.5.5 Compliance with the study medication*

Compliance with the study product will be described and listed by study product group.

#### *8.6.5.6 Final evaluation*

Final evaluation and reasons will be described and listed by treatment arm. The drop-outs reason will also be studied in mFAS, PP and Safety populations.

## *8.7 Baseline measurements and baseline adjustments*

For any variable and for comparison purposes, the prior closest value to the administration of the study medication will be used as the baseline measurement. Variables specified as 'changes from baseline' will be calculated as absolute differences. The absolute differences will be computed as the differences between the baseline and the post dose measurements:

(Post-dose value at each time-point – Baseline value)

The statistical plan follows the regulatory recommendations regarding the use of covariates[37]. As such, the stratification variables except centre will be included in the analysis of the main and secondary efficacy outcomes.

## *8.8 Subgroup analyses*

The following 4 subgroups are declared of special interest and they will be investigated for proportion of patients with improves mTICI 2b score:

- IV Alteplase in admission (Yes versus No)
- MT started within 7.3h of symptoms onset versus MT started between 7.4h and 24h.
- Admission serum glucose concentration ≤100 mg/dl versus >100 mg/dl.

- Males versus females.
- Baseline angiographic score >90 and <100 brain reperfusion (eTICI2c) versus baseline angiographic score ≥50 and <91% (eTICI2b50 and eTICI2b67).

No other subgroup analyses are planned. In case of any post-hoc subgroup analysis, they will be justified and identified as data-driven and, they will follow the principles and regulatory recommendations[38].

The same log-binomial regression model for the main analysis will be applied to test the treatment and subgroup interaction (including subgroup and treatment per subgroup in the model). If treatment per subgroup interaction will be statistically significant (with a significant level of 10%) then the primary analysis will be performed separately by each category of subgroup.

These analyses will be performed using imputed data on mFAS population.

## *8.9 Computation of Derived Variables*

To estimate day differences the following strategy will be applied: (final date) – (initial date) + 1.

## *8.10 Additional statistical analyses*

Not applicable.

# 9 DATA BLIND REVIEW (DBR)

The Data Blind Review (DBR) will be performed before lock of database. Data will be examined for compliance with the trial protocol by the monitor and the data manager. Criteria for deviations will be sent to the project statistician to plan listings for the Data Blind Review (DBR). The objective is to carry out the population selection and definition of the final study populations as well as a preliminary assessment of the quality of the trial data and the applicability of some statistical procedures such as the handling of missing data.

# 10 DATA SAFETY MONITORING BOARD (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be established. The purpose of the DSMB is to review, on a regular basis, accumulating data from the on-going trial. The DSMB will be composed of two stroke neurologists and a statistician who are not participating in the study and are not affiliated with the sponsor. The role of the DSMB will be to: 1/Review the occurrence of AEs and SAEs and 2/ Make recommendations to the Executive Committee regarding safety of the study. A strict control of predefined AEs and SAEs will be ensured through monitoring by the CRO.

The membership, frequency and method of the DSMB, and the study aspects to be reviewed, will be specified in the DSMB Charter.

A DSMB wills follow-up the safety of the study. DSMB will be review the data in a blinded manner so that the study will maintain the integrity and will avoid any operational bias. Any potential analysis amendment will be traced and justified, if applicable. The study followed the regulatory recommendations regarding the functions and procedures of these committees.

# 11 LIST OF TABLES AND LISTINGS

## *11.1 TABLES*

### 11.1.1 Demographic characteristics, pre-randomization and baseline.

Table 1. Study population.
Table 2. Informed consent. mFAS set.
Table 3. Inclusion and exclusion criteria. mFASset.
Table 4. Demographic data including age, sex, race and weight. mFAS set.
Table 5. Substance use. mFAS set.
Table 6. Medical history. At least one medical/surgery history. mFAS set.
Table 7. Medical history. Descriptive table by type. mFAs set.
Table 8. Previous medication. At least one previous medication. mFAs set.
Table 9. Previous medication. Descriptive table by type of medication. mFAS set.
Table 10. Pregnancy test. mFAS set.
Table 11. Procedure clinically general information. mFAS set.
Table 12. Previous IV r-TPA. mFAS set.
Table 13. Strake etiology. mFAS set.

### 11.1.2 Primary endpoint efficacy analysis

Primary efficacy analysis will be indexed A for the mFAS population and indexed B for the PP population with the same numeration (all these analyses will be performed for both populations).

Table 14. Proportion of patients with an improved mTICI score ten minutes after the end of study treatment. Descriptive table by treatment group. mFAS on imputed approach.

Table 15. Proportion of patients with an improved mTICI score ten minutes after the end of study treatment. Log-binomial regression model. mFAS set on imputed approach.

Table 16. Proportion of patients with an improved mTICI score ten minutes after the end of study treatment. Log-binomial regression model. mFAS set on multiple imputation with the observed rates in the placebo group in all cases.

Table 17. Proportion of patients with an improved mTICI score ten minutes after the end of study treatment. Log-binomial regression model. mFAS set on imputing to failure all cause of missingness.

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Table 18. mRS. The shift analysis of the modified Rankin scale at day 90. Descriptive table by treatment group. mFAS on imputed approach.

Table 19. mRS. The shift analysis of the modified Rankin scale at day 90. Proportional odds model. mFAS on imputed approach.

Table 20. Infarct expansion Ratio on DWI-MRI at 24 h of stroke. Descriptive table by treatment group. mFAS on ADO approach.

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Table 24. Proportion of patients with/without infarct expansion. Descriptive table by treatment group. mFAS set on imputed approach.

Table 25. Proportion of patients with/without infarct expansion. Log-binomial regression model. mFAS set on imputed approach.

Table 26. Infarction volume on DWI-MRI at 24h of stroke onset. Descriptive table by treatment group. mFAS set on imputed approach.

Table 27. Infarction volume on DWI-MRI at 24h of stroke onset. Quantile regression. mFAS set on imputed approach.

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Table 31. Ischemic worsening within 72 hours of stroke onset not attributable to stroke recurrence. Log-binomial logistic. mFAS set on ADO approach.

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